# BREAST CANCER WHAT SCIENCE KNOWS WHAT WOMEN THINK



### **ENVIRONMENT & HUMAN HEALTH, INC.**

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# BREAST CANCER WHAT SCIENCE KNOWS WHAT WOMEN THINK

## TABLE OF CONTENTS

OVERVIEW
Study Background and Materials7
How Does the Science About Breast Cancer Risks Compare with Women's Views?
Breast Cancer Incidence
Women's Perception of Their Lifetime Risks
Geographic Differences in Breast Cancer
RISK FACTORS FOR BREAST CANCER
Age14
Genetics and Family History15
LIFESTYLE FACTORS
<b>O</b> BESITY17
Low-Fat Diet18
Alcohol Consumption
Vegetables/Fiber
VITAMIN INTAKE
CAFFEINE
Physical Activity21
TOBACCO USE AND SMOKING21
EXPOSURE TO SECONDHAND SMOKE
Reproductive and Hormonal Risk Factors
Timing of Pregnancy
Age at Menarche (First Period)

Age at Menopause25
NOT HAVING BREAST-FED
HORMONE REPLACEMENT THERAPY (HRT)
BIRTH CONTROL PILLS
HAVING TAKEN FERTILITY DRUGS
HAVING A ABORTION
BENIGN BREAST DISEASE
How Women's Views Contrast with the State of the Science
Environmental Exposures
EARLY SCREENING AND DETECTION
SERIES OF TRUE OR FALSE SURVEY QUESTIONS
QUESTIONS ABOUT BREAST CANCER PREVENTION AND SCREENING
ARE MAMMOGRAMS IMPORTANT IF YOU HAVE NO FAMILY HISTORY?
WHAT PRECAUTIONS, IF ANY, DO YOU TAKE TO PREVENT BREAST CANCER?40
FAMILIARITY WITH PREVENTIVE MEDICATIONS FOR BREAST CANCER41
WHERE DO YOU GET YOUR INFORMATION ABOUT BREAST CANCER?41
MINORITY WOMEN: A VULNERABLE POPULATION
QUANTIFYING BREAST CANCER RISK
Models of Risk and Prevention
RECOMMENDATIONS
<b>R</b> ECOMMENDATIONS FOR THE FEDERAL GOVERNMENT
RECOMMENDATIONS FOR STATE GOVERNMENTS
Recommendations for Foundations
RECOMMENDATIONS FOR THE MEDICAL COMMUNITY
RECOMMENDATIONS FOR INDIVIDUALS
References
Appendix I: Regulating Exposures to Carcinogens
Appendix II: American Cancer Society's <i>Facts &amp; Figures</i> 64

# Overview

### Breast Cancer

This study compares the state of the science concerning risk factors for breast cancer with women's perceptions of those risks.

**B**reast cancer is a disease that continues to afflict a growing number of women of all ethnic backgrounds in the United States. According to the latest estimates from the American Cancer Society, breast cancer accounts for one-third of all cancers diagnosed in women. With over 212,000 women in the U.S. projected to be diagnosed with breast cancer this year, it is imperative that medical researchers and public health officials put their energies and resources into the prevention and cure of this disease.

Estimated New Breast Cancers in Women in 2006

#### 212,920

Among the Leading Sites of Cancer in Women, Breast Cancer is the Most Frequently Diagnosed

© 2006, American Cancer Society, Inc., Surveillance Research

Limited information exists about how different ethnic

groups view their risks for getting breast cancer. Science does not yet have full insight about the causes of this devastating disease in any individual, but it can provide in-depth information about a number of known, as well as suspected, risk and protective factors. Currently, a significant disconnect exists between what the public believes about the causes of breast cancer and what the state of the science actually says about the many known risk factors and their relative impact on this disease. In order to better understand what various ethnic groups know



about their risks, as well as prevention strategies for breast cancer, this study includes a survey instrument that was designed to answer some of these questions. The survey over-sampled the African-American and Hispanic populations in order to obtain an accurate representation of their respective opinions. This report compares the responses of participants to the state of the science on different issues in question.

The purpose of this project is to uncover the information gaps among the various ethnic groups with respect to the risk factors

and prevention strategies for breast cancer and to propose strategies to fill those gaps. A public armed with more complete information will provide women of all ethnic backgrounds a better chance for improving their breast cancer outcomes.

# Study Background and Methods

Environment and Human Health, Inc. commissioned the University of Connecticut's Department of Public Policy to conduct a survey of female Connecticut residents about their knowledge, opinions and attitudes on breast cancer. The survey was conducted as part of the research initiative to better understand how women view their risks for getting breast cancer, as well as their knowledge of prevention strategies and screening opportunities.



In total, 669 telephone interviews were completed with adult women across the state of Connecticut. Extra interviews were

conducted with African-American and Hispanic women to allow for adequate subgroup analysis. The interviews were conducted between July 19 and August 5, 2005.

The sample was generated using Random Digit Dialing (RDD) Techniques to ensure that all Connecticut households with a telephone had an equal probability of selection. The data were



weighted to the Current Woman Population Survey statistics for age, race and education. The margin of error is +/- 3.8% at the 95% level of confidence for the total adult population. This means that there is less than one chance in twenty that the results of a survey of this size would differ by more than 3.8% in either direction from results that would be obtained if all adult women in Connecticut had been interviewed. The sampling error is larger for the subgroups assessed.

The survey instrument used in asking women their thoughts on breast cancer risks had the responding choices of: very important; somewhat important; not too important; not at all important; don't know.

The survey instrument can be found on EHHI's website at www.ehhi.org.

# How Does the Science About the Risks of Breast Cancer Compare with Women's Views?

Approximately 212,000 women are diagnosed each year with breast cancer in the United States. Breast cancer accounts for 30% of all new cases of cancer in women each year. It represents

the most common cancer diagnosed in women, followed by lung cancer. In addition, about 1 in 100 cases of breast cancer occurs in men. While most women are cured of breast cancer and many women live with the disease, each year more than 40,000 women in the United States die of complications related to the disease. For women between the ages of 40 and 55, breast cancer is the leading cause of death, exceeding deaths from other malignancies, heart disease and stroke.<sup>1</sup>



To assure continuing strides in reducing breast cancer mortality, both early detection through screening efforts to reach all women at risk, and the appropriate multidisciplinary treatment

after detection of the disease, are crucial. In addition, with accurate information about risk, women have the opportunity to make lifestyle and other changes that may reduce their breast cancer risk.





**B**reast cancer is a heterogeneous disease. Many breast cancers are estrogen-sensitive (estrogen receptor or "ER" positive) and require estrogen for growth. These cancers are responsive to treatments that either reduce estrogen availability or interfere with its effects. These ER positive (ER+) cancers are more common in older, post-menopausal women. Recent large studies have assessed the ability of some breast

cancer hormone treatments, such as tamoxifen and raloxifene, to prevent breast cancer in women who are felt to be at an increased risk but do not yet have cancer. This concept, "chemoprevention," will be discussed later in the report.

In contrast, breast cancer in younger, premenopausal women is more frequently estrogenindependent (ER-). When follow-up, or "adjuvant," treatment is deemed appropriate for these patients, the use of chemotherapy is often necessary. Newer chemotherapy regimens often

require biweekly treatments with careful monitoring to reduce treatment-related toxicity and assure timely completion of therapy. Treatment has been clearly shown to reduce breast cancer recurrence and mortality. In some ER+ cancers, the combination of both chemotherapy and hormone treatments may be necessary.

Newer "targeted" therapies such as Herceptin take advantage of unique biological characteristics of some breast cancers (Her-2-neu expression in cancer cells) and, when added to standard chemotherapy treatments, substantially reduce breast cancer recurrence and improve long-term survival. In addition, radiation to the breast is often necessary if initial surgery involves removal of only the



tumor itself, sparing the remaining breast, or after mastectomy if the tumor is large or involves multiple lymph nodes. Because these complex treatments result in greatly improved outcomes, it is critical that all women have access to optimal breast cancer care.

# A large majority of the women surveyed (83%) said they are somewhat (40%) or very concerned (43%) about breast cancer.

Although over three-quarters of women in all ethnic groups surveyed expressed significant concern about breast cancer, their level of concern varies. African-American women are significantly more likely to be *very concerned* about breast cancer (61%) than Hispanic (43%) or Caucasian (Non-Hispanic white) women (40%). Overall, 5% of women surveyed have a personal history of breast cancer, including 6% of Caucasian, 4% of Hispanic and 3% of African-American women.

Lighteen percent (18%) of surveyed women had a family history of breast cancer in a firstdegree relative (mother, grandmother, sister). Caucasian women had the highest family history (19%) of breast cancer, compared with 11% of Hispanic and 12% of African-American women.

- Women with a family history of breast cancer are significantly more likely to be *very concerned* about breast cancer (52%) than women without a family history (40%).
- While about half of women who have had a mammogram within the past 12 months say they are *very concerned* about breast cancer (49%), less than one third of women (30%) who have never had a mammogram felt this way.



Sixty-five percent (65%) of all women surveyed had

another relative or close friend with a personal history of breast cancer. Caucasian women had the highest (67%) while Hispanic (52%) and African-American (48%) had lower frequencies, reflecting the known racial differences in breast cancer prevalence.

There are significant differences in breast cancer mortality rates (the percentage of women diagnosed with breast cancer who will die from complications of the disease) for woman of different ethnic and racial groups. *While the mortality rate for women remained fairly constant in Caucasian women from 1970 through 1990, the death rate increased among African-American women.* During this same time period, Hispanic and Asian-American women had lower mortality rates than white or African-American women in the U.S.

Beginning in the 1990s and continuing to the present there has been a steady decline in breast cancer mortality, favoring white women disproportionately. African-American women continue to have a 30% greater mortality rate than white women.<sup>2,3,4</sup>

This overall decline in mortality rates among the Caucasian population has been attributed to both earlier detection through mammography and improvements in the adjuvant therapy of early stage breast cancer. The significant disparity in breast cancer mortality outcomes for African-American women in this country is a critical issue, and is addressed at length in a separate section of this report.

The women in this survey uniformly agreed (97%) that early diagnosis and treatment is the best way to assure a cure for breast cancer.

They also agreed (96%) that, if detected early, many cases of breast cancer can be cured.

# Breast Cancer Incidence

The chance that a woman will develop breast cancer in her lifetime varies in relation to a variety of risk factors specific to her—genetics, family history, age, reproductive and hormonal factors, and other risk factors. The chance of a woman in the U.S. developing breast cancer increases as she gets older, with a lifetime risk by age 85 of one in eight. (Turn to page 14 for an age-specific chart). The incidence of breast cancer has increased over the last 25 years, with a 4% yearly rise from 1980 through 1987 and a slower rise of 0.6% yearly from 1988 to 2000. The majority of this increase has been in estrogen-responsive (ER+) breast cancer. There has also been a marked increase in noninvasive ductal carcinoma in situ (DCIS), in part a result of increasing mammographic screening.<sup>5</sup>

### Women's Perception of Their Lifetime Risks for Breast Cancer

When asked about a woman's risk of developing breast cancer in her lifetime, respondents stated overall that 40% of all women were at risk for the disease.

African-American women thought the lifetime risk of breast cancer was higher (50%) than Caucasian (38%) and Hispanic (43%) women.



Data Sources: Incidence – Surveillance, Epidemiology, and End Results Program, 1973-2002, Division of Cancer Control and Population Science, National Cancer Institute, 2005 Deaths – National Center for Health Statistics, Centers for Disease Control and Prevention, 2005 American Cancer Society, Surveillance Research, 2005

- Only 28% of women correctly believed that a woman's lifetime breast cancer risk was between 1 and 25%. More Caucasian women (30%) held this view than African-American (15%) and Hispanic women (19%).
- Fifteen percent (15%) of African-American women believed that over three-quarters of women (>75%) will develop breast cancer in their lifetime.

Women surveyed markedly overestimated the average risk of a woman's developing breast cancer. They believed the risk was 40%, with a small but significant portion (20%) thinking the risk was over 75%, far greater than the 12.5% risk the average American woman faces.

Almost a third of Caucasian women (30%) stated correctly that the risk is between 1 and 25%; in contrast, only 19% of the African-American and 15% of Hispanic women estimated the risk at that level.

It is unclear why most women appear to overestimate lifetime risk. This may reflect the increased attention given to the "breast cancer epidemic" in the media. Media attention may also be reflected in the high level of concern most women surveyed (83%) expressed about breast cancer.

### Geographic Differences in Breast Cancer Incidence

The distribution of breast cancer around the world reveals that the highest incidence occurs in the most industrialized Western nations: the United States, Canada, England, Germany and the Scandinavian countries. In the Eastern and Southern regions of Europe, and Central and South America, rates are intermediate, while Africa and Asia have the lowest rates in the world.<sup>6</sup> Of note, as nations become increasingly "Westernized" and industrial, their breast cancer rates increase, a trend noted increasingly over the last 20 years.<sup>7</sup>

Geographic variations in breast cancer incidence can be found not only among countries throughout the world, but also regionally within countries. The lowest rates of breast cancer in the U.S. are in the South and Midwest, while higher rates are found in the Northeast, Northwest and California. High-risk areas for breast cancer—including Long Island, New York, Cape Cod, Massachusetts, and Marin County, California—to a great degree reflect these larger regional differences.<sup>8,9</sup> Increasing awareness of these differences has also raised concerns about the risk of environmental exposures.<sup>10</sup> In 2003, Connecticut was ranked first nationally among states in breast cancer incidence and continues to remain one of the highest-risk states for breast cancer (see Appendix II).<sup>11</sup>

# Risk Factors for Breast Cancer

The chance of developing breast cancer varies significantly among populations, and from individual to individual. It is critical to understand what the known risk factors are, how they promote the development of cancer of the breast and, more important, how women can reduce their risks by altering their behavior and lifestyle.

