

BREAST CANCER AND THE ENVIRONMENT RESEARCH PROGRAM (BCERP)

An Overview of Recent Research Findings Applicable to Health Professionals



www.info.bcerp.org

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Acronyms Used in This Monograph

BCERP – Breast Cancer and the Environment Research Program

BMI – Body Mass Index

BPA – Bisphenol A

CDC – Centers for Disease Control and Prevention

CHDS – Child Health and Development Studies

DBP – Dibutyl phthalate

DDT – Dichlorodiphenyltrichloroethane

DEP – Diethyl phthalate

DMBA – 7,12-Dimethylbenz(a)anthracene

DMP – Dimethyl phthalate

DNA – Deoxyribonucleic acid

DOHaD – Developmental origins of adult health and disease

ED – Endocrine disruptor

EDC – Endocrine-disrupting chemicals

EPA – Environmental Protection Agency

FDA – Food and Drug Administration

IR – Ionizing radiation (IR)

NCI – National Cancer Institute

NHLBI – National Heart, Lung and Blood Institute

NIEHS – National Institute of Environmental Health Sciences

NIH – National Institutes of Health

NLM – National Library of Medicine

PBDE – Polybrominated Diphenyl Ethers

PCB – Polychlorinated Biphenyls

PFOA – Perfluorooctanoic Acid

p,p'-DDE – p,p'-Dichlorodiphenyldichloroethane

U.S. – United States

Foreword

Public concern about breast cancer is widespread. While researchers have made great strides in understanding a woman's genetic susceptibility to breast cancer, what is not as well-known is the relationship that may exist between environmental factors, personal choices, and the risk of developing the disease. Researchers are beginning to recognize that the risk of developing breast cancer may begin early in a girl's life, during times of rapid breast development. Therefore, knowledge of the possible risk factors that may predispose a girl for breast cancer later in life is important for all health professionals, especially those who work with children. While women who have been diagnosed with breast cancer tend to think of recent causes and exposures, evidence is accumulating that the origins of breast cancer most likely began 30 to 40 years ago during puberty or *in utero*.

Breast cancer is a complex disease. It is becoming clearer that the risk for developing breast cancer could be the result of numerous environmental exposures across the lifespan, acting in concert with an individual's own genetics. Eliminating or reducing exposures may help to reduce risk, but given the complexity of breast cancer and the numerous possible causes for its development, eliminating one possible cause will not necessarily mean eliminating all risk of developing breast cancer.

The Breast Cancer and the Environment Research Program (BCERP) was created through the combined efforts of the National Institute of Environmental Health Sciences (NIEHS) and the National Cancer Institute (NCI) to further the study of how environmental factors during times of rapid breast development may influence breast cancer risk. In this document, the term "environment" refers to a range of factors, including the air we breathe, the food we eat, the water we drink, and things we touch and put on our skin. The focus of this monograph is primarily on the pre-pubertal and pubertal periods, emphasizing key findings from human studies whenever possible, and citing laboratory-based findings when there is little or no human data available.

This monograph will provide family physicians, pediatricians, internists, obstetricians, health educators, nurse practitioners, public health nurses and physicians, and others with an overview of recent research from the BCERP and other scientists on environmental exposures. These exposures have their greatest impact during periods of rapid breast development such as puberty, and they potentially affect breast cancer risk later in life. Through study of this material, NIEHS and NCI hope that health professionals will be able to better communicate with their patients, the parents of their patients, and other family members and caregivers about breast cancer risk and precautions that may ultimately decrease girls' risk of developing the disease later in life.

Goal and Learning Objectives

Goal: To raise awareness among health professionals of the role that early life environmental exposures may have on breast cancer risk later in life based on the research findings from the NIH-funded Breast Cancer and the Environment Research Program (BCERP) and other related studies.

Learning Objectives: After reading this monograph, the reader should be able to:

- Describe the most recent research on environmental exposures and breast cancer risk.
- Discuss the purpose of the BCERP's research.
- Discuss the concepts of "window of susceptibility" and the "precautionary principle" as it applies to breast cancer risk in general and how these concepts apply to children specifically.
- Educate patients, parents of patients, family members, and other caregivers about the steps they may take now to reduce girls' exposures to environmental factors that may affect breast cancer risk.
- Access additional BCERP educational materials designed for patients, parents of patients, family members, and other caregivers.

Section One:

Across the Lifespan: Recommendations for Clinical Practice

The information presented throughout this monograph is designed to bring health professionals up-to-date on the latest research in breast cancer, primarily looking at environmental exposures early in life, but which may apply across the lifespan. As research continues and new breakthroughs are made, these new findings may alter understanding of the specific risks for breast cancer. Readers are encouraged to periodically visit the BCERP, NIEHS, and NCI websites (see Appendix A: Additional Resources for Health Professionals, p. 27) to continue to learn about the latest research findings related to breast cancer risk factors and the role of environmental exposures. Ultimately NIEHS and NCI would like to help health professionals talk to their patients, parents of their patients and other family members, and caregivers about the steps they can take now to lessen their risks of developing breast cancer later in life.

There are several key messages that have arisen from the current BCERP research that may inform the health professional's discussion of breast cancer risk. This monograph provides full details and scientific background on each of these topics (see Section Two: About the Breast Cancer and the Environment Research Program, p. 9). This section provides a summary of the research and presents specific guidance on how to discuss these topics in clinical practice. The key messages are presented (Table 1) and explained in detail in the text.

The Age of Puberty

The age at which pubertal milestones are attained varies among the population and is influenced by activity level, nutritional status, and race (Blondell, Foster, & Dave, 1999; Herman-Giddens et al., 1997). Section Two reviews in greater depth the research related to pubertal development, environmental exposures and lifestyle, and risk of breast

Table 1: Key Messages

There are specific “windows of susceptibility” during pregnancy and preadolescence when the breast is undergoing its greatest development.

During these windows of susceptibility, exposure to harmful environmental factors may have a greater effect and may increase the risk of developing breast cancer later in life.

Several of the potentially harmful environmental exposures that may affect risk of breast cancer include phthalates and bisphenol A (BPA), both of which are commonly found in household and personal care products.

Additional, modifiable lifestyle factors that potentially increase risk of developing breast cancer are obesity, lack of physical activity, and diets high in animal fats.

Risks of developing breast cancer may be decreased by reducing exposure to phthalates and BPA and by modifying lifestyle factors that contribute to risk.

cancer later in life.

While the average age of pubertal development appears to be decreasing in the United States (Biro et al., 2010; Kaplowitz, 2008), when early puberty is suspected in a patient, health professionals must try to determine whether there is an organic cause that requires treatment. Idiopathic precocious puberty is diagnosed in the majority of girls with early maturation; however, treatment must be individualized based on the child's age and how rapidly she is developing (Golub et al., 2008).

A young girl who is suspected of entering puberty unusually early should be evaluated by her family physician or pediatrician, who may refer her to a pediatric endocrinologist for further evaluation. Evaluation of other causes of early puberty typically includes a medical history, physical exam, bone-age x-rays, serum hormone measurement, and possibly pelvic ultrasonography and brain MRI or CT (Blondell et al., 1999; Wilson, Mooradian, Alexandraki, & Samrai, 2011).

The Precautionary Principle

Although more research is needed to confirm the specific role that certain chemicals or lifestyle choices play in the development of breast cancer, health professionals and parents may choose to apply the “precautionary principle”—that is, until there is more certainty about the scientific findings resulting from the BCERP research, caution should be exercised and exposure to chemicals and other factors that may be harmful should be reduced. The precautionary principle states that “...when an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically” (Scientific and Environmental Health Network, 2012).

Once parents begin to understand how the environment may play a role in breast cancer risk, they may ask, “Well, what do I do now?” One piece of advice for parents, caregivers, and family members is to apply the precautionary principle—in the absence of definitive information, err on the side of caution. Another helpful message is to encourage positive actions moving forward and not to get caught up worrying over past action. Health professionals might comment that they did the best they could with the information and resources available at any given point but now that now that they know more, they can make a difference going forward.

Advise patients, parents, caregivers, and family members to learn all they can about the role of environmental exposures and breast cancer risk by visiting <http://www.info.bcerp.org>. This site contains information on both known and suspected environmental factors that increase the risk of developing breast cancer. All health professionals are encouraged to check the site periodically, as new findings will be added as scientists learn more about the environment and breast cancer risk.

Additional educational resources for health professionals may be found in Appendices A-D.

Reducing Environmental Exposures: Phthalates and Bisphenol A (BPA)

Phthalates (THA-lates) and bisphenol A (BPA) are chemicals that are added to everyday products such as certain types of plastic food containers and some personal care products such as fragrances, nail polish, deodorant, hair care products, and body lotion.

