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**The Breast Cancer and the Environment Research Centers: Transdisciplinary
Research on the Role of the Environment in Breast Cancer Etiology**

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on behalf of the Breast Cancer and the Environment Research Centers

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Abbreviations and definitions:

BBP – butyl benzyl phthalate

BCERC – Breast Cancer and the Environment Research Centers

BMI - body mass index

BPA – bisphenol A

COTC – Community Outreach and Translational Core

DDT – dichloro-diphenyl-trichloroethane

ER – estrogen receptor

FSH – follicle stimulating hormone

HPA – hypothalamic pituitary adrenal

HPG – hypothalamic pituitary gonadal

HRT – hormone replacement therapy

LH – luteinizing hormone

NCI - National Cancer Institute

NIEHS – National Institute of Environmental Health Sciences

PAH – polycyclic aromatic hydrocarbons

PBB – polybrominated biphenyl

PBDE – polybrominated diphenyl ether

PCBs – polychlorinated biphenyls

POPS – persistent organic pollutants

PR – progestin receptor

SES – socioeconomic status

TDLU – terminal duct lobular unit

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ABSTRACT

Objectives: To introduce and describe the Breast Cancer and the Environment Research Centers (BCERC), a research network with a transdisciplinary approach to elucidating the role of environmental factors in pubertal development as a window on breast cancer etiology. We describe the organization of four national centers integrated into the BCERC network.

Data Sources: Investigators use a common conceptual framework based on multiple levels of biologic, behavioral and social organization across the lifespan. The approach connects basic biologic studies with rodent models and tissue culture systems, a coordinated multicenter epidemiologic cohort study of pre-pubertal girls, and the integration of community members of breast cancer advocates as key members of the research team comprise the network.

Data Extraction: Relevant literature is reviewed that describes current knowledge across levels of organization. Individual research questions and hypotheses in BCERC are driven by gaps in our knowledge that are presented at genetic, metabolic, cellular, individual, and environmental (physical and social) levels.

Data Synthesis: As data collection on the cohort, animal experiments and analyses proceed, results will be synthesized through a transdisciplinary approach.

Conclusion: Center investigators are addressing a large number of specific research questions related to early pubertal onset, which is an established risk factor for breast cancer. BCERC research findings aimed at the primary prevention of breast cancer will be

disseminated to the scientific community and to the public by breast cancer advocates, who have been integral members of the research process from its inception.

INTRODUCTION

The Breast Cancer and the Environment Research Centers (BCERC), sponsored by the National Institute for Environmental Health Sciences (NIEHS) and the National Cancer Institute (NCI) were established to better understand how environmental factors may influence pubertal development and to enable primary breast cancer prevention strategies. In 2003, after a period of focused and thoughtful advocacy, integrated with scientific consultation, BCERCs were awarded to The Fox Chase Comprehensive Cancer Center in Philadelphia, Michigan State University in East Lansing, Michigan, the University of Cincinnati, and the University of California San Francisco Helen Diller Family Comprehensive Cancer Center.

In this paper, we define the BCERC research questions and present our common conceptual framework for the etiology of breast cancer and the rationale for a focus on puberty. Then, across multiple levels of biologic, behavioral and social organization, we highlight our current scientific understanding of the development of the normal mammary gland, the nature and action of breast cancer risk factors and our understanding of the mechanisms of breast carcinogenesis relevant to early development. Our BCERC experimental approach is driven by the knowledge gaps in this understanding. We conclude with a description of the organization of the BCERC.

RESEARCH QUESTIONS

We explore whether exposures to environmental factors (e.g., phenols, phthalates, phytoestrogens, genistein, dietary fat, ionizing radiation, psychosocial factors) prior to and during puberty might set the stage for increased breast cancer risk in adulthood. Multiple hypotheses are being tested by developing and interrogating rodent models and rodent and human cell culture systems to characterize the molecular basis of mammary gland development over the lifespan. We seek to determine how environmental agents may affect this development and to better understand the process of breast carcinogenesis. In simultaneously conducted epidemiologic cohort studies of prepubertal girls, conceptually integrated with the studies in animal and human tissue models, additional hypotheses posit roles for the environmental, psychological, behavioral, metabolic and genetic factors as determinants of puberty. This transdisciplinary approach will generate information about relevant exposures from human studies that can be applied to the animal studies. In turn, the animal studies will provide a mechanistic understanding of how environmental exposures may impact pubertal breast development and adversely influence breast cancer risk in adult life.

This research adds to the findings of other similar research relevant to breast cancer, early development and the environment including the National Growth and Health Study (Braithwaite 2008), the Child Health and Development Study (Cohn et al. 2003), the CHAMACOS cohort study (Eskenazi et al. 1999), the FELS study (Demerath et al. 2007), the Bogalusa Heart Study (Freedman et al. 2002), the ALSPAC study in England (Golding 1990), as well as other longitudinal early development studies around the world. The uniqueness of BCERC is the combination of its longitudinal design with questionnaire, and biomarker data collected prior to puberty, the determination of pubertal maturation

endpoints by physical examination, the focus on breast cancer etiology, and the transdisciplinary integration of biologic laboratory-based science, epidemiology, and community participation.

METHODS

Conceptual Framework: Breast development and carcinogenesis across the lifespan

The BCERC initiative is multidisciplinary in its approach to research questions and in the integrated nature of the science with community and advocacy participation. Although not prescribed by the NIH's request for applications, investigators are invested in making our approach truly "transdisciplinary" (Rosenfield 1992). Transdisciplinary science occurs when scientists from multiple disciplines work interactively on a common problem with a common conceptual model (or framework) and, as a result, develop novel cross-disciplinary methods, insights, and research approaches that would not have occurred with a traditional uni-disciplinary investigation. This approach is consistent with the current movement toward team science and interdisciplinary research evidenced by recent reports and funding initiatives (Hiatt and Breen 2008; Stokols et al. 2003; TREC (Transdisciplinary Research on Energetics and Cancer) 2008).

BCERC investigators have agreed on a common conceptual framework that acknowledges the complexity of breast cancer etiologic factors along a lifespan continuum from pre-natal *in utero* exposures through puberty and maturity to the postmenopausal years. Our framework permits multiple investigators to locate their particular hypotheses within it, taking into account our best understanding of pubertal

development and the environment from both a social ecologic and lifespan perspective (Smedley and Syme 2001).

At each stage of the lifespan, the framework recognizes possible influences at multiple levels from genes to cells, tissues and the organism, through individual behavior, to family, neighborhood and other “upstream” social factors.