Most women are unaware that much, though not all, risk can be explained by known risk factors which, cumulatively, can significantly change overall risk in individuals, as well as populations. The failure to appreciate the effect of these



common, cumulative factors, in part, has led to concerns about an "unknown environmental causes of the breast cancer epidemic" in some areas of the U.S. Increasingly, research also suggests that there are critical periods throughout a woman's life, beginning prior to birth and extending to early childhood and adolescence, not just the immediate years preceding a cancer diagnosis,<sup>12</sup> when a number of factors can influence the risk of developing breast cancer.

# Specific Risk Factors

Women surveyed were asked to rank the importance of a variety of factors that might contribute to the risk of a woman developing breast cancer. This report describes the role of



these factors and their relative contributions to risk, as currently understood. These factors include lifestyle-related factors, reproductive and hormonal influences, genetic and family-related risk factors and environmental exposures. Women were asked to rank them as *very important, somewhat important, not too important, not at all important* or *do not know*. These rankings follow a description of what is currently known about each factor.

### Age The State of the Science

Increasing age is the leading risk factor for the development of breast cancer in all populations. The only risk factor that outranks increasing age is having the breast cancer gene, which affects a very small segment of the population. Only 5-8% of all breast cancer cases can be attributed to one of the breast cancer gene mutations. A woman between the ages of 30 and 35 has a breast cancer risk of 1 in 120, while a woman age 70 has a risk of 1 in 24 (see chart below).

#### Age-Specific Probabilities of Developing Breast Cancer\*

If current age is:	The probability of developing breast cancer in the next 10 years is: <sup>‡</sup>	or one in:
20	0.05%	1,985
30	0.44%	229
40	0.46%	68
50	2.73%	37
60	3.82%	26
70	4.14%	24
Lifetime risk	13.22%	8

\* Among those free of cancer at beginning of age interval. Based on cases diagnosed 2000–2002. Percentages and "1 in" numbers may not be numerically equivalent due to rounding. <sup>†</sup>Probability derived using NCI DevCan Software, Version 6.0 American Cancer Society, Surveillance Research, 2005

#### What Women Think

Women in this survey believed a women's age was an important factor in risk. Seventy-six percent (76%) of women felt it was either *very* (35%) or *somewhat* (41%) *important*.

More African-American women (22%) thought age was *not at all important* than did Hispanic (11%) or Caucasian (9%) women.

Seventy-six percent (76%) of women surveyed recognized age as an important risk factor, with agreement across all ethnic groups.

# Genetics and Family History The State of the Science

Approximately 15% to 20% of women diagnosed with breast cancer will have a significant family history of the disease, which may reflect the inheritance of germ-line mutations (breast cancer gene), unrecognized inherited genetic risk factors, or the presence of shared environmental risk factors.<sup>13</sup>



The presence of an inherited "breast cancer gene" mutation (BRCA-1, BRCA-2, p53, ATM, etc.) accounts for approximately 5 to 8% of all breast cancers.<sup>14</sup> Having the "breast cancer gene" is often characterized by early onset of the disease (often before age 40), bilateral breast cancer, male breast cancer, and risks for other malignancies, such as ovarian cancer and prostate cancer.

The presence of breast cancer with the following family history strongly suggests a specific inherited breast cancer risk factor, such as BRCA-1 or -2:

- Breast cancer in two or more first-degree relatives (mother, grandmother, sister)
- Breast cancer at a young age in a first-degree relative (< 40 years)
- Bilateral breast cancer in a first-degree relative
- Male breast cancer in a first-degree relative
- Multiple cancers within a family (breast, ovary, prostate) first- and second-degree relatives (maternal, paternal aunts, uncles, first cousins)

Individuals who possess one of these mutations are at a markedly higher risk of developing breast cancer in their lifetime. Researchers estimate that having the breast cancer gene raises a woman's risk to 80% or greater. It is extremely important to note that, with some exceptions (women of Ashkenazi Jewish origins), the contribution of inherited risk factors to breast cancer in large populations is modest. More than 85% of women who develop breast cancer do not have an inherited risk factor, but may, nonetheless, be at an increased risk from additional non-inherited factors. Over 80% of women with breast cancer do not have a significant family history of the disease.

Thus, women with no family history and with no specific, inherited breast cancer gene mutation may be at average or even elevated risk based on their own risk profile.

#### What Women Think

Almost all women (95%) felt that having the "breast cancer gene" was *very* (84%) or *somewhat* (11%) *important*.

There was uniform agreement across ethnic groups on the importance of the breast cancer gene, with the majority of African-American (92%), Hispanic (92%) and Caucasian (96%) women ranking this *very* or *somewhat important*.

Similarly, 92% of the women surveyed believed that "having a close relative with breast cancer" is *very* (79%) or *somewhat* (13%) *important* as a risk factor.

- Most African-American (87%), Hispanic (93%) and Caucasian (93%) women viewed a family history of the disease as *very* or *somewhat important*.
- More African-American (10%) than Hispanic (1%) or Caucasian (3%) women felt this was *not at all important*.

Women surveyed clearly understood the critical role that possessing an inherited breast cancer gene has on an individual's risk, with 95% considering this important. All ethnic groups agreed in this opinion.



Similarly, 92% of women surveyed believed that having a close relative with breast cancer was of importance for a woman's risk.

Women surveyed believed that half of women (50%) who develop breast cancer have a first-degree relative (mother, sister, grandmother) who also has breast cancer.

- Twenty-eight percent (28%) of women believe that between 1 and 25% of women with breast cancer have a first degree relative with the disease. Caucasians were more likely to hold this view (30%) than African-American (15%) or Hispanic (19%) respondents.
- A significant number of women (20%) believe that over 75% of women with breast cancer have an affected first-degree relative.

The women in this survey markedly overestimated the role that having a close relative with breast cancer plays. They believed that over half (56%) of women who develop breast cancer have a significant family history. All ethnic groups shared this belief.

When informed that most breast cancer patients do not have a family history, almost threequarters of women (71%) admitted that they would be more likely to go for regular mammograms. This strongly suggests that women without a family history feel much less at risk and thus may be less likely to follow screening guidelines as a result. This highlights the critical importance improved education about risks can have in enhanced compliance with screening, as well as prevention efforts.

# Lifestyle Factors

The variations seen both regionally and internationally in breast cancer incidence have heightened interest in the medical community in the role of lifestyle-related influences. In general, the majority of risk in breast cancer is explained by non-inherited environmental factors. The role of diet, nutrition, and obesity as well as individual nutrients has been of interest, in light of obvious cultural and geographic variations, as well as their potential modifiability. Similarly, exposures to known carcinogens, including tobacco and radiation, have been explored in many studies.

## **Obesity** *The State of the Science*

The role of weight and weight gain and its impact on breast cancer risk is complex but significant. There is a differential effect on premenopausal vs. postmenopausal breast cancer, and a differential effect based on the age of a woman when she gains weight.<sup>15</sup>





Children who are heavier at birth seem to have a modest increase in breast cancer risk in postmenopausal years, yet an increase in weight gain in pre-adolescence has been shown to *reduce* later risk. Prenatal and early childhood weight gain is associated with increasing adult height, which may result in a modest increase in breast cancer risk. One potential mediator of this effect is higher levels of Insulin-like Growth Factor-1 (IGF-1). Thus, early childhood and even prenatal weight and height growth may play a role in later adult breast cancer risk. While premenopausal (ER-) breast cancer is increased in women at lower body weight, the risk for postmenopausal (ER+) breast cancer

is enhanced by increasing weight. Weight gain between the ages of 20 and 40 also significantly increases a woman's risk of developing postmenopausal breast cancer.

Multiple studies now indicate that increased body weight is associated with adverse outcomes in women who are diagnosed with breast cancer. This includes a higher risk of recurrence and a greater risk of mortality. This has been demonstrated for both pre- and postmenopausal breast cancer.<sup>16</sup> Multiple explanations have been suggested, including higher stage at diagnosis and inadequate dosing of therapy, as well as higher levels of tumor promoters such as estrogen and insulin. Recent information suggests an important role for weight-related insulin resistance and higher insulin levels.<sup>17, 18</sup>

#### What Women Think

A majority of women (73%) felt obesity was *very* (36%) or *somewhat* (37%) *important* in breast cancer development. All ethnic groups shared this view, including 66% of African-American, 77% of Hispanic and 73% of Caucasian women.

Twenty percent (20%) of African-American women felt obesity was *not at all important* as a risk factor, significantly greater than Hispanic (7%) or Caucasian women (8%).

A large majority of women did recognize the relationship between obesity (body weight) and breast cancer, with 73% of respondents believing it was of significance. Hispanic women (77%) were more likely to hold this view than either African-American (66%) or Caucasian (73%) women.

Despite the growing recognition of the role that obesity plays in both breast cancer development and mortality, only a small minority of women surveyed mentioned either diet (11%) or exercise (6%) as ways to limit obesity and breast cancer risk. There is particular concern about breast cancer risk in the future given the growing levels of obesity in childhood, adolescence and adulthood.

### Low-Fat Diet

#### The State of the Science

Early studies, largely international and case-control, suggested a higher risk for breast cancer with increasing total fat intake. This had been one favored explanation for the marked discrepancy between breast cancer incidence rates in Western, developed countries and those in Asia, Africa and other parts of the third world.<sup>19</sup> More recent, large, prospective cohort studies now suggest a limited association between total fat intake, even in the lowest range of dietary fat (<20%) and breast cancer risk.<sup>20</sup> Recent results



of a very large randomized trial, the Women's Health Initiative (WHI), assessing the benefits of a low-fat diet in reducing risk, were reported to be negative. However, in those women who were compliant with the low-fat diet, there was a trend toward lower breast cancer incidence.<sup>21</sup>

An increased intake of saturated fat may raise risk slightly, while intake of omega-3 fats (fish and flax oils) and, in particular, monounsaturated fats (olive oil) may lower risk.

In contrast to its uncertain role in breast cancer risk, a recent randomized trial in early-stage breast cancer has suggested that women on a very low-fat (<20%) diet may have a reduction in their chances of recurrence. This was found to be particularly beneficial in women with estrogen-

insensitive (ER-) breast cancers. Further studies are planned to confirm this benefit. Many researchers believe that the critical effect of a low-fat diet is its effect on lowering weight, thereby reducing promoters of tumor growth and progression.

#### What Women Think

Seventy-eight percent (78%) of all women surveyed believed a high-fat diet contributes to breast cancer risk. This was uniform across all ethnic groups, with a significant percentage of African-American (75%), Hispanic (82%) and Caucasian (77%) women believing a high-fat diet was *very* or *somewhat important*.

■ Fifteen percent (15%) of African-American women felt it is not at all important, in contrast to 6% of Hispanics and 7% of Caucasians.

A majority of women surveyed (78%) felt that eating a high-fat diet is a significant risk factor for breast cancer. Women in all ethnic groups, including African-American (75%), Hispanic 82%) and Caucasian (77%) shared this belief. This represented one of the most consistently highly ranked risk factors by most women.

This may reflect the long-standing and well-publicized belief in the importance of low-fat diets. Despite this widely held belief, the evidence for its role remains uncertain. The critical role of weight and excess caloric intake over a woman's life appears to be more important.

## Alcohol Consumption The State of the Science

Alcohol is the most consistent dietary factor linked to breast cancer risk, in all populations studied. There is a consistent, though small, increase in risk with increasing alcohol ingestion.<sup>22</sup> This risk is associated with all forms of alcohol, including beer, wine or spirits. Women who consume two to five drinks daily have up to a 40% higher



risk than nondrinkers; however, regular folic acid intake may limit alcohol-related risk. Because mild to moderate alcohol intake may be associated with lower overall mortality, reflecting, in large part, a reduction in cardiovascular mortality, the decision to limit alcohol should be based on a woman's overall health risks. Some studies suggest that alcohol in modest amounts has no impact on survival in women who already have breast cancer.

#### What Women Think

Overall, 56% of all women viewed alcohol consumption as a *very important* (20%) or *somewhat important* (36%) contribution to breast cancer risk.

African-American (69%) and Hispanic (65%) women were more likely to feel that alcohol was a significant risk factor than Caucasian (53%) women. However, a higher number of Hispanic women (24%) believed it was *not at all important*, in contrast to African-American (11%) and Caucasian (14%) women.

More than half the women interviewed (56%) believed that alcohol plays a significant role in breast cancer etiology, with both African-American (69%) and Hispanic (65%) women attributing greater significance to this factor than Caucasian (53%) women. Despite this belief, only a small percentage of women (3%) stated that they limit alcohol intake as a preventive strategy.

### Vegetables/Fiber The State of the Science

Eating cruciferous **vegetables** (broccoli, cabbage, cauliflower and brussels sprouts) and legumes (lentils, peas and various beans) may confer a modest, but consistent, reduction in risk with increasing vegetable intake. The benefit may be greater in pre-menopausal breast cancer and in those women with a family history of breast cancer.<sup>23</sup> Diets rich in vegetables and fruit are frequently associated with lower total caloric intake, which may in part contribute to risk reduction. **Fiber** intake does not confer a reduced lifetime risk of developing breast cancer, according to most studies.