Phthalates and BPA are thought to be “endocrine disruptors” (ED), that is, chemicals that mimic estrogen and may interfere with the endocrine system, producing adverse effects in humans. The risk caused by EDs is thought to be greater in times of breast development, such as *in utero*, puberty and pregnancy. Taking steps to reduce exposure to EDs, such as those outlined below, may be most important before a girl enters puberty or when a mother is pregnant or breastfeeding.

For a summary of some of the relevant research findings related to phthalates and BPA, see Section Two.

For information on how the government regulates potentially toxic chemicals, see Appendix C: How Chemicals are Regulated in the United States.

How to Reduce Exposure to Phthalates

Phthalates are chemicals that are used to make certain plastics more flexible and are added to many personal care products (Table 2). When products containing phthalates are used, they are absorbed through the body’s tissues. While researchers have not made a direct connection between ingesting or absorbing phthalates and developing breast cancer, it is best to apply the precautionary principle:

- Use personal care products that are labeled “phthalate free” or do not have the word “phthalate” in the list of ingredients. “Phthalate” may not be listed alone: search for ingredients like “di-n-butyl phthalate,” “diethyl phthalate,” or “benzyl butyl phthalate.”
- Purchase fragrance-free products.

Phthalates may not always be listed separately on product labels. Instead, they may be part of what is listed simply as “fragrance” in the ingredients. If the product does not say “phthalate free” on the label of a personal care product, consider purchasing the fragrance-free version when available.

- Reduce use of plastic containers for food and beverage storage, and plastic or vinyl toys with the number 3 in the recycling triangle. They contain phthalates.



- Reduce the use of plastic food and beverage containers with the number 7 in the recycling triangle. They often contain BPA.
- Use glass food and beverage containers, including baby bottles.
- Use plastic baby bottles that say “BPA free” on the label.¹
- Microwave food in glass or ceramic containers. Heating food in containers made with BPA releases it into the food (Gore, 2010).
- Use waxed paper instead of plastic wrap when microwaving food.
- Add fresh or frozen fruits and vegetables to family meals, instead of using canned foods.
- Wash hands after handling cash register receipts or ask to receive receipts by e-mail, if possible. Recent studies have found BPA in some cash register receipts. The NIEHS and the National Toxicology Program have initiated studies to see how much BPA people who handle cash register receipts are exposed to, but do not yet have any results.

Table 2: Products that May Contain Phthalates

Fragrances
Nail polish
Deodorant
Shampoo
Body lotion
Hair care products
Cosmetics
Detergents
Soap
Plastic food containers
Plastic beverage containers
Toys with “3” in recycling triangle

How to Reduce Exposure to BPA

Bisphenol A (BPA) is a man-made chemical that is added to certain hard-plastic containers often used for food and beverages. It is also used to line the inside of many of the metal cans used for canned food. The primary route of exposure is through ingestion of the chemical, which leaches from plastic food and drink containers that are made with BPA and into the food and beverages they hold (National Toxicology Program, 2010). While researchers have not made a direct connection between ingesting or absorbing BPA and developing breast cancer, it is best to apply the precautionary principle:

Additional Information on Plastics in Food Storage

When considering the purchase of a food or beverage packaged in plastic, check the number within the recycling triangle before buying.

In addition to avoiding or reducing the use of those with 3 or 7 in the recycling triangles (the former contain phthalates, the latter BPA), also try to avoid using those with the number 6. Safer choices for plastic food and beverage containers include those with 1, 2, 4, or 5 in the recycling triangle (Mount Sinai School of Medicine, 2006).



¹ The U.S. Food and Drug Administration (FDA) is supporting the industry’s actions to stop producing BPA-containing baby bottles and infant feeding cups for the U.S. market. FDA understands that the major manufacturers of these products have stopped selling such BPA-containing bottles and cups in the United States. Glass and polypropylene bottles and plastic disposable “bag” liners have long been alternatives to polycarbonate nursing bottles.

Choosing a Healthy Lifestyle

Talk with young girls and their parents or caregivers about choices they can make that may lessen the risk of developing breast cancer later in life. This includes reducing environmental exposures, eating a healthy diet, maintaining a healthy body weight and level of body fat, and getting regular exercise as an overall health strategy.

The Role of Weight and Body Fat

Studies have shown that children who are overweight or obese in childhood most likely will grow up to be adults who are overweight or obese (Biro & Wien, 2010; Whitaker, Wright, Pepe, Seidel, & Dietz, 1997). Obesity is associated with an earlier onset of puberty (Biro, Khoury, & Morrison, 2006; Cheng et al., 2012; Rosenfield, Lipton, & Drum, 2009) that in turn is a recognized factor that increases the risk of breast cancer (Clavel-Chapelon & E3N-EPIC Group, 2002; Garland et al., 1998). Advice to all children about healthy physical activity levels, food choices, and weight management during well-child visits are all important aspects of obesity prevention (Barlow, 2007).

The Centers for Disease Control and Prevention (2012), and the American Academy of Pediatrics (2012), recommend using body mass index (BMI) to screen for overweight and obesity beginning at 2 years of age and plotting weight-for-height values at least once a year. BMI is a screening tool only. However, when a child's BMI is above the 85th percentile, further medical assessments should be made before initiating specific interventions (Barlow, 2007).

When assessing a child's weight and/or body fatness, health professionals must use their best judgment in determining whether a child is at risk for health related issues. The health professional then must determine whether any intervention is needed, and discuss the results with the child and parent(s) or caregivers in a way that minimizes embarrassment.

In the National Heart, Lung, and Blood Institute (NHLBI) Growth and Health Study, girls as young as 9 years of age, especially white girls, were found to be vulnerable to developing a

negative self-esteem associated with weight and body fat, possibly reflecting a culture idealizing thinness, which contrasted with greater acceptability of obesity among the black community (Kimm et al., 1997) and among Pacific Islanders (Cinelli & O'Dea, 2009).

Most studies of lifestyle—specifically nutrition and physical activity—and risk of breast cancer have involved adults, not children (Bianchini, Kaaks, & Vainio, 2002; Ehemann et al., 2012; Friedenreich & Cust, 2008). However, these studies have shown that, in general, maintaining a healthy weight, staying physically active throughout life, and consuming a healthy diet can reduce a person's lifetime risk of developing cancer. Parents and other caregivers play a critical role in preventing childhood obesity. Studies have shown that choices made by the parent(s), especially the mother, are very often adopted by the child (Jones, McVie, & Noble, 2008; Snoek, Sessink, & Engels, 2010). Parents and caregivers need to understand their own role in how a child views food, physical activity, and sedentary behavior, which ultimately affects weight, and should be encouraged to set a good example by making healthy food choices and being physically active (Lindsay, Sussner, Kim, & Gortmaker, 2006). Parents and caregivers should also be encouraged to spend time with children food shopping, cooking, walking, and playing.

Get Active as a Family

Even at a young age, children benefit from physical activity. It is recommended that children ages 6 to 17 engage in physical activity for periods of time that add up to about an hour each day (CDC, 2011). Having parents get actively involved in exercise with their children can provide many benefits. Recommendations for getting physically active as a family include (Patz, 2012; Shape Up America, 2012; vanKampen, 2012):

- Joining a parent/child dance or gymnastics class.
- Going for walks.
- Taking the dog for a walk. Many children love interacting with dogs, so it adds an element of excitement to what could otherwise be just a walk. This could also be an opportunity to teach children responsibility and animal care by allowing them to hold the leash.

- Planning a hike around the city or on nature trails. As a family, plan the route and the supplies that will be needed.
- Riding bikes through the city or on bike trails.
- Dancing! Parents can learn their daughter's latest moves and then teach them the ones they remember from their teenage years. Plan a disco night.
- Getting rid of the remote and get off the couch to change channels, standing during commercials and walking in place; or challenging the family to see who can do the most push-ups or leg lifts during commercials.

For tools and resources focused on weight, physical activity, and nutrition, see Appendix A: Additional Resources for Health Professionals.

Empowering Patients in Clinical Practice

All health professionals want to provide patients and their family members with the most up-to-date information and the most accurate guidance to promote health and prevent disease.

The key messages (Table 1) derived from our current understanding of the possible causes of breast cancer can guide your advice to parents and young patients, and provide information on how to minimize or prevent known and potentially harmful environmental exposures. This information provides you, and your practice, with data you need to keep you abreast of the latest research, and can also empower parents, caregivers, and young girls by raising their health literacy about the role of environmental exposures in breast cancer risk. Ultimately, it can empower your clients by giving them options for managing their health risks across the lifespan.

For more information about communicating with patients, see Appendix B: Communicating about Health and the Risk of Disease.

Section Two:

About the Breast Cancer and the Environment Research Program (BCERP)

Development of a Research Program on Early Environmental Exposures and Breast Cancer Risk

The Breast Cancer and the Environment Research Program (BCERP), a joint effort co-funded by the NIEHS and the NCI, began in 2003. The BCERP supports a multidisciplinary network of scientists, clinicians, and community partners to examine the effects of environmental exposures that may predispose a woman to breast cancer throughout her life. The network conducts animal and cell-based studies as well as population-based research to study puberty and other “windows of susceptibility” or specific time periods when the developing breast may be more vulnerable to environmental exposures.