While the focus in our study of humans is limited to the pre-pubertal and pubertal stages of the lifespan, our animal models allow us to consider the mechanistic basis for the effects of environmental exposures on the mammary gland across the lifespan. This in turn will provide a bridge for the development and testing of mechanism-based prevention strategies in humans.

Rationale for Focus on Puberty

The onset of puberty in girls is defined clinically by the first signs of breast development, pubic hair and other secondary sex characteristics (Grumbach and Styne 2002). The rationale for our focus on puberty stems from the well-established observation that a later onset of menarche is associated with a decreased risk of breast cancer in adult life (Kelsey and Bernstein 1996). The magnitude of the decreased risk is in the range of 9% and 4% for each additional year of menarche delay for pre- and post-menopausal women respectively (Clavel-Chapelon 2002; Hsieh et al. 1990). The risk for breast cancer among those with an earlier age of menarche is 1.2-2.2 times greater when contrasted to those with later age of menarche (Garland et al. 1998; Titus-Ernstoff et al. 1998).

The onset of menarche has been used in studies of adult women as a marker of pubertal onset, but the relationship between the onset of puberty and menarche has not been

constant over secular time (Euling et al. 2008). In the United States, the correlation between onset of puberty and menarche was greater than 0.9 for women born in the 1930s, 0.5-.7 for those born in the 1950s, and .38-.39 for those born in the 1970s (Biro et al. 2006). To complicate matters further, a longitudinal study that followed girls annually noted that either primary breast areolar or pubic hair, usually breast, development lagged behind maturation of the other factor in over half the cohort (asynchronous maturation) (Biro 2003). These results need to be confirmed in other longitudinal studies (Euling et al. 2008), but suggest that factors contributing to onset of puberty and menarche were more similar in the past than in more recent years, and the clear differentiation between their time of onset and the duration between them ("tempo") is needed.

That both the age when girls begin puberty and their age of menarche have declined over the last century is also well established (Euling et al. 2008). This strongly suggests that changes in lifestyle and/or environmental factors have influenced these trends. Early development is considered an "adverse" effect because of its impact on outcomes in adolescence, such as accelerated skeletal maturation and short adult height, unwanted pregnancies, sexually transmitted infections, psychosocial difficulties and because of its potential impact on adult diseases such as breast cancer and elements of the metabolic syndrome (Golub et al. 2008).

When menarche is accelerated without a concomitant acceleration in the timing of menopause, it is widely thought that the increased duration of hormone exposure over a lifetime promotes the development of breast cancer (de Waard and Thijssen 2005). However, it may be that the pubertal transition itself is critical because of rapid breast

development and the susceptibility of rapidly duplicating cells to environmental insults (Berkey et al. 1999). Compared to other times in life, the pubertal breast in the rodent contains the highest number and the greatest proliferative activity of the terminal duct lobular units (TDLUs), the functional units of the breast (Rudland 1993). This may be related to the apparent susceptibility of the breast to carcinogens during puberty (Colditz and Frazier 1995; Knight and Sorensen 2001).

Thus, puberty is a critical period during which to assess the impact of exposures to endocrine disruptors in the environment that interfere with normal hormonal synthesis and metabolic pathways, such as agents in the families of phenols, phthalates, and phytoestrogens (Buck Louis et al. 2008). Endocrine disruptors found in the environment may influence both the timing and pace of the pubertal transition as well as female reproductive outcomes and early life development (Crain et al. 2008). It is also likely that constitutional factors play a role in age at puberty, and genetic variability in pathways that influence maturation, such as hormonal and growth factors, may affect onset of puberty and menses. The effects of environmental exposures or lifestyle factors may be most pronounced among those whose genetic or other biologic characteristics make them most susceptible to mediating pathways (Freedman et al. 2002; Pathak et al. 2000).

Gaps in Knowledge and the BCERC Experimental Approach

There are two major hypotheses that are being investigated by BCERC: first is that puberty is a window of biological susceptibility to carcinogenesis; second is that the advent of puberty initiates a window of hormonal stimulation ending in menopause. These are not mutually exclusive, and some environmental agents may perturb both.

The focus of the biologic studies is on the characteristics of breast development in normal and cancer-prone rodent models, as well as the influence of environmental factors on breast development and breast carcinogenesis. The focus of the epidemiologic studies is on the elucidation of multiple determinants of early puberty with data collected longitudinally over a five-year period to encompass the first signs of pubertal maturation. The cohort is composed of 1222 girls were recruited with mean ages at baseline of 7.13 years in Cincinnati, 7.34 years in New York City, and 7.38 years in the San Francisco Bay Area. A parent or guardian identified 34.4% of the girls as white, non-Hispanic, 25.3% as black, non-Hispanic, 4.3% as black Hispanic, 29.9% as Hispanic, 4.5% as Asian, and 1.7% in some other category. Integrated into the structure of the BCERCs are four Community Outreach and Translational Cores (COTC) that are participants in the research studies and whose members work to translate the current scientific knowledge, as well as findings from new research, into educational messages for the community. Simultaneously, they provide input from the community perspective into the on-going research of the BCERCs.

In Utero and Pre-pubertal Phases

Although past studies of the association between birth weight and breast cancer risk have yielded inconsistent results, recent meta-analyses have demonstrated an increased risk with larger birth weights (Park et al. 2008; Xue and Michels 2007). This suggests that the *in utero* hormonal milieu may influence breast cancer risk. Trichopoulos and others have hypothesized that higher levels of hormones during pregnancy favor the generation of a higher number of susceptible stem cells with compromised genomic stability (Trichopoulos et al. 2005). Others have posited that *in utero* exposures to

estrogens, androgens, IGF-1 and possibly alphafeto protein might be associated with increased breast cancer risk (Ekblom et al. 1997; Forman et al. 2005).

In animal models, *in utero* stem cells in the fetal breast are capable of cancer initiation, and this may be true in humans as well (Russo and Russo 1996). The presence of a population of stem cells in the fetal breast and their continued presence in the adult reproductive years has been demonstrated in rodent models (Chepko and Smith 1999). The cyclical epithelial proliferation in the breast associated with ovulatory menstrual cycles, as well as the breast's ability to repopulate itself with each pregnancy is also consistent with the presence of human mammary stem cells (Stingl et al. 2006). These cells, under the influence of hormones and growth factors, may be directly involved in carcinogenesis (Wicha 2008). Research conducted by BCERC investigators is exploring the location and function of stem cells in the mammalian breast to elucidate their possible role in carcinogenesis.