# Vitamin Intake

#### The State of the Science

An increased intake of vitamins C and E is not associated with a lower risk of breast cancer. Most studies support a modest decrease in risk with increased carotenoid intake from plant sources, but not from preformed vitamin A from animal sources.<sup>24</sup> Recent studies suggest a reduction in risk with increased ingestion of vitamin D, but the impact of the vitamin source (UV-related vs. diet vs supplement) remains unclear. Many studies support a reduction in risk with increased folate intake, either dietary or supplement, particularly in women who consume alcohol on a regular basis.<sup>25</sup>

### Caffeine The State of the Science

There is no increased risk associated with beverages containing caffeine.



### Physical Activity The State of the Science



Many, but not all, studies demonstrate a reduction in breast cancer risk with increasing physical activity. Most indirect evidence favors a reduction in risk, particularly for postmenopausal, estrogensensitive (ER+) breast cancer, because of exercise's strong association with control of weight gain and reduction in circulating estrogen levels. Lifetime physical activity can be recreational or occupational.<sup>26</sup> Recent evidence suggests a reduction in recurrence in early-stage breast cancer for women who are significantly more active.<sup>27</sup> Moderate exercise consisting of a vigorous walk for 30 or minutes or more on four to five days a week may significantly lower breast cancer mortality in women with breast cancer.

#### What Women Think

While women in this survey were not specifically asked about exercise and risk, they were questioned about what steps they took to lower risk. Only 6% mentioned exercise as an approach to reduce their risk.

This survey highlights the importance of educating women about the role of exercise and weight control in limiting the risk of breast cancer.

# Tobacco Use and Smoking

#### The State of the Science

Most studies have failed to support a significant role in breast cancer risk for either active or passive cigarette smoking, although a modest risk from very early tobacco use cannot be excluded.<sup>28</sup> Recent data from California supports a very small increase in risk with active tobacco use. This risk may be present in women with inherited



differences in metabolism of tobacco-related carcinogens. There is evidence for an increased risk in women with elevated levels of polycyclic aromatic hydrocarbons (PAHs).<sup>29</sup> PAHs are present in tobacco smoke, but they are also components of vehicle exhaust and home heating oil. Overall, the contribution of tobacco to breast cancer risk is felt to be very limited.

#### What Women Think

A very large majority of women in this survey considered smoking to be a major contributor to breast cancer risk. Eighty-eight (88%) percent of women felt it was *very* (64%) or *somewhat* (24%) *important*.

- All ethnic groups shared this view, with 75% of African-American, 74% of Hispanic and 61% of Caucasian women believing that smoking is *very important* in breast cancer risk.
- Only 9% of women felt smoking was *not too* (5%) or *not at all* (4%) *important* as a breast cancer risk factor. There were no ethnic differences in this opinion.

### Exposure to Secondhand Smoke The State of the Science

While some earlier studies suggested possible links between secondhand smoke and breast cancer risk, most studies have failed to reveal an association. The consensus among most breast cancer experts is that neither active nor passive smoking is associated with an appreciable increase in breast cancer risk.<sup>30</sup>

#### What Women Think

Nearly three-quarters of women surveyed consider secondhand smoke an *important* factor in breast cancer risk. Overall, 42% of women rank this as *very important* and 31% as *somewhat important*.

Despite the absence of a significant connection between tobacco use and breast cancer, this was the single most highly ranked breast cancer risk factor (88%) after genetics and family history, with no differences between various ethnic groups. Similarly, almost two-thirds of women



(73%) believed that secondhand smoke was a significant risk factor. Here, more African-American (87%) and Hispanic (82%) women held this view than Caucasian (70%) women.

These beliefs may reflect the widespread public awareness of smoking as the leading risk factor in lung cancer, as well as other malignancies (head and neck, pancreas). While tobacco use is clearly the single, leading public health risk factor in the U.S., there are potential adverse consequences to this belief. Nonsmoking women who hold this belief may feel less vulnerable to breast cancer and thus less inclined to follow screening recommendations. As with genetics and family history, nonsmoking women should be aware they may be at average or even increased risk of breast cancer, based on their own risk profile.

# Reproductive and Hormonal Risk Factors

After increasing age, reproductive and hormonal risk factors represent the most important risk factors in the general population.<sup>31</sup> In contrast to genetic risk factors that affect only a small percentage of women, hormonal and reproductive risk factors can influence a large percentage of the population and cumulatively contribute to a significant increase in that population's risk for the disease. These risk factors also represent common variations, both within societies and internationally, that contribute significantly to regional differences in breast cancer incidence.<sup>32</sup>



In addition, factors such as a woman's age at her first period may, in part, reflect non-reproductive factors such as nutrition and caloric intake.

Women surveyed, in general, viewed reproductive factors as of lesser importance than lifestyle factors. In addition, external hormonal factors, such as hormone replacement therapy, were given greater emphasis for breast cancer risk than the hormonal factors of a woman's own reproductive system.

# Timing of Pregnancy The State of the Science

A woman's lifetime risk of developing breast cancer is influenced by whether or not she has ever had a full term pregnancy, as well as her age at the time of her first pregnancy. A woman who completes her first full term pregnancy before the age of 20 substantially reduces her risk, while never giving birth (nulliparity) or having a first full-term pregnancy over the age of 30 increases the risk of breast cancer. There is no risk reduction when a woman fails to complete a pregnancy. There is evidence that multiple full-term pregnancies may be beneficial in reducing risk. The benefit to women from pregnancy is largely seen in a reduction in postmenopausal breast cancer, which



represents at least two-thirds of all breast cancers in the U.S. Recent studies indicate that an increased number of full-term pregnancies reduces breast cancer risk in both sporadic breast cancer (cancers not associated with a hereditary risk) and breast cancers in women with the "breast cancer gene" (BRCA-1 or BRCA-2). The benefit was an approximate 14% reduction for each additional childbirth beyond the first full-term pregnancy.



#### What Women Think

#### AGE AT WHICH A WOMAN HAS A CHILD

Fifty-three percent (53%) of women viewed age at first full-term pregnancy as *very* (16%) or *somewhat* (37%) *important.* 

#### **NEVER HAVING BEEN PREGNANT**

Overall, 47% of women felt that this factor was *very* (14%) or *somewhat* (33%) *important* while 43% felt it was *not at all* (22%) or *not too* (21%) *important*.

- More Hispanic women (42%) felt it was *not at all important* than African-American (30%) or Caucasian (20%) women.
- All ethnic groups were similar in ranking this factor, with 51% of African-American, 56% of Hispanic and 52% of Caucasian women feeling this was *very* or *somewhat important*.
- More Hispanic (31%) women than African-American (18%) or Caucasian (19%) women ranked this as *not at all important*.

#### THE NUMBER OF CHILDREN A WOMAN HAS

Overall, 34% of women interviewed felt the number of children a woman has is *very* (8%) or *somewhat* (26%) important while 57% felt it was *not too* (28%) or *not at all* (29%) important.

 Hispanic women (44%) were more likely to rank this as *very or somewhat important* than African-American (37%) or Caucasian (32%) women.





# Age at Menarche (A Woman's First Period) *The State of the Science*

An earlier age at menarche is associated with an increased lifetime risk of developing breast cancer.<sup>33</sup> The onset of menses between 11 and 13 years vs. 16 years results in a 10-30% increase in breast cancer risk.

#### What Women Think

Thirty-nine percent (39%) of women believed that age of menarche was *somewhat* (27%) or *very important* (12%) while 47% believed this factor was *not too* (24%) or *not at all* (23%) important.

More African-American (23%) and Hispanic (21%) than Caucasian (9%) women felt this was a *very important* factor.

# Age at Menopause The State of the Science



Later onset of menopause also increases a women's risk of developing breast cancer. Both earlier menarche and later menopause lead to greater lifetime exposures to endogenous reproductive hormones, particularly estrogen, which enhance a woman's lifetime breast cancer risk, particularly for postmenopausal, estrogen-sensitive cancer. Women who become menopausal at age 55 or older have a 50% higher lifetime breast cancer risk compared with women who cease menstruating between ages 45 and 50. Cessation of menses prior to age 45 results in a further 30% reduction in risk. Surgical removal of ovaries prior to age 40 may lower breast cancer risk up to 60%.

Early menarche, combined with late menopause, may raise a women's breast cancer risk by 30-50%.

### Not Having Breast-Fed The State of the Science

Increasing duration of breast-feeding lowers breast cancer risk. For every 12 months of breast-feeding, a 4% decrease in breast cancer risk occurs. Even breast-feeding for a shorter duration contributes to risk reduction. The American Academy of Pediatrics has recommended that mothers breast- feed at least six months. In 2000, more than 60% of women bottle-fed, and 27% were breastfeeding by six months post-partum. Breast-feeding rates are substantially lower for African-American and Hispanic mothers than their white counterparts.



Researchers in one study have estimated that if women in developed countries, like the U.S., had the number of pregnancies and breast-fed for the same duration as women in developing countries, the cumulative risk of breast cancer through age 70 would be reduced by up to 60%.

#### What Women Think

Forty-two percent (42%) of respondents felt that breast-feeding was *very* (14%) or *somewhat* (28%) *important*.

More African-American women (18%) and Hispanic (18%) ranked this factor very important than Caucasian women (9%).

The women surveyed consistently ranked reproductive and hormonal factors lower than other influences, with the exception of external hormone use (see survey results below). In fact, the lowest-ranked of all the risk factors were reproductive factors such as never having had children (nulliparity), breast-feeding, age of a woman's first period (menarche), number of children and history of abortion (in declining order of assigned importance).

The cumulative influence of these factors, such as early onset menses, late age at first pregnancy, limited or no breast feeding and late onset of menopause can together markedly increase a woman's risk of breast cancer. Women in this survey, as has been reported elsewhere, appear to be either unaware of, or to significantly underestimate the impact of these factors on breast cancer risk. With the exception of breast-feeding, these factors are cultural and socioeconomic and therefore often beyond most women's control.

# Hormone Replacement Therapy (HRT) The State of the Science

Use of HRT prescribed after menopause may moderately increase breast cancer risk, particularly for combined estrogen-progestin (synthetic progesterone) taken for a prolonged period of time.<sup>34</sup> This effect appears to be influenced by a woman's body weight. In heavier women, the additional fat results in higher circulating estrogen levels in the postmenopausal years. After loss of ovarian function, the sole source of a woman's estrogen results from the transformation of adrenal androgens into estrogen by the aromatase enzyme. In postmenopausal women, HRT appears to confer less additional risk in overweight older women than in lean older women.



Since the risk is cumulative, combined estrogen-progestin therapy taken over a period of 10 years may increase a woman's breast cancer risk by up to 80% above that of a non-hormone user. Risks for short-term users and those who have ever taken HRT ("ever-takers") appear to be substantially lower. Recent studies suggest that estrogen-only HRT does not carry the same risk as combined replacement therapy.<sup>35</sup> The risk for breast cancer appears only after prolonged use (more than 10 years). However, there was an increased risk of stroke in estrogen-only treated women.

#### What Women Think

More than three-fourths of women surveyed believed that HRT is a significant risk factor, with 40% ranking it *very* important and 38% ranking it *somewhat* important. There were no differences among ethnic groups in these rankings.

- African-American (18%) and Hispanic women (18%) were more likely than Caucasian (8%) women to say they "don't know."
- African–American (67%) and Hispanic (65%) women are less likely to view HRT as a significant risk factor than Caucasian women (81%).



In the opinion of respondents, the use of external hormones was given greater weight among hormonal factors. Hormone replacement therapy, particularly long-term combined estrogenprogestin, is clearly linked to increased risk. Women surveyed were aware of this risk, although both Hispanic and African-American women felt it was less important than other factors. This may reflect the traditionally lower rates of HRT use in these populations.

### Birth Control Pills

#### The State of the Science

The use of combined oral contraceptive (OC) agents increases lifetime risk only slightly and only among long-term users.<sup>36</sup> The risk disappears several years after discontinuation of use. There may be a slightly higher risk associated with the triphasic oral contraceptives that contain differing amounts of hormones throughout their active cycle. There does not appear to be any increase in risk related to long-term use of progestin-only agents, such as the Depo Provera shot or the progestin-only pill. Because it is primarily young women who use hormonal contraceptives, they are already at low risk for breast cancer and therefore their risk increases only minimally during OC use. This risk quickly returns to baseline after OC discontinuation.

Most women (69%) interviewed believe oral contraceptives are an important risk factor, ranking it *very* (32%) or *somewhat* (37%) *important*.

- African-American (63%) were somewhat less likely to view birth control as important than Hispanic (78%) or Caucasian (75%) women.
- Significantly more African-American women (22%) viewed this as *not at all important* than Hispanic (7%) or Caucasian women (6%).



Older women (age 65 and older) were much more likely to answer that they "don't know" about the risk of birth control pills (20%) than younger women (5-7%). Older women are less likely to believe it is a significant risk factor than younger women.



## Having Taken Fertility Drugs The State of the Science

A growing number of women are using hormonal agents, both to assist in becoming pregnant and to help sustain their pregnancies. Most studies indicate a limited association between hormonal treatments for infertility and the risk of breast cancer, although longer-duration studies are needed.

#### What Women Think

Sixty-one percent (61%) of women believe that fertility drug use is a *significant risk* factor for breast cancer, with 25% saying it is *very important*.

- 18% of women say they "*do not know*" enough to have an opinion about the risk of fertility drugs.
- Caucasian women (58%) are less likely to say it is a *significant risk* factor than Hispanic (72%) and African-American (73%) women.

Despite the limited evidence of significant breast cancer risk associated with either hormonal contraceptive agents or fertility drugs, women ranked these almost as high in importance as HRT. Of the women surveyed, 69% felt oral contraceptive use was a significant risk factor for breast cancer, while 61% felt that fertility drug use was a significant risk factor.