Ongoing BCERP Research

The Program consists of a Puberty Study (BCERP, 2010b), an ongoing multi-site epidemiologic cohort study with more than 1,200 young girls that is looking at determinants of pubertal maturation, and the Windows of Susceptibility studies (BCERP, 2010c), which addresses environmental influences on breast cancer risk throughout the lifespan through laboratory and epidemiological studies.

Investigators in all studies are collaborating with breast cancer advocate(s) and/or members of the engaged community to build and promote partnerships among researchers, community members, and other stakeholders; ensuring bi-directional communication between researchers and the engaged community regarding environmental exposures of high and relevant importance; assisting with participant retention in epidemiologic studies; and developing and implementing tools and materials to communicate study findings to the public and policy makers. Some of the questions BCERP researchers are

trying to answer through their studies involving young girls are:

- How does lifestyle, dietary intake, physical activity, and environmental exposures, such as endocrine-disrupting chemicals, affect the age at which girls enter puberty and the age at which they have their first period?
- Do certain genetic factors cause some girls to mature earlier?
- Are there psychological or social factors that influence timing of puberty, such as family structure, income level, and neighborhood environment?
- Do certain genetic factors or a family history of breast cancer affect how environmental, lifestyle, or social factors influence how the girls' bodies mature?
- Is there a relationship between obesity, genetics, and the onset of puberty?
- What other physical characteristics (e.g., age when breasts develop, how fast girls mature, height and weight, body composition and fat distribution, and the amount of bone minerals in a girl's body as she enters puberty) contribute to a higher risk for developing breast cancer?
- What is the best way to inform families about the potential breast cancer risks of specific environmental exposures?

Questions BCERP researchers are trying to answer using cellular and animal models include:

- Do certain types of dietary fat, when combined with exposure to endocrine-disrupting chemicals, affect breast cancer risk later in life?
- How do hormones affect normal mammary gland development?
- Do high-fat diets increase the risk of tumors in mammary glands?
- Does obesity after pregnancy increase the risk of breast cancer?
- What is the effect of timing of phthalate/phenol exposure at different points in the life cycle on gene expression in normal mammary tissue?

The National Institutes of Health (NIH) is committed to supporting research aimed at answering these and other questions about the mechanisms involved in the development of breast cancer. An increasing amount of NIH-supported and other research focuses on the role the environment plays in heightening breast cancer risk. The following section provides additional, and more detailed, exposition of the research to date and what it may mean for clinical practice.

Selected Research Findings

Environmental Exposures and Breast Cancer Risk

Breast cancer is a complex disease that develops over decades. When women are diagnosed with the disease, they tend to think of recent causes and exposures; however, evidence is accumulating that the origins of breast cancer may begin earlier in life, during puberty or *in utero* (Birnbau & Fenton, 2003; Cohn, 2011; Fenton, Beck, Borde, & Rayner, 2012; Moral et al., 2011). It is now becoming clearer that disease risk is the result of numerous exposures across the lifespan acting in concert with an individual's own genetics (Barker, 2003; Diamanti-Kandarakis et al., 2009; Gluckman, Hanson, & Beedle, 2007). Eliminating or reducing exposures early in life may help to reduce breast cancer risk, but given the complexity of the disease and the numerous possible causes, eliminating one possible cause does not necessarily mean the risk of developing the disease will be eliminated. However, genetics and lifestyle choices by themselves cannot account for the upward trend in breast cancer incidence in the United States (Kortenkamp, 2006). According to the NIH (2007), only 5 to 10 percent of all breast cancers are hereditary, and less than half of breast cancer cases can be attributed to well-established risk factors. (Madigan, Ziegler, Benichou, Byrne, & Hoover, 1995)

For most of the 20th century, the dominant view regarding cancer development was based on a theory of cell proliferation caused by mutations in genes that control the cell cycle (Soto, Vandenberg, Maffini, & Sonnenschein, 2008). However, this theory fails to explain all the causes

of cancer. Since the early 1990s, the NIEHS and NCI have been funding studies that examine the environment as an integral part of the interplay between gene expression and breast cancer risk. This monograph emphasizes key findings from human studies whenever possible, and cites laboratory-based findings when there is little or no human data available. Animal studies can provide an understanding of how environmental exposure may affect breast development during puberty and have an adverse influence on breast cancer risk in adult life (Hiatt, Haslam, & Osuch, 2009)

For additional information on animals in cancer research, see Appendix D: Animal Research.

Pubertal Development and Breast Cancer Risk

Alterations in breast development are most likely to occur when the timing of certain environmental exposures overlaps with periods of rapid cellular growth (Fenton et al., 2012). Periods of rapid cellular growth are considered “windows of susceptibility” as rapidly dividing cells are more vulnerable to environmental exposures than non-dividing cells. These windows occur throughout life, but include perinatal, postnatal, pubertal, pregnancy, lactational, and menopausal stages of a life (Diamanti-Kandarakis et al., 2009; Fenton et al., 2012; Hiatt, 2011). To date, epidemiologic studies in adult women have not led to the discovery of environmental causes of breast cancer (Hiatt, 2011). As a result, researchers are focusing increasingly on the impact of early life exposures to environmental factors during different windows of susceptibility, such as the pre-pubertal and pubertal periods.

A child's body goes through many changes in puberty. Girls usually enter puberty between the ages of 8-13; however, there are wide individual differences for the age of onset. Studies of twins have confirmed that both genetics and environmental factors affect pubertal maturation, although the exact mechanisms require further study (Ge, Natsuaki, Neiderhiser, & Reiss, 2007; Mustanski, Viken, Kaprio, Pulkkinen, & Rose, 2004). Signs of maturation include breast development (thelarche), and the

appearance of pubic and axillary hair, as well as adult sweat gland odor (pubarche). Adrenarche, the pubertal maturation of the adrenal gland, is reflected by the physical features of pubarche (Wilson et al., 2011). Most girls enter puberty through the thelarche and adrenarche pathways concurrently. However, a number of girls may experience the two pathways in two distinctly separate phases, known as asynchronous maturation (Biro et al., 2003). Pubertal maturation also involves a growth spurt, ending with peak height, or close to adult height. Pubertal maturation ends with menstruation, or the onset of menarche.

Since the mid-1900s there have been multiple studies measuring the timing of puberty in girls. While the timing of puberty is different for every child, an expert panel (Euling et al., 2008) believed that, overall, girls' bodies have begun to show signs of entering puberty earlier now than in the recent past. Initial results from the ongoing BCERP research also show a trend towards earlier breast development and found 10% of white girls, 23% of African American girls, 15% of Hispanic girls, and 2% of Asian girls in the study started developing breasts by age 7 (Biro et al., 2010).

Studies have shown that obesity in childhood is a contributor to early pubertal maturation in girls (Adair & Gordon-Larsen, 2001; Biro et al., 2006; Kaplowitz, 2008). The mechanisms by which body fat may influence pubertal development are not yet understood, but may involve the action of adipokines, such as leptin; endocrine-disrupting chemicals acting on adipocytes or other hormonally responsive tissues (Biro, Greenspan, & Galvez, 2012); and insulin resistance, hyperinsulinemia, and the action of insulin on insulin-like growth factor (Solorzano & McCartney, 2010).

In addition to earlier breast development across all ethnic and racial populations, studies have shown that Black girls enter puberty earlier than do their white counterparts (Lee et al., 2007). Many researchers have attributed this early entry into puberty to increases in childhood BMI (Biro, Wolff, & Kushi, 2009). A retrospective study by Kaplowitz (2008) found that 22% of Black girls were obese before reaching adolescence (ages

6-11). He noted that this is the same group of girls who experience an earlier onset of puberty. Biro et al. (2006), citing other research (Grumbach, 2002; Kaplowitz, Slora, Wasserman, Pedlow, & Herman-Giddens, 2001; Shalitin & Phillip, 2003; Wong et al., 1998), postulated that, in addition to BMI, differences in leptin levels among races may explain earlier puberty in Black girls. Leptin is a metabolic signal for puberty to progress. Leptin levels are higher in Blacks, even after adjustment for fat mass and pubertal stage, which increased the speculation that greater body fat in pre-pubertal Black girls may increase the likelihood for the earlier onset of puberty.

Scientists are still trying to understand what factors are causing girls to enter puberty earlier, but these factors are thought to include changes in food intake and physical activity, higher levels of obesity, and exposure to endocrine-disrupting chemicals (EDCs) (Biro et al., 2012; Rosenfield et al., 2009). Other epidemiologic studies have shown that girls who enter puberty at earlier ages may have a greater risk of developing breast cancer later in life (Clavel-Chapelon & E3N-EPIC Group, 2002; Garland et al., 1998).