At birth, the breast consists of a rudimentary ductal system. The degree of development at birth is due to the influence of maternal hormones (Anbazhagan et al. 1991). By two years of age, the breast undergoes involution, and is composed of a primitive ductal system without alveoli (Howard and Gusterson 2000). BCERC investigators are seeking a more detailed understanding of the nature of normal mammary development in animal models to provide insights into normal breast development and breast carcinogenesis in humans.

Puberty

Until the onset of puberty, the breast remains in a dormant state. At puberty the exact mechanisms responsible for breast development have not been defined, but the initiation of puberty in girls is coincident with the activation of the hypothalamic-pituitary-gonadal (HPG) axis, or thelarche, and the activation of the hypothalamic pituitary adrenal (HPA) axis, or adrenarche, which are independent events. A surge of pituitary FSH, associated with HP axis activation, results in the stimulation of primordial ovarian follicles to secrete estrogen. Circulating estrogen in turn induces mammary duct, mammary stromal connective tissue, pituitary luteinizing hormone, and vascular proliferation and growth (Rogol 1998). The ratio of FSH to LH favors FSH at the onset of puberty, and even with the onset of menarche, ovarian function continues to be anovulatory (MacMahon et al. 1982b). The activation of the HPA axis stimulates the adrenal production of dehydroepiandrosterone, dehydroepiandrosterone sulfate, and androstenedione, which lead to the development of secondary sexual characteristics including pubic hair, acne, and body odor. The relative timing of thelarche and adrenarche may differentially determine the onset of menarche (Biro et al. 2006). The duration of anovulatory menstrual cycles after the onset of menarche varies from one to more than six years, with longer intervals to ovulation in women with a late menarche (Clavel-Chapelon 2002; MacMahon et al. 1982a). The shorter the period of anovulation, the higher the breast cancer risk (Henderson et al. 1981).

It is important to note that the manifestation of breast development that we are studying in the epidemiological project is assumed to reflect the underlying mammary biology studied in rodent models in the biology project. In rodent models, we are characterizing the rate of development, extent and character of the mammary epithelium. With

improved animal models and biomarkers to study the impact of environmental stressors on breast cancer we can elucidate the effects of the timing of these exposures during critical windows of vulnerability.

Focusing now on the phase of pubertal development, we describe factors of influence at multiple levels of organization starting with genes and concluding with the social environment.

Genes

Relatively little is known about how genetic make-up influences breast cancer risk at the time of puberty. It is unclear, for example whether BRCA mutations interact with environmental factor to increase risk (Chang-Claude et al. 2007; Kotsopoulos et al. 2007). Mutations and polymorphisms in genes that control the synthesis and metabolism of hormones or environmental toxicants that act as endocrine disruptors may, however, have some role in pubertal development.

It has been demonstrated, for example, that high activity *CYP3A4* alleles, which primarily metabolize testosterone, are associated with early puberty and are more common in African-American than Hispanic or white girls (Kadlubar et al. 2003). There may also be important interactions of these genes with body mass, such that girls with higher BMIs are more likely to over express these genes and enter puberty at earlier ages. BCERC investigators are utilizing new technologies to assess gene and protein expression in order to elucidate the effects of multiple genetic polymorphisms, including those affecting hormone synthesis and metabolism and carcinogen metabolism. As another example, leptin is important in normal regulation of childhood weight gain,

maturation and development of secondary sexual features. Leptin levels, which are thought to reflect body composition and are best predicted by BMI (Charmandari et al. 2002), rise with age prior to puberty, suggesting that a threshold effect may trigger puberty (Ong et al. 1999). Polymorphisms in the promoter region of the leptin gene, which have been shown to affect tissue leptin secretion rates (Hoffstedt et al. 2002), could impact age at onset of puberty, particularly in relation to other factors such as BMI, diet and physical activity. Although analysis of a large data set did not show associations between polymorphisms in the leptin receptor and BMI in adults (Heo et al. 2002), these variants could play a greater role in pubertal development.

Common variants in *LH* and *FSH* genes could also impact timing of puberty (Lamminen and Huhtaniemi 2001). The FSH receptor gene has two distinct isoforms, with ovarian response to FSH stimulation dependent on the FSHR genotype (Perez Mayorga et al. 2000). FSH secretion is regulated, in part, by inhibin, and inhibin B levels correlate positively with age and FSH concentrations several years before the onset of puberty, with concomitant increases during breast development (Crofton et al. 2002).

Genetic variability may also influence age at puberty indirectly, such as genetic predictors of body size. Furthermore, the potential effects of environmental exposures may be mediated by genetic differences in metabolic pathways. The effects of lifestyle factors, such as physical activity, on maturation could be influenced by constitutional factors. In the BCERC, we will investigate the role of genetic polymorphisms that may

directly influence maturation, or that may interact with environmental and lifestyle factors to impact age at puberty.

Metabolic Pathways

The exact mechanisms through which underlying hormonally related risk factors work are not known (Aupperlee et al. 2005; Clavel-Chapelon 2002). However, the ovarian hormones, estrogen and progesterone, are believed to play an important role in the etiology of breast cancer (Henderson and Feigelson 2000). A recent systematic review found 15 prospective studies of endogenous hormones and breast cancer risk in postmenopausal women that consistently showed that the highest quintile of estradiol and testosterone conferred an increased relative risk in the range of 2.0 to 2.2 compared to the lowest quintile (Cummings et al. 2009). Also exogenous progestins, used in combination with estrogens in menopausal hormone replacement therapy (HRT), increase breast cancer risk, whereas estrogen-alone HRT is not associated with an increase (Greiser et al. 2005; Rossouw et al. 2002). Thus, to achieve a better understanding the mechanisms of progesterone action in the breast, BCERC investigators are using *in vivo* and *in vitro* mouse and rat mammary gland models to advance our understanding of the mechanisms of action of the two isoforms of progesterone, PR A and PR B, and their specific functions in normal mammary gland development during puberty, at sexual maturity, during and after pregnancy, and after carcinogen exposure in mammary cancer development.

There is also evidence that certain transcription factors such as Stat5, Id2 and C/EBP β are involved in alveologensis and are effectors of progesterone and prolactin-driven mammary gland development (Miyoshi et al. 2002; Seagroves et al. 1998). Beyond the

potential for dysregulation by steroid disruptors, Stat5 (Paukku and Silvennoinen 2004) and C/EBP β (Ramji and Foka 2002) can also be activated by proinflammatory cytokines, thus presenting another avenue for environmental influences on mammary gland development being explored by BCERC scientists.