One possible explanation is the relative significance women assign to factors within their control, such as use of external hormones. This contrasts with the lower ranking given to natural variations in their reproductive lives.

## Having An Abortion The State of the Science

Termination of an early pregnancy, whether spontaneous or induced, appears to carry with it no increase in risk of breast cancer. Although there have been several studies that have attempted to link induced abortion with an increase in breast cancer risk, the studies in question were statistically flawed and, after careful re-analysis, the lack of association is quite clear.

#### What Women Think

While 25% of all women surveyed viewed having had an abortion as a significant risk factor for breast cancer, there were striking differences among different ethnic groups.

- Hispanic (51%) and African-American (40%) were at least twice as likely to believe that having an abortion was an important risk factor compared to Caucasian (20%) women.
- Views of abortion and associated breast cancer risk varied significantly among women of differing income level and education.
- The greater a women's income level, as well as the higher her education level, the less likely she is to rank abortion as a significant risk for breast cancer.

The role of abortion has remained controversial within the media and is reflected in the significance attributed to it by women in our survey. Despite this, the scientific evidence for any association with risk is limited.

## Benign Breast Disease

Women with a history of fibrocystic disease, including atypical ductal and lobular hyperplasia, as well as multiple prior biopsies, appear to be at greater risk. Recent evidence now recognizes increasing breast density (by mammographic criteria) as a significant risk factor. Breast density generally correlates with other known hormonal risk factors related to prolonged estrogen effects and may also impair the efficacy of mammographic screening. Because of the role of estrogen in increased breast density, it tends to increase during the premenopausal years, then decline after menopause.

# How Women's Views Contrast with the State of the Science

The chart below shows WHAT WOMEN THINK about lifestyle choices and breast cancer risk.

Women surveyed were aware of the risks associated with the breast cancer gene, a family history of breast cancer, and hormone replacement therapy. However, the survey shows that women ranked the relative risks of many factors in a way that are at odds with the state of the science.

For instance, women underestimated reproductive factors such as age of first menstruation, age at which a woman has her first child, and not having breast-fed, while they overestimated factors such as eating a high-fat diet, smoking, and oral contraceptives.

A woman's age, which is the single biggest risk factor for breast cancer after having the breast cancer gene, is ranked lower by women surveyed than smoking or eating a high-fat diet—both of which have limited evidence as risk factors for breast cancer.

### SURVEY QUESTION

Having the breast cancer gene
Close relatives with breast cancer
Smoking
Environmental pollution
Hormone replacement therapy
Eating a high fat dist
A woman's age
Exposure to second hand smoke
Obesity
Birth control pills
X-ray exposure
Having taken fertility drugs
Alcohol consumption
The age at which a woman has children
Never having been pregnant
Not having breast-fed
Age of first menstruation
The number of children a woman has
Having had an abortion

I am going to read a list of factors that often come up when people talk about cancer in general. For each, please tell me if it is a very/somewhat/not too/not at all IMPORTANT factor in INCREASING the risk of a woman getting breast cancer.



# Environmental Exposures Environmental Pollution/Chemical Exposures

The role of environmental exposures in the development of breast cancer is currently unclear, but remains an area of great concern across the U.S. and around the world. Because there are significant regional differences in breast cancer risk across the U.S., the role of pesticides and other synthetic chemicals has been, and should remain, an area of active investigation.<sup>37</sup>

Organochlorine pesticides such as DDT, DDE and polychlorinated biphenyls (PCBs), which are now banned in the U.S., have been a particular focus of study because of their estrogenic activity. These chemical compounds, called xenoestrogens (*xeno* is the Greek word for foreign), mimic the natural estrogen produced by the human body. Xenoestrogens are commonly known as endocrine disrupters.

There have been a number of small case-controlled studies, some of which have shown a positive association between DDE, PCBs or dioxin exposure and breast cancer, but the larger prospective cohort studies, as well as meta-analysis, have failed to confirm any relationship.<sup>38</sup>

There is increasing evidence that there exist multiple periods of vulnerability in breast cancer development.<sup>39</sup> Both *in utero* and early childhood influences may impact later adult disease. Increased growth rates in early childhood associated with adult height may also increase breast cancer risk. In addition, the exposure of the developing breast to hormonal influences prior to puberty may impact later breast cancer risk.

Few environmental studies have adequately addressed issues



of exposure to multiple chemicals or the concern about very early (early childhood or *in utero*) exposures and later breast cancer development. In addition, the impact on human health and the cancer-causing effects of many hundreds of manmade chemicals remains largely unexplored, either alone or in combination with other compounds. Many compounds possess endocrine-disrupting effects, including organochlorine pesticides, triazine herbicides, PCBs, plasticizers such as bisphenol A, and other organic contaminants. These compounds have the potential to affect the risk of reproductive cancers, including breast cancer. Some compounds, such as polyaromatic hydrocarbons (PAHs), possess carcinogenic potential and remain under active investigation.<sup>40</sup>

Because of methodological shortcomings, the true role of organic chemical exposures will remain an area of intense interest and debate. Nevertheless, in many areas of the U.S. where breast cancer rates have been high, including the Northeast and northern California, studies have been undertaken to try to assess the relationship between organic chemical exposures and higher rates of breast cancer. However, many epidemiologists believe that the known risk factors of reproductive and hormonal effects, such as age of menarche, age of first pregnancy, number of children, and genetic factors, may account for some, though not all, of the increased rates in those regions.

#### The State of the Science

Despite extensive research, the evidence for a significant contribution of environmental pollution or organic chemical exposure to breast cancer risk currently remains uncertain.<sup>41, 42, 43</sup> However, because of significant limitations in research to date, there still may be an important role for chemicals as both carcinogens and endocrine-disrupters. Many studies, in cell culture and laboratory animals, have identified chemicals with carcinogenic potential in breast tissue. While some studies have identified an association between pesticides and breast cancer, larger studies have failed to confirm a link. This will continue to be an area of active investigation.

#### What Women Think

#### **Environmental Pollution**

More than three-quarters of women surveyed believe that environmental pollution is an important breast cancer risk factor, with 40% viewing it as very important.

- African-American (90%) women are more likely to say it is a significant risk factor than Hispanic (77%) or Caucasian (77%) women.
- The youngest and oldest age groups are less likely to believe environmental pollution is a significant risk factor. Women from ages 35 to 49 (83%) and 50 to 64 (85%) felt this factor was more important than those ages 18 to 34 (71%) and those 65 and over.

#### REGULATING EXPOSURE TO CARCINOGENS

See Appendix I page 56.

In keeping with other studies, a majority (78%) of Connecticut women believe environmental pollution and chemicals are significant risk factors for breast cancer. Among the women surveyed, this risk factor was exceeded only by smoking. As noted, the role of environmental pollution and pesticide exposures needs to remain open to further research.

The difficulty in assessing the contribution of environmental pollution to breast cancer, coupled with known relationships to other adverse health outcomes, warrants limiting exposures as a precautionary measure. This particularly applies to vulnerable individuals such as young children, pubescent females and pregnant women.

## X-Ray Exposures The State of the Science

Lonizing radiation to the chest at moderate to high dose results in an increased lifetime risk of developing breast cancer. Both the age at which exposure occurs and the overall dose are



important.<sup>44</sup> Exposure in the first two decades of life increases the risk significantly more than exposure that occurs later in the adult years. Atomic bomb survivors exposed at less than 10 years of age had the highest risk, while there was almost no risk in women exposed after age 40. Women who receive radiation therapy for the treatment of cancers, such as Hodgkin's lymphoma, are at an increased risk of developing breast cancer. This risk is directly related to the total radiation dose and the age at which it is given. Early and frequent exposures to lowdose radiation may have a cumulative effect and increase the lifetime risk for breast cancer. Newer computer-based

radiation approaches reduce normal tissue exposures and are likely to reduce the risk of treatment-related second cancers, including breast cancer.

There has been increased concern about the association between exposure to residential electromagnetic field exposure (EMF) and malignancies, including breast cancer. Larger studies have failed to confirm an association suggested by smaller case-control studies.<sup>45</sup>

#### What Women Think

More than two-thirds of women surveyed believe X-ray exposure is a *significant* risk factor for breast cancer with 25% viewing it as *very important*.

- African-American women (84%) are more likely to view this as a significant risk factor than Hispanic (69%) or Caucasian (66%) women.
- Women with a close relative or friend with breast cancer and women who have had mammograms are more likely to believe that X-rays are an important risk factor for breast cancer.
- The higher a woman's income, the less likely she is to believe that x-rays are an important risk factor.

# Early Screening and Detection Mammography

Numerous large studies have documented the benefit of screening mammography in the early detection of breast cancer. The increasing use of mammography over the last two decades has contributed to the declining mortality rates of breast cancer in most populations.<sup>46</sup> On average, mammograms will detect 80% to 90% of asymptomatic breast cancers, although diagnosis may be less accurate during premenopausal years. Additional studies, including ultrasound and magnetic resonance imaging (MRI) are often useful as a supplement to mammograms in improving detection in some individuals.



To be effective in reducing breast cancer mortality, it is critical that women obtain regular mammograms in accordance with guidelines. Delay in screening follow-up can contribute to increased tumor growth, resulting in larger tumors with corresponding higher stage cancer and a



worse prognosis at diagnosis. This is particularly true in women at higher risk. An annual exam by a woman's physician is also recommended beginning at age 40, along with self-examination. In women at higher risk, initial mammograms may be appropriate before the age of 40. In addition, recent studies<sup>47</sup> indicate that women at high risk, particularly those with an inherited risk such as BRCA-1 or BRCA-2 gene, may benefit from newer and more sensitive screening approaches such as MRI.

#### What Women Think

Almost all the women surveyed (93%) know that it is important for a woman to get a mammogram every year even if she does not have a family history of the disease or a breast cancer gene mutation.

#### American Cancer Society Guidelines for the Early Detection of Breast Cancer in Asymptomatic Women

#### Age 40 and older

- Annual mammogram
- Annual clinical breast examination
- Monthly breast self-examination (optional)

#### Age 20-39

- Clinical breast examination every three years
- Monthly breast self-examination (optional)

Perhaps screening opportunities should be expanded for women under 40 who are in the most vulnerable sub-groups, including African-Americans, Ashkenazi Jews, and women with a strong family history of the disease.



- Seventy-one percent (71%) of the women surveyed over the age of 50 had had a mammogram within the previous year.
- Of the women surveyed over the age of 50 who had not had a mammogram within the last year, 20% had a mammogram within the past two years.
- Six (6%) percent of women over 50 had not had a mammogram in the past three years, and two percent had never had a mammogram.
- Hispanic women were less likely than either African-American or Caucasian women to have never had a mammogram.
- Twice as many Hispanic women as African-American or Caucasian women mentioned problems with screening times and locations.



# Series of True or False Survey Questions

Women answered a variety of questions regarding their beliefs about the value of early screening, as well as their own screening history. **Survey questions are shown in blue.** 

#### "MANY CASES OF BREAST CANCER CAN BE COMPLETELY CURED IF DETECTED EARLY."

#### The State of the Science

There is uniform agreement among cancer experts that early detection in breast cancer is critical to cure. When women are followed on a regular basis with mammograms, as well as self-examination, breast cancers are often detected at a lower stage (smaller tumors and more limited spread to lymph nodes), resulting in a significant improvement in long-term prognosis. In addition, evidence suggests that increased mammographic screening is leading to the detection of non-life-threatening early cancers, such as ductal carcinoma *in situ*, that if left untreated, would likely progress to invasive cancers, accompanied by a risk of recurrence and death from breast cancer.



#### What Women Think

Most women (97%) agree that early detection can lead to cure for breast cancer.

- Younger women (<35) are *somewhat less likely* to agree with this statement. Seventy-five percent (75%) of women under 35 *strongly agree* with this statement, compared to 84–90% of women age 35 and older.
- Women who have never had a mammogram are *less likely* (76%) than women who have undergone mammographic screening (88%) to *strongly agree* that early detection can lead to cure.

# "EARLY DETECTION AND TREATMENT IS THE BEST WAY TO ASSURE A CURE, BASED ON CURRENT KNOWLEDGE."



Similarly, almost all women (97%) agree either *strongly* (90%) or *somewhat* (7%) with this statement.

Younger women are less likely to agree with this statement. Eighty-two percent (82%) of women under age 35 strongly agree with this statement, compared to 91–93% of women 35 years and older.

#### "IF BREAST CANCER OCCURS BEFORE MENOPAUSE, IT IS HARDER TO CURE."

#### The State of the Science



Some, but not all, studies have indicated a higher risk of breast cancer recurrence in women who are premenopausal. This has been believed to be, at least in part, a consequence of the biological differences in pre- vs. postmenopausal breast cancer. Premenopausal cancers are more likely to be estrogen-receptor negative (ER-), to have more aggressive features, and to be Her-2 positive. The HER-2 protein is over-expressed in about one-fourth of women with metastatic breast cancer. Recent trials of increasingly effective, multi-

agent follow-up, or "adjuvant," chemotherapy delivered in a dose-dense fashion (every two weeks), as well as the introduction of a drug, Herceptin, that specifically targets the Her-2 receptor, are likely to lead to significant improvement in the outcome for women with premenopausal breast cancer.<sup>48, 49</sup>

#### What Women Think

Approximately one-third of women surveyed (31%) agreed with this statement.

- Hispanic women (46%) are twice as likely to believe that breast cancer is harder to cure before menopause than are African-American women (20%). About a third of Caucasian women (31%) hold this belief.
- Women who have had breast cancer are more likely to agree with this statement. Forty percent (40%) of women with a breast cancer history believe it is harder to cure breast cancer before menopause, compared to 30% of women without a breast cancer history.