Growth rate is also being studied as a potential breast cancer risk factor (Cohn, 2011). A review by Forman et al. (2005) showed the most consistent associations between birth length and linear growth velocity in adolescence and breast cancer risk. A later review conducted by Ruder et al. (2008) concluded that the available evidence suggests a positive relationship between birth length, birth weight, and adolescent height, and breast cancer risk. According to Cohn (2011), this is further evidence that links development during childhood and adolescence to breast cancer risk.

Endocrine Disrupting Chemicals

There are many hormonally active chemicals present in the environment that may alter the course of puberty in young girls and affect their risk of developing breast cancer in the future. Some of these chemicals (Table 3), which can be found in household and personal care products people use every day, are phenols, phthalates, and phytoestrogens (discussed in the section

“Diet” on p.15). The current evidence is strong that the cumulative effect of low-dose exposure to EDCs, especially during particularly vulnerable developmental windows, can lead to long-term consequences in later health (Gore, 2010). Although EDC exposures may occur early in life and continue for many years, the results may not manifest themselves for 50 or 60 years.

The BCERP is studying the impact of several of the chemicals listed Table 3 on the timing of pubertal development in girls enrolled in an epidemiologic study. Initial findings from an assessment of urinary biomarkers of nine phthalates, seven phenols, and three phytoestrogens detected the biomarkers in almost all urine samples tested (Wolff et al., 2010) at concentrations similar to those reported previously by the National Health and Nutrition Examination Survey (NHANES) for children age 6 to 11 years. Wolff et al. (2010) observed weak associations between increasing low molecular weight phthalates levels and breast and pubic hair development. However, because exposures are widespread in the population, even small impacts on pubertal timing could still have a significant public health impact.

Table 3: Chemicals with ED Properties

(Kortenkamp, 2006; NIEHS, 2012)

Polychlorinated biphenyls (PCBs)
 Polybrominated biphenyls (PBBs)
 Dioxins
 Plastics [bisphenol A (BPA)]
 Plasticizers (phthalates)
 Pesticides
 Methoxychlor
 Chlorpyrifos
 Dichlorodiphenyltrichloroethane (DDT)
 Fungicides (vinclozolin)
 Pharmaceutical agents [diethylstilbestrol (DES)]
 Dioxin-like compounds

Phenols

Phenols are a class of weakly acidic water-soluble chemical compounds used as a slimicide (slime killing pesticide) and a disinfectant, as well as a reagent in research laboratories. They may also be found in medical products. Phenol ranks

in the top 50 chemical volumes produced in the United States. They are readily absorbed following inhalation, ingestion, or skin contact. Some phenols are weak endocrine disruptors. Research studies investigating the association of phenols with breast cancer risk, sources of exposures, effects on puberty, and general effects in the body are ongoing (BCERP, 2010a).

Bisphenol A (BPA)

One widely used phenol is bisphenol A (BPA). Existing evidence suggests that the effects resulting from exposures to BPA during specific windows of susceptibility may not be observed until long after the exposure has occurred.

BPA, a clear plastic widely used in consumer products and in epoxy resins, has been known to have estrogenic effects since 1936. In the 1990s it was discovered that BPA could be released from polycarbonate plastics in concentrations high enough to change gene expression patterns (Gore, 2010). Incomplete manufacturing processes (polymerization) and/or depolymerization resulting from heating the plastic allows BPA to be released from plastic into foods and beverages (Gore, 2010; vomSaal et al., 2007). Other sources of BPA exposure come from materials used in dentistry, from sewage treatment plant wastewater, and releases from landfills (vomSaal et al., 2007). The primary concern is for individuals who are exposed to these sources through their occupation. BCERP researchers have been investigating the impact of BPA on breast development and breast cancer using animal models.

Lamartiniere and colleagues (Betancourt et al. 2012; Jenkins, Wang, Eltoum, Desmond & Lamartiniere, 2011; Moral et al., 2011; Betancourt, Eltoum, Desmond, Russo & Lamartiniere 2010; Jenkins et al., 2009; Moral et al., 2008; Jenkins, Rowell, Wang & Lamartiniere 2007; and Moral et al., 2007) conducted a series of studies using a rodent model of cancer initiation to investigate two different windows of susceptibility: *in utero* (dosing the dams directly while pregnant) and neonatal/pre-pubertal (newborns receiving BPA through the dam's milk) (Lamartiniere, Jenkins, Betancourt, Wang, & Russo, 2011). The investigators found

reproducible gene expression patterns at specific days after birth that correlated with changes in cell proliferation and reduced apoptosis in mammary glands.

A number of conclusions resulted from this body of work: BPA exposure during specific windows of susceptibility (*in utero* and neonatal/pre-pubertal) increases mammary cancer susceptibility in the rodent DMBA cancer initiation model, increasing the multiplicity of mammary tumors and decreasing the latency period (Betancourt et al., 2010; Betancourt et al., 2012; Jenkins et al., 2009; Lamartiniere et al., 2011). BPA exposures during these same windows of susceptibility alter protein expression patterns for key proteins involved with the regulation of cell proliferation (Betancourt et al., 2010; Lamartiniere et al., 2011); and BPA exposure shifts the timing of the windows of susceptibility (Betancourt et al., 2010), possibly making the animal vulnerable to other environmental factors.

Triclosan

Another commonly used phenol is triclosan. Triclosan is a polychloro phenoxy phenol used as a synthetic broad-spectrum antibacterial. The EPA classifies it as a pesticide. Triclosan is an active ingredient contained in a variety of products where it acts to slow or stop the growth of bacteria, fungi, and mildew. Among the products it is used in are personal care products such as antibacterial soaps and body washes, toothpastes, and some cosmetics. It is not known to be hazardous to humans, but new studies in animals have been published that show triclosan alters hormone regulation. As a result of these studies, the FDA is engaged in an ongoing scientific and regulatory review of this ingredient. There is not sufficient safety evidence to recommend changing consumer use of products that contain triclosan at this time (FDA, 2012).

Phthalates

Phthalates are a group of chemicals, commonly called plasticizers, which are used to make plastics more flexible and harder to break. Phthalates are used in hundreds of products, including toys, detergents, food packaging,

pharmaceuticals, blood bags and tubing, and personal care products, such as nail polish, hair sprays, soaps, and shampoos. The principal phthalates used in cosmetic products are dibutyl phthalate (DBP), dimethyl phthalate (DMP), and diethyl phthalate (DEP). They are mostly used in concentrations of less than 10% as plasticizers in products such as nail polishes (to reduce cracking) and hair sprays (to help eliminate stiffness) and as solvents and perfume fixatives in various other products (FDA, 2011).

Other Suspected Influencers of Breast Development and Breast Cancer Risk

DDT and Its Metabolites

Dichlorodiphenyltrichloroethane (DDT) is a potent insecticide that was extensively used for agricultural and public health purposes from the 1940s to the 1970s. In the 1960s Rachel Carson, in her book *Silent Spring* (1962), raised the first concerns about DDT and the long lasting effects it may have on animals and human. Her insights started an environmental movement focused on the toxic effects of DDT, its environmental persistence, and its concentration in the food supply, eventually leading to the ban of all general uses of DDT in 1972 (Eskenazi et al., 2009).

A 2004 meta-analysis of the literature on p,p'-dichlorodiphenyldichloroethane (p,p'-DDE), the main metabolite of DDT, did not support the hypothesis that exposure to DDT was a risk factor for breast cancer (López-Cervantes, Torres-Sánchez, Tobías, & López-Carrillo, 2004). However, most of the studies examined in the analysis were unable to measure the exposure of young women during the period when DDT was most heavily used, and so the observed levels of main components of DDT were very low (Cohn, Wolff, Cirillo, & Sholtz, 2007).

Cohn and colleagues (2007) overcame this barrier in their study to test the hypothesis that DDT exposure in childhood and adolescence could increase breast cancer susceptibility by using archived serum samples from women enrolled in the Child Health and Development

Studies (CHDS), one of several studies that has been initiated to examine the health of children. The results showed that women who were younger than 14 years at the time DDT was introduced into public use (1945) with the highest blood concentrations of DDT were five times more likely to develop breast cancer than women who were not exposed before age 14 (born in 1931 or earlier and over 27 years at peak DDT use). Cohn et al. concluded that women exposed at a young age to DDT might be most strongly affected by exposure. Women who were born in the 1950s and 1960s who were heavily exposed to DDT when young have not yet reached the age of greatest breast cancer risk.

Perfluorooctanoic Acid (PFOA)

Because of its widespread presence in the environment, in wildlife and humans, along with the fact that it persists and accumulates, PFOA has raised significant health concerns (Yang, Tan, Harkema, & Haslam, 2009). PFOA is a synthetic chemical that does not occur naturally in the environment. PFOA is used to make non-stick surfaces on cookware and waterproof, breathable membranes for clothing. They are used in aerospace, automotive, building/construction, chemical processing, electronics, semiconductors, and textile industries (EPA, 2012). PFOA can also be produced by the breakdown of some fluorinated telomers.² The EPA specifically notes that consumer products made with fluoropolymers and fluorinated telomers, including Teflon® and other trademark products, are not PFOA, though they may contain trace amounts of it and other related perfluorinated chemicals as impurities. However, available information does not indicate that the routine use of consumer products poses a concern (EPA, 2012).