Cells and Tissues

The cells in the TDLU of the human breast are at their peak of cell replication during puberty and through early adulthood. In animal studies, the susceptibility of the TDLU to neoplastic transformation has been confirmed by *in vitro* studies, which have shown that this structure has the highest proliferative activity and rate of carcinogen binding to DNA. More importantly, when treated with carcinogens *in vitro*, the epithelial cells express phenotypes indicative of cell transformation (Russo et al. 1993). These studies indicate that, in the human breast, the target cell of carcinogens is found in a specific compartment whose characteristics are the determining factors in initiation. These TDLU are believed to contain stem cells that will become the targets of the neoplastic event, depending upon: (a) topographic location within the mammary gland tree, (b) age at exposure to a known or putative genotoxic agent, and (c) reproductive history of the host. Further, this structure has the highest proliferative activity, estrogen receptor content, and rate of carcinogen binding to DNA (Russo and Russo 2008).

Epidemiologic studies demonstrate that an early first pregnancy and an increase in parity are associated with a decrease in the risk of breast cancer, each additional live birth conferring a 10% risk reduction (Lambe et al. 1994). A number of hypotheses have been put forth to explain the protective effect of early pregnancy: induction of differentiation, decreased proliferative activity, altered hormonal milieu, and alteration in cell fate

(Sivaraman and Medina 2002). In both rats and mice, estrogen and progesterone, in the absence of pregnancy, can reproduce the protective effect. Induction of differentiation *per se* cannot explain the beneficial effect since treatments with differentiation-inducing hormones or drugs fail to confer the protective effect (Guzman et al. 1999). Likewise, it is unlikely that decreased proliferative activity or reduced cellular levels of ER and PR in parous animals can explain the protective effect of pregnancy (Kariagina et al. 2008; Sivaraman and Medina 2002). An alternative cell-fate hypothesis (Russo et al. 2008; Sivaraman and Medina 2002) proposes that the hormones of pregnancy induce a molecular switch in stem cells that produces cells with persistent changes in regulatory pathways that control proliferation and response to DNA damage. These cells may be able to metabolize carcinogens and repair DNA damage more efficiently than cells of the virginal gland, and are thus less susceptible to carcinogenesis. The higher incidence of breast cancer observed in nulliparous women may be the result of the persistence of “unmodified” stem cells.

Pregnancy also can confer an increased risk of breast cancer for a period of time after delivery (Pathak 2002). Post-lactational involution has been shown to cause profound changes in the stromal environment. It has been hypothesized that this stromal environment change may favor the growth of incipient cancers and be the basis for increased risk of breast cancer after pregnancy (Schedin et al. 2007). Understanding the basis of pregnancy-induced protective and/or promotional effects may lead to the development of novel strategies for the prevention of breast cancer.

Mammary epithelial development also depends on molecules produced by the stromal cells (Wiseman and Werb 2002), including fibroblasts, adipocytes (Iyengar et al. 2003),

macrophages, eosinophils (Gouon-Evans et al. 2002) and mast cells. Molecules involved in the communication between the microenvironment and the epithelial cells include EGF, FGF2, FGF10, HGF, fibroblast secreted protein 1 (FSP-1), transforming growth factor β (TGF- β) (Bhowmick et al. 2004; Muraoka-Cook et al. 2006), the chemokine CXCL-12, (stromal derived factor 1 α , SDF-1 α), type I collagen (Ingman et al. 2006), matrix metalloproteinase (MMP)-13, MMP-3, and MMP-14 (membrane-type MMP, MT1-MMP) (Page-McCaw et al. 2007; Sternlicht et al. 2006). Stromal cells also influence steroid hormone responses in the epithelium (Haslam and Woodward 2003). Changes in these stromal cells as the result of environmental stressors may, therefore, not only perturb normal pubertal development, but create a nurturing environment for a developing mammary neoplasm (Barcellos-Hoff and Ravani 2000; Maffini et al. 2004).

The microenvironment can even prevent malignant cells from committing to neoplasia. Restoration of normal microenvironmental signaling can reverse the malignant phenotype even though the cancer cells retain all of their neoplastically transforming mutations (Bissell and Radisky 2001). Also, while a normal stroma may protect the epithelium from tumorigenesis, an aberrant stroma can initiate tumorigenesis (Barcellos-Hoff and Ravani 2000; Bhowmick et al. 2004; Maffini et al. 2004). Alterations in stromal composition can also alter steroid hormone responses in cancer cells and affect responses to endocrine therapies (Xie and Haslam 2007). These stromal cells appear to carry on many normal functions, but they drive transformation by hijacking normal cellular responses and inducing them at the wrong place or at the wrong time (Jessani et al. 2004). Further elucidation of the interactions between of the epithelial and stromal elements of the developing breast and the susceptibility of these interactions to environmental factors is a key focus for BCERC investigators.

Individual Behavior and Psychosocial Factors

Diet and the nutritional content of food consumed in the pre-pubertal years may be the key factor leading to pre-pubertal overweight and obesity, which is at the forefront of suspected contributors to early puberty (Kaplowitz 2008). Recent national surveillance data show that 19% of U.S. children ages 6-11 years of age are overweight as defined by being over the 95th percentile for their age in BMI (Ogden et al. 2006). Although studies have established that girls with higher BMIs are likely to experience puberty at an earlier age (Biro et al. 2003), the mechanisms by which this occurs and the determinants of pre-pubertal obesity are not well understood (Jasik and Lustig 2008).

Obesity during childhood may be associated with increased risk of pre-menopausal breast cancer (Weiderpass et al. 2004). Obesity in the pre-pubertal period may also set the stage for the effects of overweight and obesity in later life. During adulthood, most data suggest that obesity is associated with increased risk of post-menopausal breast cancer, even though it is protective for pre-menopausal breast cancer (Magnusson et al. 2005; Verla-Tebit and Chang-Claude 2005). Obesity represents a constellation of physical attributes that include BMI and waist and hip circumference. This is relevant because in the New York University Women's Health Study and EPIC Study, premenopausal breast cancer risk was inversely correlated with BMI; however, when adjusted for BMI, waist and hip circumference were associated with increased breast cancer risk (Sonnenschein et al. 1999). Mechanistic explanations as to how obesity may be protective in premenopausal women include decreased estrogen levels in obese women, who have anovulatory cycles (Pike et al. 1993), but the epidemiological evidence to support this is inconsistent (Garland et al. 1998).