Women with a family history of breast cancer (39%) are more likely to agree with this statement than women without a family history (29%).

Many studies indicate that premenopausal breast cancer is more aggressive and has a worse prognosis than postmenopausal breast cancer. More important, there are significant differences among women of different ethnicities. Many studies have shown a much higher mortality rate for premenopausal breast cancer in African-Americans. Despite this fact, African-American women surveyed were the least likely group to hold this view, suggesting that they are largely unaware of their higher-than-average risk at a young age.

#### "REDUCING STRESS IS ONE OF THE MOST IMPORTANT PARTS OF CURING BREAST CANCER."

#### The State of the Science



The role of stress in both cancer causation and outcome remains highly speculative. The majority of studies have failed to show an impact of self-perceived stress, stressful life events or personality characteristics on either cancer risk or outcome. The critical role of psychosocial support may mitigate the effect of stress and improve cancer outcomes, and continues to be an area of active investigation. While critical for a woman's quality of life, the impact of stress-reduction on cancer prognosis is unclear and is likely to be less important than most women believe. Women need to be aware of this, particularly in light of the fear and anxiety accompanying a breast cancer diagnosis and the guilt accompanying those feelings.

#### What Women Think

Most women (68%) felt that reducing stress is important in curing cancer.

There was uniform agreement among all ethnic groups about the value of stress reduction, with 69% of African-American and Hispanic and 68% of Caucasian women strongly or somewhat agreeing that reducing stress is important in curing breast cancer.

#### "IF YOU DO NOT HAVE A FAMILY HISTORY OF BREAST CANCER AND IF YOU DO NOT HAVE THE 'BREAST CANCER' GENE, IT IS <u>NOT</u> AS IMPORTANT FOR YOU TO GET A MAMMOGRAM EVERY YEAR."

Nearly all women surveyed (93%) disagreed with this statement, saying that it is just as important for a woman without a family history or breast cancer gene to get a mammogram. The response was similar across all ethnic groups.

# "CONNECTICUT HAS ONE OF THE HIGHEST RATES OF BREAST CANCER IN THE UNITED STATES."

#### The State of the Science

Connecticut has some of the highest rates of breast cancer in the nation and was ranked number one in the nation as recently as 2003 (see Appendix II, page 64).

See APPENDIX II

page 64.



#### What Women Think

Nearly half of women (49%) surveyed **did not believe** that Connecticut had one of the highest breast cancer rates nationally; only 37% of women agreed with this statement.

- Fewer African-American (29%) women agreed with this statement than Hispanic (40%) and Caucasian (38%) women.
- Women with a history of breast cancer are more likely to agree (49%) with this statement than women without a breast cancer history (36%).

#### "HAVE YOU FOUND THAT SCREENINGS FOR BREAST CANCER ARE AVAILABLE AT CONVENIENT TIMES AND LOCATIONS IN YOUR AREA?"

Seventy-eight percent (78%) of women found screenings to be available at convenient times and locations.

 Slightly fewer Hispanic (69%) women agreed than African-American (74%) and Caucasian (81%) women.

#### "IF YOU DO NOT HAVE A FAMILY HISTORY OF BREAST CANCER AND IF YOU DO NOT HAVE THE "BREAST CANCER" GENE, IT IS <u>NOT</u> AS IMPORTANT FOR YOU TO GET A MAMMOGRAM EVERY YEAR."

Nearly all women surveyed (93%) disagreed with this statement, saying that it is just as important for a woman without a family history or breast cancer gene to get a mammogram. The response was similar across all ethnic groups.

#### "MOST WOMEN WHO GET BREAST CANCER DO NOT HAVE A FAMILY HISTORY OF THE DISEASE. DOES KNOWING THIS MAKE YOU MUCH MORE LIKELY, SOMEWHAT MORE LIKELY, SOMEWHAT LESS LIKELY OR MUCH LESS LIKELY TO GO FOR REGULAR SCREENING MAMMOGRAMS?"

Armed with this knowledge, a majority (71%) of women surveyed say they would be *much more likely* to have regular screening mammograms. Only 18% say it would not make a difference in their screening behavior and very few women say it would make them *less likely* (6%) or *much less likely* (3%) to go for regular screening.



When informed that most women who get breast cancer do not have a family history of the disease, more African-American (84%) and Hispanic (90%) women than Caucasian (68%) women indicated that they would be *more likely* to go for regular screening mammograms.

Despite surveyed women's understanding that women without a family history of breast cancer should have regular screening mammograms, the majority of women, particularly African-American and Hispanic women, indicated that they would change their screening behavior when told that a majority of women with breast cancer do not have a family history of the disease. This likely reflects their overestimation of the role of family history in breast cancer. This also highlights the critical role of education about common, non-inherited risk factors and the importance of screening for all women.

#### "WHAT PRECAUTIONS, IF ANY DO YOU TAKE TO PREVENT BREAST CANCER?"

In addition to mammograms, only 23% of women surveyed did breast self-examinations. Lifestyle modifications, including healthy diet (11%), exercise (6%), moderate alcohol intake (3%), and tobacco avoidance, both active (8%) and passive (1%), were mentioned far less often than screening-related behaviors. There were no significant differences in the various behaviors among ethnic groups.

#### "How familiar are you with any prescription medications that may help prevent breast cancer for those who have an increased risk for the disease?"

Only a small minority (14%) of women were familiar with the use of preventive medication to reduce the risk of breast cancer. In contrast, 67% of women surveyed were not at all familiar with such medications. Black women (75%) were somewhat more likely to be unfamiliar with these medicines than were Hispanic (52%) or Caucasian (68%) women.



#### Breast Cancer Information Sources

#### "IN GENERAL, WHERE WOULD YOU SAY YOU GET MOST OF YOUR INFORMATION REGARDING BREAST CANCER?"

A majority of women (58%) obtain breast cancer information through media sources, including radio, TV, newspapers, and magazines (see chart). One quarter of women (26%) mentioned physicians or other health professionals. One-third or more of African-American (37%) and Hispanic (32%) women obtain their information from media sources, in contrast to only one-quarter (24%) of Caucasian women.

- Women who have had breast cancer (48%) are almost twice as likely to get their information about breast cancer from their private physician or another health professional.
- The older a woman is, the more likely she is to use media sources for information. Nearly threequarters (73%) of women age 65 and older get their information from media sources, compared with 59% of women age 50 to 64, 56% of women age 35 to 49 and 45% of those 18 to 34.



# Minority Women: A Vulnerable Population

Differences exist in both the incidence and mortality of breast cancer for women of different racial and ethnic groups.<sup>50,51,52</sup> The lifetime risk of breast cancer for a Caucasian woman is 1 in 8, while the lifetime risk for African-American women is 1 in 10. Despite the lower overall risk, *younger* African-American women have a higher risk than *younger* white women until approximately age 45, when risk reverses and the risk for white women exceeds that of black women. Since the 1990s, the Caucasian population has experienced a decline in breast cancer mortality, while the mortality in the African-American women, who have experienced both a higher incidence as well as a higher mortality from breast cancer. Overall, 90% of white women diagnosed with breast cancer survive more than five years, while only 75% of black women survive beyond five years. The lower survival rates for African-American women are evident in all age groups, in both premenopausal and postmenopausal patients. In contrast, Hispanic, Asian-American and Native American women have both a lower incidence of breast cancer than Caucasian and African-American women and lower overall breast cancer mortality rates.



\* Rates are age-adjusted to the 2000 U.S. standard population

† Persons of Hispanic origin may be any race

Data Sources: Incidence – Surveillance, Epidemiology, and End Results Program, 1973-2002. Division of Cancer Control and Population Science, National Cancer Institute, 2005. Incidence data for Hispanics do not include cases from Detroit, Hawaii, Alaska Native Registry, and rural Georgia. Deaths – National Center for Health Statistics, Centers for Disease Control and Prevention, 2005. For Hispanics, information is included for all states except Connecticut, Maine, Maryland, Minnesota, New Hampshire, New York, North Dakota, Oklaboma, and Vermont. American Cancer Society, Surveillance Research, 2005

# This survival differential has been attributed to several factors, including biological features such as higher-stage (tumor size and lymph node status), more aggressive tumor histology, and a

higher frequency of ER (estrogen-), PR (progesterone-) negative tumors.<sup>53</sup> Gene analysis studies distinguish higher-risk subtypes of breast cancer ("basal-like") that are estrogen non-responsive and possess higher growth rates. Recent studies show a much higher prevalence of this subtype among premenopausal African-American women compared to postmenopausal African-American and Caucasian women.<sup>54</sup>

The higher frequency of aggressive breast cancers, particularly in younger black women, may reflect several factors. While screening mammography rates have improved in black and Hispanic women in recent years, they still lag behind the Caucasian



population. Recent studies suggest that black women are also much less likely to obtain yearly follow-up screening mammograms. This is particularly critical for younger women who experience more rapid tumor growth and are at greater risk of increased tumor size and stage from delays in follow-up screening. A recent NCI study of over 1 million women confirms that a significant explanation for the higher prevalence of advanced breast cancers is, indeed, inadequate mammographic screening.<sup>55</sup> More than 34% of African-American women with breast cancer had inadequate screening prior to their diagnosis, and were found to have larger and more aggressive cancers than Hispanic, white, Asian-American and Native American women.

Also contributing to adverse outcomes is the increasing incidence of obesity in the young black female population, a well-defined adverse prognostic factor linked to both larger tumors and more aggressive histologic features.<sup>56, 57, 58</sup> Increasing abdominal obesity and insulin resistance are also growing more common in the young African-American population, particularly among the urban poor, and have been linked to worse outcomes in breast cancer.<sup>59</sup>





The lower risk of postmenopausal breast cancer in the African-American population may reflect influences known to be protective, and more common, in the black population, including earlier age at first pregnancy and a larger number of children. In contrast, black women are much less likely to breast-feed than other ethnic groups. Since breast-feeding is most protective in the premenopausal years, this difference is believed to account, in part, for a higher breast cancer risk in young black women.

Kecent data confirm the critical role of timely adjuvant therapy in early-stage breast cancer. In younger women with ER-negative cancers, newer approaches utilize more frequent, "dosedense" chemotherapeutic approaches that have significantly enhanced both freedom from recurrence and long-term survival in these women.<sup>60</sup> In underserved minority populations, it is more common to find both delays in initiation of treatment, as well as premature termination of therapy for a variety of reasons. In minority populations, these factors can also adversely influence long-term outcomes in young women with more aggressive cancers.

#### Women in all ethnic groups express a high level of concern about breast cancer.

- All ethnic groups <u>overestimated</u> the role that having a family history of the disease plays in the incidence of breast cancer.
- More Hispanic (90%) women mentioned that they would be more likely to go for regular mammographic screening when told most breast cancers were not related to family or genetic risk factors. This contrasted with 74% of African-American women and 68% of Caucasian women.
- Both African-American and Hispanic women recognize the importance of early detection and treatment as the best way to achieve a cure for breast cancer. There were no differences among African-Americans, Hispanics and Caucasians.



- As with the overall group, ethnic minority women tended to view reproductive and hormonal risk factors as less important than other exposures.
- All ethnic groups believed environmental pollution plays a significant role in breast cancer causation.

# Quantifying Breast Cancer Risk

It is now possible to assign the relative contribution of various factors to the risk of developing breast cancer. Each factor can be assigned a "relative risk" in numerical terms. As an example, if the "average risk" in the U.S. population—at 12% over a woman's lifetime—is defined as a relative risk of 1, then a factor having a relative risk of 2 will double that woman's risk to approximately 24% in a lifetime. Because of the profound importance that possessing an inherited "breast cancer gene" has for the individual possessing it, the relative risk may be between 4 and 8 (4 to 8 times greater risk for those individuals). Most non-inherited risk factors, particularly reproductive factors, will increase risk to a smaller degree (relative risk under 2). However, women will frequently have multiple risks, and the risks are additive. For many women these additive risks will become significant when calculating their total risk for developing breast cancer.

 $B_{elow}$  is a list of factors with their accompanying **relative risk contribution** to breast cancer:

Relative Risk >4.0	Age > 65 years						
	Inherited Breast Cancer Mutation (BRCA-1, BRCA-2)						
	<i>Two or more first degree relatives with breast cancer</i> <i>at an early age</i>						
	Prior history of breast cancer						
	High breast density						
Relative Risk 2.1-4.0	One first degree relative with beast cancer						
	Biopsy-confirmed atypical hyperplasia						
	High-dose radiation to the chest						
	High bone density						
Relative Risk 1.1-2.0	Late age first full-term pregnancy (>30 years)						
	Early menarche (<12 years)						
	Late menopause (>55 years)						
	No full-term pregnancies						
	Never breast-fed						
	Recent oral contraceptive use						
	Recent and long-term HRT use						
	Obesity (postmenopausal)						
	History of uterine, ovarian or colon cancer						
	Alcohol consumption						
	Tall stature (height)						
	High socioeconomic status						

# Models of Risk and Prevention Gail Model

L here are numerous factors that play a role in enhancing or reducing a woman's risk of developing breast cancer. While many, such as age of menarche or menopause, are non-



modifiable, many others, including breast-feeding, weight control and diet, as well as the use of hormone replacement at menopause, are within a woman's control (modifiable). In addition, newer approaches to breast cancer reduction have sought to incorporate medications that may reduce breast cancer development (chemoprevention). In order to assess the relative benefit of chemoprevention approaches, in light of potential risks with the use of such pharmacologic approaches, quantitative models have been developed to assist women and their caregivers in determining their individual risk and whether the benefit exceeds risk. The Gail model<sup>61</sup> is a scale, including many of the known

risk factors, that calculates a woman's risk of developing breast cancer over time. Many, but not all, of the known influences on breast cancer risk are included in the model.