PFOA has been found at very low levels both in the environment and in the blood of the general U.S. population and remains in people for a very long time. In addition, it has been found to cause developmental and other adverse effects in laboratory animals (EPA, 2012). One study found

that PFOA stimulates mammary gland development in a certain strain of mice by promoting steroid hormone production in the ovaries and increasing the levels of a number of growth factors in mammary glands (Zhao, Tan, Haslam, & Yang, 2010). Another study found PFOA to be detrimental to lactational function and postnatal mammary gland development after gestational exposure in mice (Yang et al., 2009). While researchers have become more knowledgeable of the effect of PFOA in strains of mice and rats, there are significant differences between the half-life of PFOA in rats (days) and human (years). Even low levels of exposure to PFOA can lead to elevated body burden over time (White, Fenton, Yang, & Haslam, 2011). Additional studies are needed that look at the dose-response relationships, routes and timing of exposure, and the underlying mechanisms of PFOA-induced effects in animals in the context of different genetic backgrounds, especially during mammary gland development periods (White et al., 2011). It is thought that further studies of this nature will provide information that will be relevant to the identification of potential hazards to human health that have previously gone unrecognized (White et al., 2011).

Polybrominated Diphenyl Ethers

Polybrominated diphenyl ethers (PBDEs), flame retardant chemicals, are ubiquitous in the environment (Hites, 2004). PBDEs can be found in various forms in polyurethane foams used in mattresses, upholstered furniture, and carpet padding; computer, television, and appliance casings; in some polymers used in adhesives and wire insulation; and in some non-clothing textiles (CDC, 2009). People may be exposed to PBDEs through consumption of food, including breast milk, or breathing air contaminated with PBDEs (Agency for Toxic Substance and Disease Registry, 2011).

PBDE has the same chemical properties and structure as PCBs (polychlorinated biphenyls), which were banned in the United States in the 1970s (Chevrier et al., 2010). While production of some of the PBDEs has been phased out in the

² Surface treatment chemicals used in many personal care, cleaning products, repellant coatings and as high performance surfactants in products that must flow evenly, such as paints, coatings, and cleaning products, fire-fighting foams for use on liquid fuel fires.

United States, concentrations are expected to remain in the environment for a long time due to their persistence and resistance to degradation (Schechter et al., 2010). Unlike PCBs, which have been decreasing in the environment, studies have shown that there has been a marked increase in PBDE concentrations in humans over the past decades (Doucet et al., 2008; Schechter et al., 2005). There is evidence indicating that these chemicals demonstrate endocrine disrupting activities in animal models.

BCERP researchers sought to investigate PBDE exposures in children (ages 6 to 9 years) using the cohorts enrolled in the puberty studies. Children are naturally exposed to PBDE mostly through their diet, as well as through exposure to household dust (Lorber, 2008). Windham et al. (2010) showed that levels of PBDEs varied with the girls' geographical location, with the California cohort having higher levels than others, possibly due to California's stringent furniture flammability standards. In addition, Black girls had the highest mean levels of PBDE, when compared to White and Hispanic girls. Levels of PBDEs were similar in Asian and White girls. Researchers theorized that the levels of chemicals found in the cohort corresponded to the level of exposure and may reflect exposure pathways.

Diet

Food and dietary choices play a role in the risk for breast cancer later in life (Ruder et al., 2008). In a systematic review and meta-analysis of dietary patterns and breast cancer risk, there was evidence that diets containing high amounts of fruits, vegetables, poultry, fish, low-fat dairy, and whole grains were associated with a lower risk of breast cancer (Brennan, Cantwell, Cardwell, Velentzis, & Woodside, 2010).

Dietary Fat

The impact of dietary fat on breast cancer risk in women is not clear. An analysis of dietary fat intake and breast cancer risk was assessed among 90,655 premenopausal women participating in the prospective Nurses' Health Study II. Cho et al. (2003) found an association between premenopausal consumption of animal

fat, largely from red meat and high-fat dairy foods, and breast cancer risk. Grouping the women's intake of the percent of animal fat they consumed and comparing that to a reference group who obtained less than 14% of their energy from animal fat, the researchers found that breast cancer risk was 1.28 to 1.54 times higher among those with higher percentage of energy from fat than that of the reference group, though a clear dose-response was not observed. Because of the observational nature of their study, Cho et al. could not determine whether the increased risk observed was due to animal fat itself, or other components in the foods, such as heterocyclic amines in cooked red meat or fat soluble hormones or growth factors in high fat dairy foods. Another pooled analysis of 8 prospective studies found a weak positive association between saturated fat and breast cancer risk (Smith-Warner et al., 2001). Researchers have found little to no relationship between reductions in total dietary fat intake and reductions in breast cancer risk (Kushi et al., 2012).

In contrast, evidence from a rat study indicates that exposure to high levels of various dietary fats *in utero* and during puberty enriches mammary gland expression of cell cycle genes and increased mammary gland proliferation during puberty (Medvedovic et al., 2009). This proliferative effect, however, appeared to be strain-dependent in a study involving mouse models (Olson et al., 2010). In a subsequent study, animals on a high-fat diet had reduced tumor latency and increased incidence of mammary gland tumors (Costa et al., 2011). Rats that were exposed to a high-fat diet at different periods of the life (*in utero*, post-natal, at puberty, early adulthood, late adulthood, or throughout their life, beginning *in utero*) showed significantly higher incidences of mammary tumors in the *in utero* (60%), adulthood (61%) and whole life (91%) exposure groups compared to the unexposed group (32%). The puberty and adult groups both demonstrated a 44% mammary tumor incidence.

Phytoestrogens

Phytoestrogens are estrogen-like substances found in some plants and plant products. They

bind to estrogen receptors and have weak estrogenic and weak anti-estrogenic effects. There are three major classes of phytoestrogens that have estrogen-like actions in the human body. They are lignans, isoflavones, and coumestans (BCERP, 2010a).

Isoflavones and lignans are present in foods such as soy, lentils, beans, chickpeas, whole-grain cereals, legumes and various vegetables and fruits, particularly berries (Bondesson & Gustafsson, 2010). Isoflavones and lignans show weak estrogen receptor (ER) binding activity and, depending on the context, they can act to either mimic or counteract the effects of endogenous estrogen, 17 β -estradiol (Bondesson & Gustafsson, 2010).

Because isoflavones can have both estrogenic and anti-estrogenic effects, it has been suggested that they can modulate breast cancer risk (Bondesson & Gustafsson, 2010). However the effects of isoflavones on early breast cancer markers differ between pre- and post-menopausal women. Exposure to isoflavones in mice and rats models have either protected against or promoted breast cancer development and growth and results vary between different studies (Bondesson & Gustafsson, 2010). Looking at the conflicting results between human and animal studies and the effect of soy, researchers postulated that the reason may be due to the differences in how isoflavone was metabolized (Setchell et al., 2011). They found markedly higher concentrations of biologically active genistein (an isoflavone) in certain strains of mice and questioned the use of these rodents for gaining insight into the effects of isoflavones on human breast tissue.

Most epidemiological studies show a small inverse association between soy intake and breast cancer risk in both Western and Asian women (Trock, Hilakivi-Clarke, & Clarke, 2006). In two studies, high soy intake during childhood has been found to have a particularly strong association with reduced breast cancer risk later in life (Korde et al., 2009; Lee et al., 2009). Caution is urged in the interpretation of epidemiological studies as they may be affected by dose and type of soy product, and the timing of exposure during a woman's life (Trock,

Hilakivi-Clarke, & Clarke, 2006). Epidemiologic findings may also represent a "healthy user effect"—in which the participants in the studies are more likely to have healthy lifestyles than the general population—and not be reflective of direct effect of soy intake (Bondesson & Gustafsson, 2010).

More research, both in animals and humans, is necessary before any definitive recommendations can be made regarding soy and its ability to reduce breast cancer risk.

Neighborhood Environment

BCERP scientists are examining the relationship between the neighborhood in which girls live, obesity risk, and early onset of puberty. Recent research has highlighted the need to consider the role of the "built environment" as one of several key social determinants of health (Galvez, Pearl, & Yen, 2010). The "built environment" encompasses housing, roads, walkways, density, transportation networks, shops, parks, and public spaces.