Overall caloric intake, the role of individual nutrients and dietary intake of substances such as phytoestrogens, may also play a role in pubertal development. For example, urinary concentrations of phytoestrogens, and in particular daidzein and genistein, have been associated with later age of breast development in girls in New York City, and this “protective effect” was more pronounced in girls with lower BMIs (Wolff et al. 2008). Further investigation of the effects of these substances is another focus of BCERC investigators.

The impact of decreased physical activity independent of energy intake, and its effects in different subgroups of children, requires further investigation. In the BCERC epidemiologic study, investigators are assessing dietary intake by 24-hour recalls administered to the primary caregiver at four times each year during the pre-pubertal baseline year. Likewise, detailed physical activity patterns are being assessed. Growth patterns are being closely monitored by annual or bi-annual assessments of height, weight, anthropometric measures and body fat measurements.

Psychosocial factors are of interest because they have also been found to influence timing of puberty among girls (Bogaert 2005; Ellis and Garber 2000; Graber et al. 1997). Reproductive maturation appears to accelerate in stressful family contexts, characterized by low-quality parental investment, high levels of stress, negative relationships, and prolonged distress (Romans et al. 2003). In contrast, family relationships characterized by warmth, cohesion, and stability consistently appear to have a protective effect and predict later pubertal onset (Graber et al. 1995). Maternal depression, which is characterized by withdrawal and lack of engagement, has also been

linked to early maturation for female children (Ellis and Garber 2000). The proposed mechanism through which acceleration likely occurs is via activation of the stress-mediating hypothalamic-pituitary and sympathoadrenal systems (Grumbach and Styne 2002). Moreover, studies have linked absence of a biological father to early pubertal maturation and indicate that girls growing up in father-absent homes are about twice as likely to experience menarche prior to age 12 (Mustanski et al. 2004; Quinlan 2003). A review of the father-absence literature suggests that menarche among girls in father-absent homes occurs two to five months earlier than in homes with father involvement (Ellis 2004), while mother absence does not appear to influence pubertal timing (Bogaert 2005). Although more tenuous, childhood psychopathology may also be a significant risk factor for early puberty. A short-term longitudinal study (Hayward et al. 1997) indicated that a cluster of internalizing symptoms, including depression, predicted advanced puberty among girls about 5 months prior than their same-age peers and symptoms of anxiety, increases in prepubertal anxiety have also predicted earlier pubertal onset, independent of family adversity (Tremblay and Frigon 2005).

In BCERC, to assess the importance of these and other psychological factors, standardized measures are being used longitudinally to evaluate constructs, including child psychopathology (Behavior Assessment System for Children, Parent Report (Reynolds and Kamphaus 2002)), maternal depression (Center for Epidemiologic Studies Depression Scale (Radloff 1977), family environment (Family Environment Scale (Moos 1990) and, in the Cincinnati Center only, child self-reported depression (Childhood Depression Index (Kovacs 1992)).

Environment

Factors at the environmental level can influence pubertal development and ultimately breast cancer in three major ways: the physical environment, by which we mean exposure to environmental pollutants or toxicants; the built environment that influences whether children have a healthy place to live, play and go to school; the social environment, by which we mean the associations with socioeconomic status (SES) and race/ethnicity, social norms of behavior and culture. These are "contextual" aspects of place as opposed to "constitutive" aspects, which are the sum of the individual characteristics of persons living in any particular geographically defined area.

The Physical Environment. The impact of putative environmental toxicants on breast development and carcinogenesis is at the heart of BCERC studies. A broad array of environmental carcinogens is being evaluated in animal models and/or in the epidemiologic studies.

Xenoestrogens are part of a large group of synthetic and naturally occurring agents termed endocrine disruptors because of their capacity to perturb normal hormonal actions. It has been suggested that some endocrine disruptors may contribute to the development of hormone-dependent cancers (Sonnenschein and Soto 1998). One ubiquitous source of endocrine-disrupting chemicals are personal care products and cosmetics (Wolff et al. 1996), which may include substances in the categories of parabens, phthalates and organic solvents. Butyl benzyl phthalate (BBP) is an estrogenic compound and a partial agonist for the ER (Zacharewski et al. 1998), which is widely used in plastic food wraps, and other plastics as well as in cosmetic formulations. Animal studies in rats have shown that prenatal exposure to 500, or 1000 mg/kg of BBP,

or 250 or 375 mg/kg of its major metabolite, monobenzyl phthalate, induced significant alterations in the reproductive system of male offspring, including undescended testes and decrease in the ano-genital distance (Ema and Miyawaki 2002; Ema et al. 2003). Several *in vitro* tests have demonstrated the estrogenic activity of BBP (Hong et al. 2005; Zacharewski et al. 1998), but there is poor evidence on the mechanism mediating BBP's effect on cell proliferation. It is likely that the estrogenic response is not only elicited via the ER, but also through the activation of other still unknown pathways (Baker et al. 1999).

The widely used industrial monomer bisphenol A (BPA), another xenoestrogen, is polymerized in the manufacture of polycarbonate plastic and epoxy resins. Human exposure occurs by the leaching of BPA from plastic-lined food and beverage containers and from some dental sealants (Brotons et al. 1995; Olea et al. 1996) and the rate of leaching may greatly increase when the polycarbonate polymer is scratched and discolored (Howdeshell et al. 2003). BPA was found in 95% of urinary samples tested in a large study in the United States (Calafat et al. 2005). Evidence for estrogenic effects of BPA has been reported in several studies showing that it activates estrogen receptors alpha ($ER\alpha$) and beta ($ER\beta$) (Matthews et al. 2001; Routledge et al. 2000), and stimulates MCF-7 breast cancer cell growth (Krishnan et al. 1993). There is some uncertainty as to the level and risk of exposure to BPA in humans, but evidence suggests that it can disrupt normal reproductive tract development in male and female rodents (Ramos et al. 2001; Suzuki et al. 2002).