### Chemoprevention

The development of quantitative approaches, such as the Gail Model, were in part designed to assist women in making decisions about the use of medications capable of preventing breast

cancer. Because most breast cancers are estrogen-dependent and occur in the postmenopausal years, the use of agents active in treating breast cancer were assessed for their effect in preventing new breast cancers. Tamoxifen, the first active anti-estrogen compound, was found to significantly reduce the development of contralateral breast cancers in women being actively treated to prevent breast cancer recurrence. A large subsequent trial, NSABP P-1<sup>62</sup> confirmed the benefit of a five-year course of Tamoxifen in reducing breast cancer by up to 50% in a large group of women at increased risk



(using criteria derived from the Gail Model). Since that study, women at increased risk have been reluctant to consider tamoxifen, in part due to its well-documented side-effects (including endometrial cancer, thromboembolic disease, and cataracts). Newer agents, such as raloxifene (Evista), that have similar benefits in reducing breast cancer but a lower side-effect profile, appear to be more acceptable and may add to the options for women at higher risk.

# Recommendations for the Federal Government

- Increase federal funding through the National Institutes of Health (NIH) to promote greater research into the prevention of breast cancer.
- Increase funding for research into the causes of disparities in breast cancer incidence and outcomes among the different ethnic groups. Increased research must address the economic, social and cultural factors that interfere with access to modern, curative therapies, delivered in a timely fashion so as to maximize their benefit. Particular attention should be paid to the higher risk and mortality in younger African-American women.
- Increase funding aimed at eliminating barriers to screening for breast cancer for all women, especially those groups with the lower utilization of these services and more adverse outcomes after treatment. Hispanic women in our study reported more barriers to access for screening and had lower rates of mammography.
- Recommend that women at high risk consider screening before age 40. African-Americans, Ashkenazi Jews, and women with a strong family history of breast cancer are at potentially higher risk and may warrant earlier screening than the general population. These screenings should remain available and insurable.



- Provide guidance to state and local governments to assist them in the publication and distribution of informational materials so that women can better understand that the majority of breast cancer cases occur among women who have no family history of breast cancer. All women need to understand the importance of yearly screening mammograms beginning at age 40, as well as other measures important in limiting risk. Information should highlight differences among ethnic groups with regard to breast cancer risk. Women surveyed uniformly overestimated the role of family history and genetics in breast cancer, which may adversely affect many women's screening behavior. EHHI's study showed that if women where made aware that over 80% of all breast cancers occur in women with no family history, they would be more vigilant about mammographic screening.
- Expand the effort to identify or exclude causal roles for a variety of environmental contaminants in breast cancer. Increased effort should be directed to assessing exposures that occur both during the prenatal period, as well as in early childhood and adolescent years, in relationship to breast cancer risk.

# Recommendations for State Governments

- States should provide information about known risk factors for breast cancer to allow women to assess their own relative risks. Materials should describe prevention strategies and how to access screening opportunities within the state.
- States should establish and regularly update a website that provides information about the known and suspected risk factors for breast cancer. The website should include:



- The number of women diagnosed with the disease, both nationally and within each state, updated on an annual basis. Data should include ethnic differences within those statistics;
- How women can reduce their risk factors for breast cancer within their control;
- How and where women can access screening opportunities within each state.
- States should provide *free* or *limited-cost* (by sliding scale) counseling and breast cancer screening services targeted to minorities and the uninsured. These services should be available at convenient locations and times to ensure accessibility for women facing economic and social barriers. Innovative efforts to partner with not-for profit organizations, corporate and local businesses, as well as the medical community, should be encouraged to widen access to these services.
- States should undertake a broad public health campaign targeted to enhancing women's understanding of breast cancer risks to increase women's utilization of screening tests. Women in this survey uniformly overestimated the role of family history and genetics in breast cancer. This overestimation may adversely affect many women's screening behavior. When women were made aware that more than 80% of all breast cancers occur in women without a family history, they reported that they would be more vigilant about mammographic screening. States should use the media to publicize this fact, along with other breast cancer prevention strategies. EHHI's study showed that the majority of women surveyed said they obtained their information about breast cancer from media sources.

# Recommendations for Foundations

- Both increased funding and education are needed to address the disparities in both breast cancer incidence and mortality in the minority community, particularly among young African-American women.
- Women uniformly overestimate the role of family history and genetics in breast cancer, which may adversely affect many women's screening behavior. EHHI's study shows that women would be more vigilant about getting mammographic screening if they were aware that more than 80% of all breast cancers occur in women without a family history of the disease. This fact needs to be publicized.
- Assist in the dissemination of information about breast cancer to women at high risk for the disease, including African American women, Ashkenazi Jews, and those with a strong family history of the disease. Women in high-risk groups need to be better informed of their risk of early-onset breast cancer so they can consider screening before age 40. Mammographic screenings should remain available and insurable for these vulnerable groups.
- Increase funding for research into effective treatments for breast cancer in all women, paying particular attention to African-American women and other at-risk minority populations.
- There is a growing need for research and education efforts devoted to lifestyle factors that may contribute to adverse breast cancer outcomes. The growing obesity epidemic in early childhood, adolescence, and young adulthood is a critical influence in breast cancer development and outcome, and should be a priority for research and intervention. Partnerships among organizations can broaden these efforts and serve as models for the governmental, corporate and the not-for-profit community.
- The majority of women get their breast cancer information from the media. Given the many areas of misunderstanding about breast cancer among the surveyed women, there is a great need for wider dissemination of accurate information through media sources. Foundations can be helpful in supporting these educational efforts.
- Access to breast cancer screening should be improved. Women would also benefit from better education about the critical need for timely screenings and the importance of yearly follow-up exams for all women, irrespective of level of risk, beginning at age 40. Foundations, in cooperation with the medical community, can offer significant support for these activities.

# Recommendations

for the Medical Community: Institutions, Physicians and Healthcare Providers



- Healthcare providers and institutions must focus their educational efforts on emphasizing the importance of screening for all women, paying particular attention to vulnerable populations.
- Healthcare institutions should educate primary care providers, including internists, family practitioners, gynecologists, and physicians in training—as well as nurses working with minority populations—about the higher incidence of breast cancer among younger African-American women who have a higher risk of more aggressive cancers. The critical need for patient follow-up, appropriate screenings, and lifestyle interventions cannot be overemphasized.
- Institutions should maximize continuity of care for women who lack a single primary care provider. Fragmentation of care for minority women remains a significant barrier that reduces the likelihood of timely and appropriate care.
- To limit barriers to screening and treatment, institutions should strongly consider the use of patient "navigators" who can facilitate timely follow-up studies and care involving multiple practitioners and services.
- African-American women should be educated about their higher risk for early-onset breast cancer and the critical importance of early detection through mammographic screening. Educational efforts could be facilitated by African-American groups, including the National Medical Association (NMA) and the NAACP, as well as local community and church-affiliated organizations. The goal should be to encourage understanding of breast cancer risk factors and the benefits of early detection in improving cancer survival. Medical institutions should partner with community organizations in these efforts.
- Assure the timely start of adjuvant therapy for early-stage breast cancer, including chemotherapy in the most effective dose and schedule; hormonal treatments when appropriate; and localized breast irradiation in the appropriate setting. Healthcare providers and institutions should make every effort to educate minority populations, in particular, about treatment benefits, while limiting barriers (social, economic, educational or geographic) that may impair full and timely compliance with these important therapies.

- Women should be apprised of the potential benefits of breast-feeding and, whenever possible, be encouraged to breast-feed for at least six months, in line with the American Academy of Pediatrics recommendations. African-American women, who are at higher risk for premenopausal breast cancer, but whose breast-feeding rates are lower, should be made aware of the the protective effects of breast-feeding.
- Institutions should recognize the barriers to care represented by the costs incurred by low-income women for screening, transportation and childcare needs, as well as the out-of-pocket expenses for treatment. This is particularly problematic for women requiring on-going chemotherapy and radiation with multiple visits to a variety of service providers.
- Additional resources and education should be devoted to systems that facilitate rapid and complete follow-up after abnormal tests and studies.
- Minority women are more likely to receive care that does not reflect standards of the 2000 National Comprehensive Cancer Network. All institutions should strive to provide care in accordance with evidence-based guidelines for all patients diagnosed with breast cancer.



- Increased research should be devoted to the role of genetic risk factors in breast cancer within the minority community.
- Institutions and practitioners must be knowledgeable about modifiable breast cancer risk factors, including obesity, inactivity, alcohol consumption and hormone replacement therapy, in order to counsel patients about healthy lifestyles. Physicians need to be aware of the role of excessive weight in adverse outcomes. Most research indicates that physician recommendations about diet, exercise and weight control are important in ensuring compliance.
- Multiple programs have been instituted to provide financial assistance to low-income women, such as the National Breast and Cervical Cancer Early Detection Program (NBCCEDP), the Breast and Cervical Cancer Prevention Act of 2000, and the Avon Foundation's AVONCares. These and similar programs should be accessed wherever possible to help disadvantaged populations.

# Recommendations for Individuals

- Women should follow recommended guidelines for mammographic screening, including follow-up studies on a regular basis. This is particularly important for African-American women who are, according to our survey, largely unaware of their higher risk for early-onset breast cancer. Mammographic screening at a younger age should be considered for this group.
- In addition to African-American women, others at high risk, such as those with a strong family history and those with the BRCA-1 or BRCA-2 gene, should consider obtaining a screening mammogram before age 40. They should also consider MRI screening at appropriate intervals based on their physician's recommendations.



- Women should avoid weight gain in early adulthood by eating a healthy diet, rich in vegetables and fruit, low in saturated fat, with a moderate intake of monounsaturated fat (olive and canola oils), along with regular exercise and physical activity. Avoiding weight gain is crucial for all women, but is of particular concern for African-American women, in whom increased body weight may contribute to their adverse breast cancer outcomes.
- Beginning in childhood, parents should foster a healthy diet and include regular exercise for their children. Avoidance of obesity and providing physical activity is critical.
- Women should avoid the use of long-term HRT, particularly combinations of estrogen and progestins.
- Women at higher risk for breast cancer should limit alcohol intake to one to two drinks per week. If women consume alcohol on a regular basis, they should consider taking a daily multivitamin containing folic acid.
- Women at high risk should exercise at least four to five times a week.

Women at significantly higher risk, such as those with a family history or prior benign breast disease, should discuss with their physicians the option of preventive medications,

such as tamoxifen, or other hormonal treatments. In many cases, the benefit of these agents may significantly exceed their risk. Because EHHI's survey showed that most women are unfamiliar with this option, greater effort should be made to explain the potential benefits of Selective Estrogen Receptor Modulator (SERMs). Recent data support the use of the alternative SERM agent raloxifene (Evista), which provides benefits similar to tamoxifen in reducing breast cancer risk,



while also improving bone density. Raloxifene has been shown to cause fewer adverse effects, including an absence of increased endometrial cancer risk, lower risks of blood clots and strokes, and lower rates of cataract formation. Because of its improved risk profile, many women may find raloxifene a more acceptable alternative to tamoxifen.

Because we do not know the exact interplay between environmental contaminants and breast cancer, women should avoid exposures to carcinogens and endocrine disrupters. Exposures to pesticides and other chemicals should be avoided, especially during vulnerable periods of growth, such as pregnancy, early childhood and adolescence. Until there is more data about the role that chemical exposures play in breast cancer incidence, reducing pesticide and chemical exposures will remain the most prudent course of action.

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# Appendix I Regulating Exposures to Carcinogens

#### FEDERAL POLICY

- In pathology, a *carcinogen* is any substance or agent that promotes cancer.
- Federal responsibility for limiting exposure to and use of carcinogens is shared among the Environmental Protection Agency (EPA), Food and Drug Administration (FDA), Occupational Safety and Health Administration (OSHA), and the Consumer Product Safety Commission (CPSC). The overall regulatory structure is complex and agency jurisdictions often overlap. For example, there are at least 14 federal regulations and three agencies that regulate occupational skin exposures in the U.S.<sup>1</sup>
- Several agencies have developed lists of carcinogens, each with a different classification system and set of substances believed to be carcinogenic.
- The International Agency for Research on Cancer (IARC) is the most widely used system for classifying carcinogens. The agency has evaluated about 900 likely cancercausing chemicals and classified them according to the groups shown in the table below.<sup>2</sup>
- The U.S. National Toxicology Program (NTP) publishes a Report on Carcinogens (RoC) about every two years. The report only includes substances for which "relevant data exists" and which have been nominated for review by the NTP. NTP lists 246 compounds "known" or "reasonably anticipated" to be human carcinogens.<sup>3</sup>
- Chemicals recognized to pose a risk of cancer include dyes, solvents, pesticides, drugs, food additives, and by-products of industrial processes. These compounds can be found in food, water, air, soil, consumer products, and many indoor environments. Research indicates that exposure to some carcinogens significantly increases the risk of cancer in humans.<sup>4</sup>
- California's Proposition 65 requires the Governor of California to publish a list of chemicals known to the state to cause cancer or reproductive toxicity. The list currently includes about 500 substances "known" to cause cancer.<sup>5</sup> Proposition 65 also requires businesses to label products to warn consumers before exposing them to a chemical on the list and prohibits companies from knowingly discharging a listed chemical when it could contaminate drinking water.<sup>6</sup>

- The "Safe Cosmetics Act of 2005" was recently passed in California requiring cosmetics companies to disclose ingredients that pose a risk for cancer, birth defects or reproductive harm. The Act requires cosmetics manufacturers to disclose to the state any product ingredient that is on state or federal lists of chemicals that cause cancer or birth defects; allows the state to demand that manufacturers supply any health-related information about cosmetic ingredients; and authorizes the state to regulate the products to protect salon workers if they determine a safety risk.
- Table 1 summarizes and compares the most authoritative programs that classify carcinogens:

Program	Cancer Categories	Number on list							
IARC	Group 1: Carcinogenic to humans (95) Group 2A: Probably carcinogenic to humans (66) Group 2B: Possibly carcinogenic to humans (241) Group 3: Unclassifiable as to carcinogenicity in humans Group 4: Probably not carcinogenic to humans (1)	<b>900</b> 5 (497)							
NTP	Known to be human carcinogens (58) Reasonably anticipated to be human carcinogens (	188) <b>246</b>							
Proposition 65	Known to cause cancer	501							

#### Table 1: Programs that Classify Carcinogens

Many known or anticipated carcinogens appear on all three lists. Chemicals that do not appear on one list may not have been evaluated by the agency. The lists themselves say nothing about how likely the agents are to cause cancer or how dangerous exposures may occur.