Galvez et al. (2010) reviewed the literature on links between childhood obesity and neighborhood factors using the Ecological Systems Theory of the "built environment" as their framework. In several studies focusing on access to food sources (Galvez et al., 2009; Hackett et al., 2008; Oreskovic, Kuhlthau, Romm, & Perrin, 2009), the researchers found that children with less desirable eating habits lived in areas with little open space and small streets bounded by busy roads and many food outlets selling snack food, sweets and take-away meals, whereas children with more desirable eating habits lived in areas with open green space, wider streets and fewer food outlets. These studies also found that children living on the same block as a convenience store were at increased risk for childhood obesity.

In other studies, researchers (Babey, Hastert, Yu, & Brown, 2008; Galvez et al., 2010; Veugelers, Sithole, Zhang, & Muhajarine, 2008) found that children who were able to spend more time outdoors had a greater level of physical activity; having safe access to a park was associated with

regular physical activity in urban areas, but not rural areas; and those children with the best access to parks and recreational facilities engaged in more sports and spent less time watching television or playing on the computer.

In their study of the impact of neighborhood environment on pubertal maturation, Deardorff et al. (2012) found that African American girls who lived in neighborhoods with availability to parks, walking or hiking trails, playing fields, and basketball or tennis courts had lower onset of breast and pubic hair development by ages 10 to 12 years. The effects were not seen in girls from other ethnic groups, even when strong predictors of puberty such as income and BMI were considered. Understanding of how neighborhood factors, particularly opportunities for physical activity, influence girls' pubertal timing may inform successful intervention strategies and policy development to promote better health over the life course for women.

Physical Activity

Research has shown that regular physical activity not only helps to control weight, it reduces the risk for chronic diseases, promotes psychological well-being, and can affect the risk of cancer, especially of the colon and breast (National Cancer Institute, 2009). Being active is a critical component of energy balance, the combination of weight, diet and physical activity on health. Despite these benefits, it is known that more than half of Americans adults and 65% of adolescents do not engage in enough physical activity (CDC, 2008).

Moderate to vigorous physical activity appears to decrease breast cancer risk by about 25%, and the strongest associations were for those activities that were sustained over a lifetime and performed regularly (Friedenreich, 2011; Friedenreich & Cust, 2008; Kushi et al., 2012; Norat, Chan, Lau, & Vieira, 2008). Physical activity may reduce breast cancer risk through multiple interrelated biologic pathways that may involve weight gain, sex hormones, insulin resistance, and chronic inflammation (Friedenreich, 2011; Lynch et al., 2011).

Psychosocial Stressors

It has been documented that girls who grow up in homes that do not have a father are twice as likely to experience menarche prior to age 12 (Bogaert, 2005; Quinlan, 2003). Through animal models, scientists have learned how physiological mechanisms of the parent-offspring relationship affect maturation of the hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary-adrenal axes (HPA). In rodents, alterations in the parent-offspring interaction caused by changes in the physical and social environment induced changes in reproductive strategies, including pubertal timing (Cameron et al., 2008). Other studies confirm that ecological stress causes low-quality parental care, which predicts a faster reproductive strategy in offspring (Deardorff et al., 2011).

There are several hypotheses regarding early pubertal development that focus on absent fathers, however, research to date has not confirmed these hypotheses conclusively. What is known is that physiological factors, such as BMI, neither accounts for all of the variance in pubertal onset nor operates as a mechanism in the causal path between father absence and puberty (Deardorff et al., 2011). Taking into account BMI, ethnicity and income, as well as the effect of an absent father on breast and pubic hair development, researchers studying a cohort of girls in the National Heart, Lung, and Blood Institute Growth and Health Study found that higher-income girls are at greater risk for earlier maturation; and among African Americans, girls from higher-income families are at greater risk for early menarche compared to their lower-income counterparts (Braithwaite et al., 2009).

Deardorff et al. (2011) postulated that African American girls from higher-income families may be exposed to discrimination or negative self-perception of social status, which would influence the biophysiological stress responses that initiate pubic hair development.

Future research may elucidate the precise mechanisms by which psychosocial stressors, such as absent fathers, affect breast cancer risks and identify other specific psychosocial stressors that affect the risk of disease. Since there is

evidence that even a small change in the timing of puberty is associated with a relatively large change in the fertile menstrual cycle, which increases breast cancer risk, this additional information will be important for determining how much of a role psychosocial stressors play in early maturation and early menarche.

Radiation

The mammary gland is very sensitive to ionizing radiation (IR) associated carcinogenesis, especially after exposures at young ages (Ronckers, Erdmann, & Land, 2005). Current epidemiological evidence shows that while women more than 50 years old have no measurable increase in breast cancer risk, women who were exposed to IR at ages younger than 20 have an increased risk of radiation-associated breast cancer (Preston et al., 2002). Though radiation therapy for cancer is effective, it comes at the price of an increased cancer risk as a life-long burden, especially for those diagnosed during childhood.

An important determinant of carcinogenesis is the tissue microenvironment (Nguyen, Oketch-Rabah, et al., 2011). Evidence suggests that cell function and dysfunction during cancer development are highly intertwined with the microenvironment (Barcellos-Hoff & Medina, 2005; Gonda, Tu, & Wang, 2009). In addition to causing DNA damage, which results in genomic changes, IR can also alter multicellular interactions and phenotypes that influence the carcinogenesis process (Barcellos-Hoff & Nguyen, 2009; Barcellos-Hoff, Park, & Wright, 2005). Research has shown that radiation has very early and persistent effects on the microenvironment of the tissue that are critical to its carcinogenic potential (Nguyen, Oketch-Rabah, et al., 2011). Ongoing research suggests that IR leads to rapid changes in extracellular signaling, which could affect cancer development by deregulating mammary stem cells, cells that are capable of both self-renewal and differentiating into diverse, specialized cell types (Barcellos-Hoff et al., 2005; Nguyen, Bochaca, & Barcellos-Hoff, 2011). More stem cells could lead to a greater risk of developing breast cancer since stem cells are the longest lived cells (Nguyen, Bochaca, et al., 2011).

Using primarily culture from human mammary epithelial cells (HMEC), Mukhopadhyay et al. (2010) set out to determine if IR could promote the outgrowth of cells bearing a pre-malignancy-associated epigenetic change. Such epigenetic changes include modifications to the genome that may influence disease outcome by turning on or off key regulatory gene expression. Through radiation exposure, the researchers were able to determine how radiation can promote the outgrowth of pre-malignant cells by accelerating the senescence of normal breast cells. In addition, Heissig et al. (2005) found that low-dose irradiation fosters vascular regeneration which could support the growth of tumors.

Conclusion

As more information comes to light regarding the developmental origins of adult health and disease (DOHaD), scientists are becoming increasingly more aware that the basis for breast cancer in adults may have its roots as far back as the womb. Breast cancer before the age of 30 is rare, but after that the incidence steeply rises until about 50 years, with incidence increasing with age, but more slowly. It is theorized that the strong age dependence in cancer in adult women is most likely related to the accumulation of genetic damage which occurs over the lifespan (Ronckers et al., 2005).

Breast cancer is a complex disease and is of great public concern as it is one of the most common forms of cancer among women. Approaches for reducing the risk of developing breast cancer include reducing exposure to environmental factors or changing behaviors that increase breast cancer risk. Scientists are beginning to recognize that breast cancer risk may begin early in life, when physiological changes occur that may predispose a girl to breast cancer later in life. Epidemiologic studies have shown that girls who enter puberty at earlier ages may have a greater risk of developing breast cancer later in life, but a lot remains to be understood about the biological mechanisms that will help scientists better understand this association between pubertal development and breast cancer risk later in life.

As a health professional, it is important to provide patients and family members with the most up-to-date and accurate guidance as possible to promote health and prevent disease. Even though the understanding of the causes of cancer is imperfect, helping patients make informed decisions with the information known at the present time empowers them to take an active role in managing their health risks across their lifespan.

Health professionals, parents, and probably children too, understand that maintaining a healthy weight, eating healthy foods, and being physically active provide many health benefits. What may be less known is the connection these actions have in relation to reducing breast cancer risk later in life. It is the hope of those involved in BCERP that this monograph helps to reinforce the importance of these lifelong behaviors. Additionally, the monograph should provide health professionals with an increased awareness of the risks from environmental exposures that may affect their patients. More research, both in animals and humans, is necessary before any definitive recommendations can be made.

Through study of this material, NIEHS and NCI hope that health professionals will be able to communicate better with patients, their parents and other caregivers about breast cancer risk and precautions that may ultimately decrease girls' risk of developing the disease later in life. Until there is more certainty about the relationship between environmental exposures, in the broadest sense, the best course of action in trying to minimize future disease risk is for individuals to reduce exposures to chemicals and other factors whenever possible that may have potentially negative health implications later in life.

To download patient education materials, visit www.info.bcerp.org.

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Appendix A.

Additional Resources for Health Professionals

See the resources below for additional information contained in this monograph.