Persistent Organic Pollutants (POPs) are a class of chemical that are lipophilic and resistant to degradation and thus persist in the food chain and individual fat stores. POPs

include chemicals such as aldrin, chlordane, DDT, dieldrin, heptachlor and polychlorinated biphenyls (PCBs), which have become highly prevalent in the environment of industrialized countries since World War II. A study of brominated flame retardants (polybrominated biphenyls, PBBs) among accidentally exposed farm workers in Michigan revealed an association with earlier pubic hair, but not breast development, in the daughters of exposed mothers (Blanck et al. 2000). Polybrominated diphenyl ethers (PBDEs) are a subgroup of flame retardants, which are now being phased out because of proven toxicity, but a number are still in common use and are under study in relationship to pubertal development. Pesticides, which are ubiquitous in the environment and can be measured in biospecimens from all U.S. adults and children, are POPs that have been associated with earlier menarche in several (Gladen et al. 2000; Ouyang et al. 2005; Vasiliu et al. 2004), but not all studies (Denham et al. 2005). A recent study made use of long term human data and found that girls who had been exposed to DDT before age 14 years had a higher incidence of breast cancer than those who had not been exposed (Cohn et al. 2007). PCBs have been inconsistently related to breast cancer in adult women in observational studies, but there is evidence from at least four studies of a gene-environment interaction with *CYP1A1* such that high levels of PCB exposure and expression of *CYP1A1* confers a higher risk of breast cancer (Brody et al. 2007). In another possible gene environment interaction, certain POPs may interact with *CYP3A4*, which is a critical enzyme for xenobiotic metabolism as well for endogenous/exogenous hormone metabolism and inhibit the metabolism of endogenous estradiol, thereby potentially increasing serum levels and increasing breast cancer risk through this mechanism (Hodgson and Rose 2007)

Heavy metals such as cadmium and lead are both known or probable carcinogens, and also have estrogenic properties (Choe SY 2003). Lead exposure has been associated with later pubertal onset or menarche in several studies (Denham et al. 2005; Selevan et al. 2003; Wu et al. 2003), but both lead and cadmium have been associated with increased breast cancer risk in human epidemiologic studies (Cantor KP 1995; McElroy JA 2006). Environmental tobacco smoke (ETS) has been assessed in girls and associated with early menarche (Reynolds et al. 2004; Windham et al. 2004). However, mechanisms by which ETS might contribute to earlier menarche remain to be elucidated especially by examining possible gene-environment interactions such as those with *NAT2* slow acetylator and *GSTM1* null genotypes that may be associated with breast cancer in adults (Ambrosone et al. 2008).

Polycyclic aromatic hydrocarbons (PAHs) are a large class of chemicals formed by the incomplete combustion of coal, oil, and gas, as well as tobacco smoke and other substances to which humans are exposed in ambient air. These substances are genotoxic and known to be potential breast carcinogens (Morris and Seifter 1992), perhaps by damaging DNA through oxidative stress. Animal experiments indicate that puberty and early development may be the period when the breast is most sensitive to these effects (Fenton 2006). Also, since air pollution can vary by neighborhood environments, there may be an interaction between PAH exposure and the social environment (Morello-Frosch and Jesdale 2006).

One of the most commonly voiced cancer-related public concerns is the possible impact of hormones in food, because US animal food sourced are frequently exposed to growth hormones to boost production of meat, dairy products and eggs. Since higher levels of

estradiol may induce the hypothalamic burst of gonadotropin that initiates puberty, the impact of hormone-treated cattle deserves further study (Massart et al. 2006). In the BCERC studies, questions are being directed to the consumption of "organic" food consumption as an indirect measure of such exposures.

Finally, among environmental factors, ionizing radiation exposure has long been recognized as a risk factor for breast cancer in humans, probably as a result of the induction of DNA double-strand breaks. An increased risk of breast cancer has been consistently reported for radiation exposure from various sources, including the atomic weapon explosions in Nagasaki-Hiroshima (Tokunaga et al. 1991), medical treatments for a large number of conditions (Boice et al. 1991; John and Kelsey 1993; Shore et al. 1993) and among radiologic technologists (Boice et al. 1995). Among atomic bomb survivors, increased risk clearly has been related to younger age at exposure (Land et al. 2003). Elevated breast cancer risk in areas with relatively low doses of radiation contamination from the Chernobyl accident has been noted in Belarus (average cumulative dose ≥ 40 mSv) about 10 years after the incident, and risk was greater among women younger at exposure (Pukkala et al. 2006). BCERC investigators are using radiation as a prototypical breast carcinogen to evaluate genetic and molecular mechanisms of carcinogenesis in rodent models and we are assessing exposure by questionnaire in the epidemiology study.

For even the partial list of putative environmental agents presented above, much remains to be elucidated, not only in terms of their biologic effects in animal models, but also the risks for adverse outcomes as assessed by human epidemiology. Furthermore, it is likely that chemicals interact with each other and that their individual effects are

modified by the presence of genetic polymorphisms and by the social context in which the exposure plays out. It is only with a prospective, longitudinal study with input from multiple disciplinary perspectives, such as in the BCERC, that these effects and interactions can be illuminated.

The Built Environment. In addition to chemical toxicants in the physical environment, there are also aspects of the built environment that can lead to childhood obesity and may contribute to earlier puberty and breast cancer incidence later in life.

For example, it is known that people who live in socioeconomically deprived neighborhoods are more likely to be physically inactive (Cubbin et al. 2006; Yen and Kaplan 1998), to have less healthy dietary habits (Lee and Cubbin 2002), and to be obese (Cubbin et al. 2006). Socioeconomically deprived areas tend to have fewer food stores, more fast food stores, and more liquor stores (Morland et al. 2002). In addition, economic and social measures and other macro-level elements, such as urban sprawl, have been associated with higher rates of obesity (Ewing et al. 2003). The urban design, planning, and transportation literatures show that population density, connectivity, and land use mix are related in many studies to higher rates of walking and cycling for utilitarian purposes (Saelens et al. 2003). These factors may, in turn, be influenced by existing policies on land use, zoning and other factors that impact the built environment. BCERC investigators will explore the relationship of the built environment as determined both from interviews with caregivers as well as, in the Bay Area Center, on-the-ground audits of the characteristics of neighborhoods where the girls live. The audit observations will be linked to individual data from longitudinally obtained interviews with the girls.

The Social Environment. Childhood obesity is more prevalent in non-white and low-income children and, thus, factors associated with SES, race and ethnicity could be contributing to observed disparities in the onset of puberty. However, the relationship of SES, as well as race/ethnicity, to breast cancer is complex. Breast cancer is one of the few cancers that is related directly to higher SES and to being self-identified as white as compared to black (above the age of about 40 years), Hispanic, and Asian women. Within race/ethnic groups, there is also a direct relationship with SES (Kelsey and Bernstein 1996). The most accepted explanation for the direct positive relationship with SES is that higher SES women tend to have their first child later in life, have fewer children, and have menopause later, all of which raise the risk of breast cancer.