#### CHEMICALS IN COMMERCE

EPA's Toxic Substances Control Act Chemical Substance Inventory (TSCA) includes over 75,000 existing chemicals in commerce.<sup>7</sup> Between 3,000 and 4,000 are high production volume chemicals (produced or imported into the U.S. in annual volumes above one million pounds or more per year).<sup>8</sup> Drugs, cosmetics, foods, food additives, pesticides, and nuclear materials are not included in this estimate.<sup>9</sup> Cosmetics, for example, include over 25,000 product formulations and about 5,300 different cosmetic ingredients. Due to the voluntary nature of reporting, this figure may under-estimate the actual number of ingredients in cosmetics on the market.<sup>10</sup>

#### STATUS OF CHEMICAL TOXICITY TESTING

- Extremely limited information is available about the toxicity of chemicals in commerce. TSCA requires chemical companies to submit information to the EPA only if it demonstrates that the chemical "may present an unreasonable risk or substantial exposure."<sup>11</sup> However, data are often not available to make this determination. Among the 3,000 to 4,000 high production volume chemicals, about 40% have no data on basic toxicity. Of the remaining chemicals, 7% have a full set of basic test data,<sup>12</sup> and 93% are missing one or more basic tests.
- To generate more data on chemical toxicity, the EPA entered into a voluntary program with the American Chemistry Council to encourage industry to provide basic screening level data on high production volume chemicals.<sup>13</sup> These data vary in quality among chemicals. The program generated volumes of toxicity data that EPA has not determined how to use for risk management decisions.
- EPA reviewed about 500 chemicals used by children and families in consumer products and found that only 25% have data on acute toxicity, chronic toxicity, developmental/



reproductive toxicity, and mutagenicity. The agency concluded that it "...cannot begin to judge the hazards and risks of such consumer chemicals without basic information, and in fact substantially more detailed and exhaustive testing is needed to assess these high exposure chemicals."<sup>14</sup> The agency found that only 53% of the high volume chemicals with Permissible Exposure Limits (PELs)—set by the Occupational Safety and Health Administration (OSHA) for hazardous chemicals in the workplace—have basic screening tests for human health studies. These studies include acute toxicity, chronic toxicity, developmental/reproductive toxicity, and mutagenicity. Only

5% of the non-PEL High Production Volume (HPV) chemicals were subjected to all four health effects tests and 49% had no health test data available. According to the agency, "it is clear that the bulk of HPV chemicals without PELs lack even the minimal data needed to support development of a PEL value to protect workers."<sup>15</sup>

- Few data are available on individual chemicals, but even less is available on mixtures of chemicals. Additive and synergistic effects resulting from mixtures are not considered when regulators set limits for individual chemicals.
- According to the General Accounting Office (GAO), chemical companies have provided health data to EPA for only 15% of the chemicals introduced over the last 30 years.<sup>16</sup> It is therefore not surprising that EPA has had difficulty proving that chemicals pose unreasonable health risks.

#### **RESTRICTING CARCINOGENS**

- When data demonstrate that a chemical is carcinogenic, federal and state authorities rarely ban the chemical. Instead, uses may be restricted, allowable contamination limits may be reduced, hazard warnings may be required, or products labeled. The EPA has placed restrictions on only five chemicals (PCBs, chlorofluorocarbons, dioxin, asbestos, and hexavalent chromium) using TSCA authority, and one of these restrictions (asbestos) was overturned.
- The FDA does not review or regulate cosmetic products or ingredients for safety before they are sold to the public and has no legal authority to recall hazardous products.<sup>17</sup> Manufacturers and distributors of cosmetic products have the responsibility to assure the safety of each product. Without substantiation of safety, the product must carry the following label: "Warning: The safety of this product has not been determined."<sup>18</sup>
- FDA may request removal of a cosmetic from the market. However, only nine cosmetic ingredients are specifically prohibited or restricted from use in cosmetics, three due to concerns about carcinogenicity (chloroform, vinyl chloride and methylene chloride).<sup>19</sup> Cosmetic and fragrance trade associations have recommended eliminating six other ingredients associated with health risks, several for carcinogenicity.<sup>20</sup>
- Coal tar hair dyes are one of the few products for which FDA requires safety precautions.<sup>21</sup> In the late 1970s, FDA proposed to require a warning on the labels of hair dyes containing two coal-tar ingredients<sup>22</sup> found to be carcinogenic in lab animals. After FDA adopted the requirement of a warning, manufacturers stopped using these and several other similar chemicals in their hair dyes. FDA notes that these compounds were replaced by similarly structured chemicals.<sup>23</sup>
- While federal agencies have been slow to remove products from the market or to require warnings, California's Proposition 65 has resulted in many changes in consumer products, including:
  - Lead and Drinking Water: elimination of lead-bearing brass from brass faucet fixtures, submersible well pumps, and brass check-valves.<sup>24</sup>
  - Food: shift to lead-free calcium supplements;<sup>25</sup> shift to non-leaded cans, capsules on wine bottles for all California wineries, glaze and decorations in ceramic ware, and crystal; and Proposition 65 compliance as a condition of purchase by market chains.<sup>26</sup>

Other Consumer Products: shift to cleaner fuel trucks,<sup>27</sup> removal of mercury compounds from hemorrhoid suppositories, elimination of paradichlorobenzene from diaper pail deodorizers, removal of toluene from nail polish, and removal of perchloroethylene from spot removers.<sup>28</sup>



In Europe, where only 14% of nearly 3,000 high production chemicals have data publicly available at the base set used for new chemicals,<sup>29</sup> a program called REACH (Registration, Evaluation and Authorization of Chemicals) has been developed that places responsibility for chemical safety on the chemical producer or importer into the European Union (EU). For carcinogens, approval is required for their use and their placement on the market.<sup>30</sup> The EU has also amended the *cosmetics directive* (76/768/EEC)<sup>31</sup> to ban carcinogens from cosmetics.

#### **ROUTES OF EXPOSURE**

Carcinogens are ubiquitous. People are exposed to natural and synthetic carcinogenic substances via inhalation, ingestion, or through their skin. Yet little is known about the extent of their exposure to single compounds or chemical mixtures. The GAO compiled a list of 1,400 chemicals believed to threaten human health and found that efforts to collect human exposure data by federal agencies measured exposure in the general population for only 6% of the 1,400 chemicals. For chemicals that were measured, information was often insufficient to identify smaller population groups at high risk, including women.<sup>32</sup> The GAO concluded that health officials cannot communicate risks from environmental contaminants when information is unavailable to help them interpret the risks.<sup>33</sup>

#### FEDERAL RISK ASSESSMENT METHODS & ACCEPTABILITY

There is no agreement on the level of risk considered acceptable by the FDA, EPA, and OSHA.<sup>34</sup> Different statutes and agencies allow different residual cancer risk (see opposite page). Debates over the magnitude of cancer risk concern the availability and sufficiency of data, the methods of inference from uncertain data, appropriate models of mechanism of action, and whether exposure to carcinogens at a young age conveys heightened risk. These debates delay regulation, and have often permitted exposures to continue.

#### ACCEPTABLE RESIDUAL CANCER RISK POLICIES IN THE UNITED STATES

Federal Law/Agency	Exposure	Risk Policy
Clean Air Act/EPA	Hazardous air pollutant emissions	Stationary sources of HAPs: residual-risk standards apply after industry has implemented the maximum achievable control technology. Most- exposed individual: protected against risks greater than 1 in 10,000 (regardless of feasibility and cost). As many citizens as possible: protected against risks as small as 1 in 1 million (taking into account scientific uncertainty, feasibility and cost considerations). <sup>35</sup>
CLEAN WATER ACT/EPA	Industrial discharges of carcinogens to surface water	EPA guidance to the states: carcinogenic risk from each contaminant in surface water should be reduced into the range from 1 in 100,000 to 1 in 10 million, with a preference for 1 in 1 million. EPA has promulgated ambient water quality criteria for states at a lifetime risk level of 1 in 1 million. <sup>36</sup>
Safe Drinking Water Act/EPA	Carcinogenic contaminants in drinking water	Maximum Contaminant Level Goals (MCLGs): For carcinogens, MCLGs are typically set at zero. Maximum Contaminant Levels (MCLs): set as close to MCLGs as is "feasible with the use of best available technology." <sup>37</sup>
Food Quality Protection Act/FDA	Food	"Reasonable certainty of no harm." Can allow minor cancer risks.
Federal Insecticide, Fungicide, and Rodenticide Act	Levels for pesticide residues in food	FIFRA defines "unreasonable" in a way that includes the "economic, social and environmental costs and benefits of the use of the pesticide. <sup>38</sup>
FOOD DRUG COSMETIC ACT/FDA	Drugs, Cosmetics, Food Additives	FDA does not review or regulate cosmetic products or ingredients for safety before they are sold to the public and has no legal authority to recall hazardous products.
TOXIC SUBSTANCE Control Act	Approval of new commercial chemicals	Under TSCA, EPA can place restrictions on chemicals that pose "unreasonable risks." Chemicals regulated by EPA include asbestos, chlorofluorocarbons, lead, and polychlorinated biphenyls. <sup>39</sup>
RESOURCE CONSERVATION AND RECOVERY ACT/EPA	Hazardous waste characterizations	Classification of a chemical as "hazardous" is determined either by the MCLs or risk assessment if there are no MCLs. If the lifetime risk associated with the leaching of wastes is greater than 1 in 100,000, the wastes are classified as hazardous. <sup>40</sup> The study of cleanup options is required if the risk is greater than 1 in 1 million. The cleanup options selected must bring risk within an acceptable risk range of 1 in 10,000 to 1 in 1 million.
Comprehensive Environmental Response, Compensation, and Liability Act/EPA	Site-specific cleanup decisions at Superfund sites	<i>The National Contingency Plan has designated an acceptable risk range of 1 in 10,000 to 1 in 1 million.</i> <sup>41</sup>
Occupational Safety and Health Administration/ OSHA	Workplace environment	OSHA has generally used 1 in 1,000 as a benchmark of significance. <sup>42</sup>

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- <sup>2</sup> International Agency for Research on Cancer (IARC). Monograph: Overall Evaluations of Carcinogenicity to Humans. 2004. Available at: http://www-cie.iarc.fr/monoeval/crthall.html. Accessed January 30, 2006.
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- <sup>4</sup> Wogan GN, Hecht SS, Felton JS et al. Environmental and chemical carcinogenesis. Semin Cancer Biol. 2004 Dec;14(6):473-86.
- <sup>5</sup> Office of Environmental Health Hazard Assessment. Chemicals Listed Effective February 3, 2006 as Known to the State of California to Cause Cancer. http://www.oehha.ca.gov/prop65/prop65\_list/Newlist.html
- <sup>6</sup> All California companies with ten or more employees must comply.
- <sup>7</sup> USEPA. What is the TSCA Chemical Substance Inventory? March 2006 http://www.epa.gov/oppt/newchems/pubs/invntory.htm
- <sup>8</sup> USEPA. Chemical Information Collection and Data Development (Testing). Chemical Testing Overview. http://www.epa.gov/opptintr/chemtest/view.htm
- <sup>9</sup> USEPA. Chemical Information Collection and Data Development (Testing). Chemical Testing Overview. http://www.epa.gov/opptintr/chemtest/view.htm
- <sup>10</sup> FDA/Center for Food Safety Applied Nutrition (CFSAN). Cosmetics Compliance Program. Domestic Cosmetics Program. Issued July 31, 2000. Data updated October 26, 2005. Chapter 29 - cosmetics and color technology. http://www.cfsan.fda.gov/~comm/cp29001.html
- <sup>11</sup> Lowell Center for Sustainable Production. The Promise and Limits of the United States Toxic Substances Control Act. October 10, 2003. http://www.chemicalspolicy.org/downloads/Chemicals\_Policy\_TSCA.doc
- <sup>12</sup> There are six basic tests (Screening Information Data Set, or SIDS) which have been internationally agreed for screening high production volume chemicals for toxicity: acute toxicity; chronic toxicity; developmental/reproductive toxicity; mutagenicity; ecotoxicity and environmental fate.
- <sup>13</sup> Lowell Center for Sustainable Production. The Promise and Limits of the United States Toxic Substances Control Act. October 10, 2003. http://www.chemicalspolicy.org/downloads/Chemicals\_Policy\_TSCA.doc
- <sup>14</sup> USEPA. Chemical Hazard Data Availability Study. Last updated March 3rd, 2006 http://www.epa.gov/opptintr/chemtest/hazchem.htm
- <sup>15</sup> USEPA. Chemical Hazard Data Availability Study. Last updated March 3rd, 2006 http://www.epa.gov/opptintr/chemtest/hazchem.htm
- <sup>16</sup> GAO. Chemical regulation: options exist to improve EPA's ability to assess health risk and manage its chemical review. June 2005. GAO-05-458.
- <sup>17</sup> "When consumers notify FDA of problems with cosmetics, the agency evaluates evidence on a case-by-case basis and determines if follow-up is needed." Harper, Allen. FDA consumer safety officer. Heading Off Hair-Care Disasters: Use Caution With Relaxers and Dyes. U.S. Food and Drug Administration. FDA Consumer. January-February 2001. http://www.cfsan.fda.gov/~dms/fdahdye.html.
- <sup>18</sup> FDA/CFSAN/Office of Cosmetics and Colors. Prohibited Ingredients and Related Safety Issues. March 30, 2000; Revised May 2005.
- <sup>19</sup> For complete details, see 21 CFR, Parts 250.250 and 700.11 through 700.23. See also FDA/CFSAN/Office of Cosmetics and Colors. Prohibited Ingredients and Related Safety Issues. March 30, 2000; Revised May 2005. http://www.cfsan.fda.gov/~dms/cos-210.html