BREAST CANCER AND THE ENVIRONMENT RESEARCH PROGRAM (BCERP)	
General information on BCERP for parents and caregivers, health professionals, and outreach organizations	www.info.bcerp.org
BCERP scientific publications	www.bcerp.org/pubs.htm
BCERP FUNDERS	
National Institute of Environmental Health Sciences (NIEHS)	www.niehs.nih.gov
National Cancer Institute (NCI)	www.cancer.gov
BREAST CANCER	
Centers for Disease Control and Prevention (CDC) Breast cancer home page	www.cdc.gov/cancer/breast
NCI	
Breast cancer home page	www.cancer.gov/cancertopics/types/breast
Breast cancer prevention (patient version)	www.cancer.gov/cancertopics/pdq/prevention/breast/Patient
Breast cancer prevention (health professional version)	www.cancer.gov/cancertopics/pdq/prevention/breast/HealthProfessional
ENDOCRINE DISRUPTORS	
NIEHS	
Fact sheet: Endocrine Disruptors	www.niehs.nih.gov/health/materials/endocrine_disruptors_508.pdf
Overview of endocrine disruptors	www.niehs.nih.gov/health/topics/agents/endocrine/index.cfm
U.S. Environmental Protection Agency: "What are Endocrine Disruptors?"	www.epa.gov/endo/pubs/edspoverview/whatare.htm
ENDOCRINE DISRUPTING CHEMICALS—BPA & PHTHALATES	
NIEHS	
Bisphenol A (BPA)	www.niehs.nih.gov/health/topics/agents/sya-bpa
National Toxicology Program: Fact Sheet on BPA	www.niehs.nih.gov/health/assets/docs_a_e/bisphenol_a_bpa_508.pdf
Food and Drug Administration (FDA)	
Bisphenol A (BPA): Use in Food Contact Application	www.fda.gov/NewsEvents/PublicHealthFocus/ucm064437.htm
Consumer Updates: FDA Continues to Study BPA	www.fda.gov/ForConsumers/ConsumerUpdates/ucm297954.htm

ENDOCRINE DISRUPTING CHEMICALS -BPA & PHTHALATES (cont.)	
U.S. Department of Health and Human Services (HHS): Bisphenol A (BPA) Information for Parents	www.hhs.gov/safety/bpa
BCERP: Phthalates Fact Sheet	www.bcerp.org/COTCpubs/BCERC.FactSheet_Phthalates.pdf
Mount Sinai Community Health Bulletin: Phthalates	www.bcerp.org/COTCpubs/GUH.Phthalates.pdf
CDC: Fact Sheet on Phthalates	www.cdc.gov/biomonitoring/Phthalates_FactSheet.html
FDA: Phthalates and Cosmetic Products	www.fda.gov/cosmetics/productandingredientsafety/electedcosmeticingredients/ucm128250.htm
Zero Breast Cancer: Phthalates, The Everywhere Chemical	www.niehs.nih.gov/research/supported/assets/docs/j_g/phthalates_the_everywhere_chemical_handout_.pdf
PATIENT COMMUNICATION	
NIH: Clear Communication	www.nih.gov/clearcommunication
HHS: Think Cultural Health	www.thinkculturalhealth.hhs.gov
Agency for Healthcare Research and Quality: National Guideline Clearinghouse - Communicating with children and families: from everyday interactions to skill in conveying distressing information	www.guideline.gov/content.aspx?id=13404&search=patient+communication
American Academy of Pediatrics: Motivational Interviewing	bit.ly/VLwUTR
UCLA Center for Human Nutrition: Sample Scripts for Stages of Change	www.cellinteractive.com/ucla/physician_ed/scripts_for_change.html
National College Transition Network: Motivational Interviewing Techniques	www.youtube.com/watch?v=T8cLM5ztc7I
PHYSICAL ACTIVITY	
CDC	
Physical Activity Resources and Publications	www.cdc.gov/physicalactivity/resources/index.html
Making Physical Activity a Part of a Child's Life	www.cdc.gov/physicalactivity/everyone/getactive/children.html
NHLBI	
Tips to Reduce Screen Time	www.nhlbi.nih.gov/health/public/heart/obesity/wecan/reduce-screen-time/tips-to-reduce-screen-time.htm
Make Family Time Active Times	www.nhlbi.nih.gov/health/public/heart/obesity/wecan/get-active/family-active-time.htm
PRECAUTIONARY PRINCIPLE	
The Wingspread Consensus Statement on the Precautionary Principle	www.sehn.org/wing.html

PUBERTY	
AAP: Puberty & Sexuality (for teens)	familydoctor.org/familydoctor/en/teens/puberty-sexuality.html
HHS Office on Women's Health	
Puberty (for girls ages 10-16)	www.girlshealth.gov/body/puberty/index.html
Puberty (for parents and caregivers)	girlshealth.gov/parents/parentsbody/puberty.html
“Study on Early Puberty Advances Breast Cancer Research” – Environmental Factor newsletter, NIEHS	www.niehs.nih.gov/news/newsletter/2010/september/science-study.cfm
“Obesogens and Early Puberty” – Pediatric Insights newsletter, Cincinnati Children's Hospital Medical Center	www.cincinnatichildrens.org/professional/resources/ped-insights/2011/october/early-puberty
Precocious puberty – Merck Manual Online	www.merckmanuals.com/professional/pediatrics/endocrine_disorders_in_children/precocious_puberty.html

Appendix B.

Communicating About Health and the Risk of Disease

Effective health messages need to help people understand and believe that they can take positive actions and make a difference in their health. As a health professional, you can help parents (or other caregivers) and their children know that they can take steps now that will make a difference in their health across their lifespan. By providing clear and achievable goals that promote overall health, health professionals play an instrumental role in providing the knowledge and encouragement individuals need to lead the healthiest life possible.

You can help parents understand that research on the causes of breast cancer is ongoing and our knowledge of the different types of environmental factors associated with risk has evolved over time, and will continue to evolve. Encourage their attempts to become more health literate, and continue your own efforts to stay abreast of advances in the field of breast cancer research. Having access to evidence-based knowledge to guide medical decision-making has been proven to promote self-efficacy among patients (Johnson, Sevelius, Dilworth, Saberi & Neilands, 2012). Your goal when discussing risk and promoting preventive measures might best focus on providing resources that increase awareness of known or possible risk factors and encourage actions, when feasible, to reduce these risks.

An additional aspect to consider in discussions with your patients and their family members is cultural sensitivity. Cultural sensitivity, or cultural competence, has traditionally been understood as the health professional's awareness of and attention to the specific background and informational needs of their patients. Based on this approach, health messages are most effective, and create less of an emotional burden, when geared to the cultural, social, historical, environmental and psychological forces that influence the target health behavior in the proposed target population (Jakobsson & Holmberg, 2012; Slean, Jacobs, Lahiff, Fisher, & Fernandez, 2012). This may involve examples citing people, places, language, food, household

products, and clothing familiar to, and preferred by, the target audience (Resnicow, Baranowski, Ahluwalia, & Braithwaite, 1999).

In discussing risk of developing breast cancer, two issues that may require some level of cultural sensitivity are discussion of weight and reference to reproductive organs and processes. As discussed earlier, there are cultural differences between African-American and Caucasian perceptions of weight that may require adapting how such advice is expressed. Studies have also shown differing perceptions regarding weight gain and obesity among other ethnic and racial groups. Pacific Islanders, for example, are more likely to desire weight gain and receive more parental and family advice about the desirability of gaining weight (Cinelli & O'Dea, 2009).

A related, and important, influence on childhood perceptions of the acceptability of higher weight was living in environments where people seen every day are overweight or obese. Targeting such misperception may be the most effective way to facilitate behavior change and improve the adoption of obesity prevention interventions (Maximova et al., 2008). In addition, for some ethnic subpopulations, such as Hmong from Vietnam, there are no specific terms for reproductive organs nor for certain reproductive processes that we commonly and openly refer to in the United States. Care should be taken to understand relevant cultural taboos among patients, their parents, and caregivers, and to provide guidance in a culturally respectful manner.

When considering how best to discuss sensitive topics, like risks for development of breast cancer across the lifespan, it may also be beneficial to consider who should deliver such messages. The gender of the health professional may be an issue for patients, parents, or caregivers from some ethnic subpopulations and should be considered when providing advice regarding pubertal development. One might expect such discussions with a gynecologist or obstetrician but not from a primary care practitioner. Another consideration is who on the healthcare team

should deliver such advice. Research since the 1990s consistently confirms the value of the specific skill sets of nurse practitioners and nursing staff to facilitate the patients' journey, to serve as a communicative bridge with physicians, and to empower patients with decision aids and educational resources (Stacey et al., 2012; Williamson, Twelvetree, Thompson, & Beaver, 2012). Through the empowering interaction with nursing and other health professionals, patients have the opportunity to become more engaged, informed, collaborative, committed, and, importantly, in relation to environmental factors, "tolerant of uncertainty" (Johnson et al., 2012).