The age of menarche has, until recently, been lower in higher SES populations and in more industrialized countries. In the last half century in the U.S., at least, this relationship may be changing. Epidemiologic evidence now suggests that lower socioeconomic status is related to earlier puberty, as determined by entry into the Stage 2 of breast development among girls in the United States (Ellis and Essex 2007). In one multiethnic cohort study, higher maternal education predicted later menarche, but income was unrelated (Windham et al. 2004). The educational dimension of parental socioeconomic status has also been associated with earlier pubertal development in other studies of predominantly white girls (Davison et al. 2003; Ellis and Essex 2007; Lee et al. 2007).

Although pathways linking socioeconomic status and menarche activation are not well understood, it appears that body composition and nutrition are essential parts of the puzzle (Lawson 1999). These nutritional factors are likely to affect the endocrine milieu

controlled by the HPG system, particularly endogenous estradiol and lower sex hormone-binding globulin (Vihko and Apter 1984). Multiple markers of social environment can alter these hormonal profiles at the time of mammary development, and may explain disparity in menarchal age between black and white girls (McClintock et al. 2005). Because distributions of genetic polymorphisms vary by race/ethnicity, the influence of constitutional factors may also influence differences in age at puberty.

BCERC ORGANIZATIONAL STRUCTURE

In addition to the four BCERCs described above, a Coordinating Center at the UCSF site exists to coordinate questionnaire development, data entry, centralized data management and pooled analyses. Bioinformatics support is being coordinated at Fox Chase Cancer Center. Other aspects being coordinated between centers include an Internet website (<http://www.bcerc.org>), an intranet website, and national meetings. A publications committee has developed and monitors procedures for the analysis of pooled data, publication tracking, authorship protocols, ancillary studies and other matters pertaining to pooled data and publications from the network.

Among the three Centers that participate in the epidemiologic cohort study UCSF (Kaiser Permanente), University of Cincinnati, and Fox-Chase (Mt. Sinai School of Medicine), there is a high degree of collaboration and standardization in the epidemiologic studies across Centers to maximize opportunities for pooled analyses (i.e., increased sample size) and cross-site comparisons.

Integrated into the structure of the BCERCs are four Community Outreach and Translational Cores (COTC). Members of the COTC include breast cancer advocates as

well as academicians with expertise in communication. The primary role of the COTCs is the translation and dissemination of major research findings to the public through their member organizations. Specifically, the COTCs conduct their own research activities in communication and dissemination, develop fact sheets and other educational materials based on BCERC research, hold 'town halls' and other community activities, and assist with recruitment and retention strategies for the epidemiological study. Members participate on both the epidemiology and biology projects, disseminate educational information and scientific findings of the BCERC and ensure the inclusion of the community perspective in the BCERC projects and in facilitating the ongoing flow of information from the study team to the community and from the community back to the study team.

Specific results of constituent studies are being published from individual centers and collaborative efforts across centers. The reader is referred to the study website www.bcerc.org for a listing of these publications to date (BCERC 2008).

CONCLUSION

The transdisciplinary nature of our approach derives first from the highly varied areas of expertise of the scientific team and the community partners. The disciplines represented include genetics, molecular and cell biology, immunology, anatomy, radiation biology, pediatrics, endocrinology, toxicology, nutritional sciences, communication science and epidemiology. The BCERC investigators within the network are addressing specific research questions that focus on the common shared goal of the overall project: to understand the role of the environment in pubertal development as a window on breast cancer etiology. The on-going and integrated involvement of community members and

advocates in the research process and in communication with the public is a unique and effective way to advance the transdisciplinary science approach we have adopted.

REFERENCES

- Ambrosone CB, Kropp S, Yang J, Yao S, Shields PG, Chang-Claude J. 2008. Cigarette smoking, N-acetyltransferase 2 genotypes, and breast cancer risk: pooled analysis and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 17(1):15-26.
- Anbazhagan R, Bartek J, Monaghan P, Gusterson BA. 1991. Growth and development of the human infant breast. *Am J Anat* 192(4):407-417.
- Aupperlee M, Kariagina A, Osuch J, Haslam SZ. 2005. Progestins and breast cancer. *Breast Dis* 24:37-57.
- Baker VA, Hepburn PA, Kennedy SJ, Jones PA, Lea LJ, Sumpter JP, et al. 1999. Safety evaluation of phytosterol esters. Part 1. Assessment of oestrogenicity using a combination of in vivo and in vitro assays. *Food Chem Toxicol* 37(1):13-22.
- Barcellos-Hoff MH, Ravani SA. 2000. Irradiated mammary gland stroma promotes the expression of tumorigenic potential by unirradiated epithelial cells. *Cancer Res* 60(5):1254-1260.
- BCERC (Breast Cancer and the Environment Research Centers). 2008. Available: www.bcerc.org [accessed 31 March 2009].
- Berkey CS, Frazier AL, Gardner JD, Colditz GA. 1999. Adolescence and breast carcinoma risk. *Cancer* 85(11):2400-2409.
- Bhowmick NA, Chytil A, Plieth D, Gorska AE, Dumont N, Shappell S, et al. 2004. TGF-beta signaling in fibroblasts modulates the oncogenic potential of adjacent epithelia. *Science* 303(5659):848-851.

Biro FM, Huang B, Crawford PB, Lucky AW, Striegel-Moore R, Barton BA, et al. 2006.
Pubertal correlates in black and white girls. *J Pediatr* 148(2):234-240.

Biro FM, Lucky AW, Simbartl LA, Barton BA, Daniels SR, Striegel-Moore R, et al. 2003.
Pubertal maturation in girls and the relationship to anthropometric changes:
pathways through puberty. *J Pediatr* 142(6):643-646.

Bissell MJ, Radisky D. 2001. Putting tumours in context. *Nat Rev Cancer* 1(1): 46-54.

Blanck HM, Marcus M, Tolbert PE, Rubin C, Henderson AK, Hertzberg VS, et al. 2000.
Age at menarche and tanner stage in girls exposed in utero and postnatally to
polybrominated biphenyl. *Epidemiology* 11(6):641-647.

Bogaert AF. 2005. Age at puberty and father absence in a national probability sample. *J
Adolesc* 28(4):541-546.

Boice JD, Jr., Mandel JS, Doody MM. 1995. Breast cancer among radiologic technologists.
JAMA 274(5):394-401.

Boice JD, Morin MM, Glass AG, Friedman GD, Stovall M, Hoover RN, et al. 1991.
Diagnostic x-ray procedures and risk of leukemia, lymphoma, and multiple
myeloma. *Journal of the American Medical Association* 265:1290-1294.