- <sup>20</sup> According to its 1999 Annual Report, the Cosmetic Ingredient Review Expert Panel has found the following ingredients unsafe due to carcinogenicity potential : HC Blue No. 1(hair coloring ingredient) 4-Methoxy-m-Phenylenediamine, 4-Methoxy-m-Phenylenediamine HCl, and 4-Methoxy-m-Phenylenediamine Sulfate (hair dye ingredients), and Pyrocatechol (hair dyes and skin care preparations).
- <sup>21</sup> FDA. Hair Dye Dilemmas. FDA Consumer. April 1993. http://www.cfsan.fda.gov/~dms/cos-818.html.
- <sup>22</sup> 4-methoxy-m-phenylenediamine (4MMPD) or 4-methoxy-m-phenylenediamine sulfate (4MMPD sulfate)
- <sup>23</sup> FDA. Hair Dye Dilemmas. FDA Consumer. April 1993. http://www.cfsan.fda.gov/~dms/cos-818.html.
- <sup>24</sup> See Examples of consumer product responses to proposition 65. January 1997. http://www.environmentaldefense.org/documents/3389\_ConsumerProdResp.pdf
- <sup>25</sup> Marian Burros. Eating well. The New York Times. Wednesday, June 1997.
- <sup>26</sup> See Examples of consumer product responses to proposition 65. January 1997. http://www.environmentaldefense.org/documents/3389\_ConsumerProdResp.pdf
- <sup>27</sup> Squatriglia, Chuck. Grocers settle air suit more clean-fuel trucks, less idling. San Francisco Chronicle. April 28, 2000. http://www.environmentaldefense.org/documents/3399\_Grocers\_Air.pdf
- <sup>28</sup> See Examples of consumer product responses to proposition 65. January 1997. http://www.environmentaldefense.org/documents/3389 ConsumerProdResp.pdf
- <sup>29</sup> University of Massachusetts. The current system for regulating the production and use of chemicals in Europe. http://www.chemicalspolicy.org/ExistingEUregulation.shtml. Accessed February 9, 2006.
- <sup>30</sup> Lowell Center for Sustainable Production. University of Massachusetts REACH the new EU chemicals strategy: a new approach to chemicals management. http://www.chemicalspolicy.org/reach.shtml
- <sup>31</sup> Consolidated version of Cosmetics Directive76/768/EEC. http://ec.europa.eu/enterprise/cosmetics/html/consolidated\_dir.htm. Accessed February 9, 2006.
- <sup>32</sup> GAO. Toxic Chemicals: Long term coordinated strategy needed to measure exposure in humans. GAO/HEHS-00-80. May 2000.
- <sup>33</sup> GAO. Toxic Chemicals: Long term coordinated strategy needed to measure exposure in humans. GAO/HEHS-00-80. May 2000.
- <sup>34</sup> Joseph V. Rodricks et. al., Significant Risk Decisions in Federal Regulatory Agencies, 7 Regul. Tox. & Pharmacology 317 (1987). March Sadowitz & John D. Graham. A Survey of Residual Cancer Risks Permitted by Health, Safety and Environmental Policy. http://www.piercelaw.edu/Risk/Vol6/winter/Sadowitz.htm#top.
- <sup>35</sup> Natural Resources Defense Council v. EPA, 838 F.2d 1224 (D.C. Cir. 1987); Clean Air Act Amendments, Conference Report to Accompany S. 1630, 101st Cong., 2d Sess., Oct. 26, 1990. As referenced in March Sadowitz & John D. Graham. A Survey of Residual Cancer Risks Permitted by Health, Safety and Environmental Policy. http://www.piercelaw.edu/Risk/Vol6/winter/Sadowitz.htm#top
- <sup>36</sup> See March Sadowitz & John D. Graham. A Survey of Residual Cancer Risks Permitted by Health, Safety and Environmental Policy. http://www.piercelaw.edu/Risk/Vol6/winter/Sadowitz.htm#top
- <sup>37</sup> SDWA Sec. 1412g-1(b)(5), 42 U.S.C. Sec. 300g-1(b)(4).
- <sup>38</sup> FIFRA Sec. 2(bb), 7 U.S.C. Sec. 136(bb).
- <sup>39</sup> USEPA. Toxics Substance Control Act. See http://www.epa.gov/oecaagct/lsca.html#Summary%20of%20Toxics%20Substances%20Control%20Act%20(TSCA)
- <sup>40</sup> USEPA, Hazardous Waste Management System; Identification and Listing of Hazardous Waste; Toxicity Characteristics Revision, 55 F.R. 11,813 (1990). See March Sadowitz & John D. Graham. A Survey of Residual Cancer Risks Permitted by Health, Safety and Environmental Policy. http://www.piercelaw.edu/Risk/Vol6/winter/Sadowitz.htm#top
- <sup>41</sup> USEPA, National Oil and Hazardous Substances Pollution Contingency Plan, 55 F.R. 8,715 (1988).
- <sup>42</sup> OSHA, Occupational Exposure to Ethylene Oxide: Final Standard, 49 F.R. 46,936 (1984); Occupational Exposure to Inorganic Arsenic: Supplemental Statement of Reasons for the Final Rule, 48 F.R. 1,864 (1983). See March Sadowitz & John D. Graham. A Survey of Residual Cancer Risks Permitted by Health, Safety+ and Environmental Policy. http://www.piercelaw.edu/Risk/Vol6/winter/Sadowitz.htm#top

#### Cancer Incidence Rates by Site and State, U.S., 1995–1999\*

	AB	9m	Brant	Galan & Lung & Bactus Branchus		ng A Inchus	Nor-Hodgida Lymphona Pratain			Colomy Maridae		
State	feinie-	Formin :	Farmin	binie -	Fermin	biais-	Fermio	<b>Main</b>	Fermie	<b>Main</b>	<b>bisis</b>	Percelo-
Alaberas (1999) Alapias (1996-99) Arizpost	418.5 527.2	313.7 443.6	105.2 135.9	51.6 61.2	35.3 51.0	96.3 67.4	40.7 65.3	15.1 22.1	11.1 17.2	99.1 152.2	24.1 38.6	60 102
Arkenses (1995-99) Celiforniert	468.8 526.3	547.8 411.4	119.2 139.2	55.5 59.4	41.2 48.5	110.4 77.0	50.9 50.6	18.8 22.9	19.7 14.9	130.5 154.3	51.1 34.0	6.9 6.6
Coloradist	512.3	395.0	132.6	56.3	41.9	69.3	41.6	20.7	15.1	155.9	34.2	9.1
Connecticut †	592.1	457.1	145.6	71.5	52.8	90.0	57.1	25.3	17.7	165.6	45.4	12.8
Delowart Dist. of Columbia Rodzieł	597.4 705.5	4313 	140.0	70.9 71.7	55.† 57.3	112.0 111.9	66.2 51.6	20.7 23.4	15.9 12.1	172.5 256.6	39.4 24.4	95
Georgie	417.A	319.3	104.5	93	35.1	86.7	40.4	16.3	11,0	190.1	25.5	6.7
fine all t	476.5	564.2	130.0	67.D	44.5	72.1	97.5	19,4	12.5	124.1	21.6	6.0
idation t	50.6	391.5	127.7	54.3	41.4	70.9	-0.1	20.7	16.2	152.0	37A	82
	500.1	420.4	133.1	71.0	51.7	100.5	94.0	223	10.8	199.2	30.0	10.0
		201.4	126.2	00.1	40.5	00.0	221	124.8	10.0	120.3	30.6	8.3
Kaonak	20/3	4017	190.7	/345	33.4	-	44.4	22.5	10.0	1361		64
Kentudiert	525.7	425.6	122.2	70.7	59.2	141.3	<b>BR 5</b>	21.5	15.3	W1.5	95.2	9.9
Louisianti	597.9	391.7	120.2	71.1	47.5	119.4	54.0	20.7	14.3	170.4	53.4	6.5
Maina	572.8	434.0	126.9	68.4	50.9	103.5	82.9	Z2.8	15.4	147.2	-6.5	12.5
Maryland	608.9	442.4	141.7	69.5	51.9	101.7	59.7	21.7	14.8	180.2	37.1	11.0
Macanthumette	591.6	444.5	144.1	72.5	51.1	80.3	57.1	23.0	16.4	174.6	45.2	12.9
Michigant	534.4	427.2	129.8	66.0	47.2	100.3	56.5	22.0	16.4	1833	40.3	10.4
Minneolst	544.1	409.6	136.5	71	67	76.1	43.5	52	17.4	174.9	<b>a</b> 7.1	9.7
Manalan (1995-999) Manalan	201.0	422.0	121.4	71.9	44.7	115.0	50.2 M D	31.2	12/4	141.4	35.3	
Aleta salati	546.6	475.2	129.7	70.		39.2	43.9	23.1	16.3	161.5	54.8	1.1
Needo	454.0	217.5	106.2	60.5	44.4	100.0	72.2	16.6	11.5	99.2	58.9	9.7
New Kempehine	551.4	428.4	137.7	68.2	49.2	90.3	59.1	20.3	14.4	150.Z	45.5	12.5
New Jerseyt	6Z2.A	455.5	139.4	78.6	55.2	93.1	54	25.8	16.4	188.8	44.8	11.7
New Mexicon	473.2	363.5	120.9	<b>51</b> .7	36.0	63 <i>3</i>	37.2	17.8	12. <b>a</b>	147.0	27.0	42
Neve York 1	557.5	434.0	152.4	73.5	53.5		53.0	24.C	16.3	152.1	31.8	11.2
North Caroline†	527.4	369.7	122.0	57.5	42.0	106.8	47.6	16.7	15.2	146.5	912	82
Marin Calcul (1997-997)	237.7	304.0	141.0	00/4	-	13.0	36.5	22.0	16.9	1/3.3	38.9	43.9
Onio (1996-99)	505.0	415.9	1.02	0.00	-	102.2	26.1	22.0	13.9	1.94.1	39.6	10.1
Caraco (1995-98)	590.0	424.9	147.5	56.9	43.1	87.1	58.4	21.2	15.4	154.8	40.8	10.4
Pennomaniat	591.1	430.0	131.3	71.2	51.9	98.3	51.5	23.9	16.7	167.0	44.5	11.5
Rhode Islandt	640.9	470.5	158.6	76.1	57.3	101.7	63.6	26.4	19.3	172.2	51.8	19.5
South Caroline (1997-99) South Dalastati	580.9	385.7	124.4	68.3	44.9	107.3	47.4	18.5	19.1	177 <u>5</u>	39.9	7.8
Tennessee (1997)	461.1	354.0	114.4	58.9	41.5	108.0	49.7	17.4	14.1	106.6	24.6	7.1
Name (1995-489)	200.7	244.6	117.2	61.4 48.6	43.1	42.6	51.1	20.7	14.2	NR 9	5411	75
View		3444.0				-20				11420	31.0	· · · ·
variation and a second s	404.4	301.0	179.1	90.4	437	40.S	46.1	19.7	12.1	145.4	21.1	93
Washington	561.1	445.7	144.7	51.1	44.7	87.4	59.2	24.4	16.9	165.2	41.0	2.6
West Virginian	569.2	424.0	111.1	69.5	51.4	125.8	65.5	212	16.4	138.0	40.2	11.6
Wisconsin t	557.9	419.1	131.7	72.0	52.1	Ø.9	49.3	23.2	16.3	160.3	28.5	10.5
Wyoeningt	527.6	335.3	120.9	60.2	45.4	74.2	45.9	18.)	1418	168.0	38.1	10.1
United States	562.6	424.1	126.7	65.1	47.5	0.26	51.4	259	15.8	168.9	36.6	9.6

\*Ner 100,000, age-adjusied to the 2000 Mit standard population. Not all status admitted data for all years. † This status's registry has submitted the years of data and passed rights a status for each year's data including completeness of separating, non-duplication of recents, parsent unknown in critical data flatte, parsent of cross registered with information from database any, and informal consistency entropy data iteres, #This status's registry and not submit lackbaser data to the Marite American Americanian of Control Concerning/Intel (MAACCI) for 1925-1939.

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American Cancer Society, Servellence Remarch, 2008