Using the Precautionary Principle

Building patients' and family members' tolerance for uncertainty may be needed to deliver effective messages about breast cancer and the environment. As more research links the effects of the environment and genetics to breast cancer risk, parents and caregivers may think about the actions they took, or did not take, and what their daughters were exposed to during their childhood. Since feelings of guilt, anger, and frustration may manifest themselves, it is very important to help parents and caregivers to minimize any feelings of guilt. A helpful message is "We all do the best we can with the information available at any given point in time and the resources available to us. Now we know more and we can make a difference going forward."

Parents may ask, "Well, what do I do now?" once they begin to understand how the environment plays a role in breast cancer risk. One thing you can tell them is to use the precautionary principle: in the absence of definitive information, err on the side of caution.

You can advise your patients to learn all they can about the role of environmental exposures and breast cancer risk by visiting <http://www.info.bcerp.org>, which contains information on both known and suspected environmental factors that increase the risks of developing breast cancer.

Techniques to Motivate Change

Many parents and young girls may be reluctant to discuss the topic of breast cancer risk, or be resistant to receiving guidance and advice about how to avoid known and suspected risks that heighten breast cancer risk. In these cases, communication techniques such as motivational interviewing may serve as useful tools to explore and resolve ambivalent feelings in order to facilitate change (Moyers & Rollnick, 2002). In motivational interviewing, the health professional first explains what is known about the risk, and then poses questions about the risks to lead the parent or caregiver to their own understanding of how that risk might affect them, or their daughter. That way, the parent or caregiver comes to the conclusion, rather than being asked to unquestionably accept the advice that the health professional provides.

By using these techniques, sensitive topics like risk factors for breast cancer, such as obesity or eating habits, can be broached and explored even if a parent or caregiver does not initially believe their daughter is at risk or that the risks will occur when they are older.

Talking with Preadolescents and Teenagers

In order for individuals to be open to messages about the risk of breast cancer, they first must perceive that they are susceptible to developing breast cancer. Silk et al., (2006), found that adolescents did not believe they were susceptible to breast cancer. However, other researchers have found that many young women were knowledgeable about genetic risks for breast cancer and, further, were aware that genetics is just one factor in the overall equation of breast cancer risk (K. O. Jones, Denham, & Springston, 2007). Other risks, such as obesity and lack of physical activity, are topics that teenagers are generally more aware of and concerned about as risks to their health (and self-esteem) and may be easier to discuss as risk factors for breast cancer. As more media attention focuses on the role of environmental exposures on cancer risk, awareness of these other factors involved in

breast cancer risk will likewise increase. The challenge in talking with your adolescent patients about breast cancer will be finding a way to make it real for them within the context of their health literacy.

When it comes to discussions about how to reduce the threat of breast cancer, “get a mammogram” or asking if they do breast self-exams would be inappropriate messages for this age group. Silk et al. (2006) suggest addressing some of the myths that are rampant in the adolescent world (such as, getting hit in the “chest” can cause breast cancer) and then moving onto the real risk factors, such as obesity, lack of exercise, and exposures to harmful chemicals. Apply the precautionary principle and urge avoidance of the environmental factors that have been associated with breast cancer (but using language appropriate to the age of the teenager). Encourage healthy practices that not only reduce the risk of breast cancer but other diseases as well. Until the risk of breast cancer can be made relevant to their lives—not an event of the distant future—your messages are not going to reach your young patients.

Talking with Mothers

Discussions with mothers to help them better understand susceptibility should provide information on how to accurately assess relative risk from both genetics and the environment. In the study conducted by Silk, et al. (2006), mothers definitely had more information about the risks that decrease or increase breast cancer than their daughters. Silk et al. (2006) found that mothers perceived that breast cancer was striking women at an earlier age, which raised their concern for their daughters. Addressing this concern with the mother will provide healthcare professionals with the opportunity for intervention messages that encourage her to discuss breast health with her daughter and lifestyle choices that may lessen her risk of developing breast cancer.

Sinicrope et al. (2009) noted mothers who have a personal history of breast cancer were significantly more likely to provide advice to their daughters about the risks of breast cancer and also advising their daughters to maintain a healthy lifestyle. Since we now know that

genetics accounts for only 5 to 10% of all breast cancer cases (National Institutes of Health, 2007), discussion of environmental factors is particularly important where there is no known family history of breast cancer. For those with a family history of breast cancer, the message should focus on the role of epigenetic changes, modifications to the genome that may influence disease outcome by turning on or off key regulatory gene expression, and a cautious approach regarding harmful exposures.

Mothers who are of childbearing age should also be told about the risks to their fetus from their exposures to environmental factors such as phthalates and BPA. Pregnancy is one of the windows of susceptibility when rapid breast development occurs and when what the mother is exposed to can affect her unborn child. The key message for these mothers is that healthy habits are critical at all stages of their child's life.

Appendix C.

How Chemicals Are Regulated in the United States

Adapted from the United States General Accountability Office report Chemical regulation: Comparison of U.S. and recently enacted European Union Approaches to protect against the risk of toxic chemicals (2007)

Chemicals play an important role in everyday life. Over the last several decades, Congress has passed legislation to increase the ability of federal agencies to identify and address the health and environmental risks associated with toxic chemicals. Some of these laws, such as the Clean Air Act; the Clean Water Act; the Federal Food, Drug and Cosmetic Act; and the Federal Insecticide, Fungicide, and Rodenticide Act, authorize the control of hazardous chemicals in, among other things, the air, water, and soil and in food, drugs, and pesticides. Other laws, such as the Occupational Safety and Health Act and the Consumer Product Safety Act, can be used to protect workers and consumers from unsafe exposures to chemicals in the workplace and the home. Nonetheless, the Congress found that human beings and the environment were being exposed to a large number of chemicals and that some could pose an unreasonable risk of injury to health or the environment.

In 1976, the Congress passed the Toxic Substances Control Act (TSCA) to authorize the Environmental Protection Agency (EPA) to control chemicals that pose an unreasonable risk to human health or the environment, but some have questioned whether TSCA provides EPA with enough tools to protect against chemical risks. Due to limited resources, EPA has moved toward using voluntary programs as an alternative means of gathering information from chemical companies in order to assess and control the chemicals under TSCA. While these programs are noteworthy, data collection has been slow in some cases, and it is unclear if the programs will provide EPA enough information to identify and control chemical risks. TSCA places the burden of proof on EPA to demonstrate that a chemical poses a risk to human health or the environment before EPA can regulate its production or use. Even when EPA has toxicity and exposure information on existing chemicals, the agency has had difficulty demonstrating that

chemicals present or will present an unreasonable risk and that they should have limits placed on their production or use.

To ensure that adequate data are made publicly available to assess the special impact that industrial chemicals may have on children, EPA launched the Voluntary Children's Chemical Evaluation Program (VCCEP). EPA identified 23 commercial chemicals to which children have a high likelihood of exposure and the information needed to assess the risks to children from these chemicals.

Appendix D.

Animal Research Used to Characterize Human Cancer Risk

Adapted from Of Mice and Women: Modeling Breast Cancer and the Environment developed by the Bay Area Breast Cancer and the Environment Research Center Community Outreach Translation Core (2010)

Mice and rats are used in breast cancer research. The model used depends upon the research question and the preference or choice of the scientist.

Both mice and rats are mammals that belong to one of numerous species of small, omnivorous rodents. Experimental animal studies using rodents play a vital role in advancing the understanding of the molecular biology of mammary gland development and tumor genesis. These studies are important to help predict breast cancer risk when human studies are not possible.

Like humans, mice and rats are mammals with mammary glands that originate from the milk bud, their glands provide nourishment to their newborns in the form of milk, and they can develop breast cancer. Unlike humans, mice and rats have short life spans and go into puberty at about three weeks of age. A woman lives on average 70 to 80 years of age and goes into puberty between 8 and 10 years of age. A genetically engineered mouse or rat can develop a breast cancer tumor at 3 months of age. A breast cancer tumor, in humans, can take decades to develop. Both the similarities and the dissimilarities offer invaluable advantages in studying breast cancer. Consequently, breast cancer research invariably deals with animals, in particular mice.

Mice and rats can be “engineered” to take advantage of the similarities between rodents and humans. For example, mice can be manipulated by inbreeding to have consistent genetic backgrounds, have their genes replaced with human gene versions, and/or have genes expressed as specific mutant genes. These types of manipulations allow scientists to test different hypotheses about what specifically gives rise to breast cancer.

In animal models, researchers can isolate biological processes to understand individual environmental exposures that may or may not contribute to abnormal tissue growth. The goal of using mice and rat models is to increase understanding of the fundamental aspects of breast biology. This understanding allows specific molecular markers to be developed to identify a woman's risk of developing breast cancer, as well as specific molecular targets to be identified that might provide a strategy for chemoprevention.

For more information, visit:

www.info.bcerp.org

The Breast Cancer and Environment Research Program (BCERP) is a network of scientists, physicians, and community partners studying the effects of environmental exposures that may affect breast cancer risk later in life.



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