Braithwaite D, Moore DH, Lustig RH, Epel ES, Ong KK, Rehkopf D, Wang MC, Miller SM,
Hiatt RA. 2008. Socioeconomic status in relation to early menarche among black
and white girls. *Cancer Causes Control*.

Brody JG, Moysich KB, Humblet O, Attfield KR, Beehler GP, Rudel RA. 2007.
Environmental pollutants and breast cancer: epidemiologic studies. *Cancer* 109(12
Suppl):2667-2711.

- Brotons JA, Olea-Serrano MF, Villalobos M, Pedraza V, Olea N. 1995. Xenoestrogens released from lacquer coatings in food cans. *Environ Health Perspect* 103(6):608-612.
- Buck Louis GM, Gray LE, Jr., Marcus M, Ojeda SR, Pescovitz OH, Witchel SF, et al. 2008. Environmental factors and puberty timing: expert panel research needs. *Pediatrics* 121 Suppl 3:S192-207.
- Calafat AM, Kuklennyik Z, Reidy JA, Caudill SP, Ekong J, Needham LL. 2005. Urinary concentrations of bisphenol A and 4-nonylphenol in a human reference population. *Environ Health Perspect* 113(4):391-395.
- Cantor KP SP, Brinton LA, Dosemeci M. 1995. Occupational exposures and female breast cancer mortality in the United States. *J Occup Environ Med* 37(3): 336-348.
- Chang-Claude J, Andrieu N, Rookus M, Brohet R, Antoniou AC, Peock S, et al. 2007. Age at menarche and menopause and breast cancer risk in the International BRCA1/2 Carrier Cohort Study. *Cancer Epidemiol Biomarkers Prev* 16(4):740-746.
- Charmandari E, Weise M, Bornstein SR, Eisenhofer G, Keil MF, Chrousos GP, et al. 2002. Children with classic congenital adrenal hyperplasia have elevated serum leptin concentrations and insulin resistance: potential clinical implications. *J Clin Endocrinol Metab* 87(5):2114-2120.
- Chepko G, Smith GH. 1999. Mammary epithelial stem cells: our current understanding. *J Mammary Gland Biol Neoplasia* 4(1):35-52.
- Choe SY KS, Kim HG, Lee JH, Choi Y, Lee H, Kim Y. 2003. Evaluation of estrogenicity of major heavy metals. *Sci Total Environ* 312(1-3):15-21.

- Clavel-Chapelon F. 2002. Differential effects of reproductive factors on the risk of pre- and postmenopausal breast cancer. Results from a large cohort of French women. *Br J Cancer* 86(5):723-727.
- Cohn BA, Cirillo PM, Wolff MS, Schwingl PJ, Cohen RD, Sholtz RI, et al. 2003. DDT and DDE exposure in mothers and time to pregnancy in daughters. *Lancet* 361(9376):2205-2206.
- Cohn BA, Wolff MS, Cirillo PM, Sholtz RI. 2007. DDT and breast cancer in young women: new data on the significance of age at exposure. *Environ Health Perspect* 115(10):1406-1414.
- Colditz GA, Frazier AL. 1995. Models of breast cancer show that risk is set by events of early life: prevention efforts must shift focus. *Cancer Epidemiology, Biomarkers & Prevention* 4:567-571.
- Crain DA, Janssen SJ, Edwards TM, Heindel J, Ho SM, Hunt P, et al. 2008. Female reproductive disorders: the roles of endocrine-disrupting compounds and developmental timing. *Fertil Steril* 90(4):911-940.
- Crofton PM, Evans AE, Groome NP, Taylor MR, Holland CV, Kelnar CJ. 2002. Dimeric inhibins in girls from birth to adulthood: relationship with age, pubertal stage, FSH and oestradiol. *Clin Endocrinol (Oxf)* 56(2):223-230.
- Cubbin C, Sundquist K, Ahlen H, Johansson SE, Winkleby MA, Sundquist J. 2006. Neighborhood deprivation and cardiovascular disease risk factors: protective and harmful effects. *Scand J Public Health* 34(3):228-237.

Cummings S, Tice J, Bauer S, Browner W, Cuzick J, Ziv E, et al. 2009. Prevention of breast cancer in postmenopausal women: approaches to estimating and reducing risk. *J Natl Cancer Inst* 101(6):384-398.

Davison KK, Susman EJ, Birch LL. 2003. Percent body fat at age 5 predicts earlier pubertal development among girls at age 9. *Pediatrics* 111(4 Pt 1):815-821.

de Waard F, Thijssen JH. 2005. Hormonal aspects in the causation of human breast cancer: epidemiological hypotheses reviewed, with special reference to nutritional status and first pregnancy. *J Steroid Biochem Mol Biol* 97(5): 451-458.

Demerath EW, Choh AC, Czerwinski SA, Lee M, Sun SS, Chumlea WC, et al. 2007. Genetic and environmental influences on infant weight and weight change: the Fels Longitudinal Study. *Am J Hum Biol* 19(5):692-702.

Denham M, Schell LM, Deane G, Gallo MV, Ravenscroft J, DeCaprio AP. 2005. Relationship of lead, mercury, mirex, dichlorodiphenyldichloroethylene, hexachlorobenzene, and polychlorinated biphenyls to timing of menarche among Akwesasne Mohawk girls. *Pediatrics* 115(2):e127-134.

Ekbom A, Hsieh CC, Lipworth L, Adami HQ, Trichopoulos D. 1997. Intrauterine environment and breast cancer risk in women: a population- based study. *J Natl Cancer Inst* 89(1):71-76.

Ellis BJ. 2004. Timing of pubertal maturation in girls: an integrated life history approach. *Psychol Bull* 130(6):920-958.

Ellis BJ, Essex MJ. 2007. Family environments, adrenarche, and sexual maturation: a longitudinal test of a life history model. *Child Dev* 78(6): 1799-1817.

- Ellis BJ, Garber J. 2000. Psychosocial antecedents of variation in girls' pubertal timing: maternal depression, stepfather presence, and marital and family stress. *Child Dev* 71(2):485-501.
- Ema M, Miyawaki E. 2002. Effects on development of the reproductive system in male offspring of rats given butyl benzyl phthalate during late pregnancy. *Reprod Toxicol* 16(1):71-76.
- Ema M, Miyawaki E, Hirose A, Kamata E. 2003. Decreased anogenital distance and increased incidence of undescended testes in fetuses of rats given monobenzyl phthalate, a major metabolite of butyl benzyl phthalate. *Reprod Toxicol* 17(4):407-412.
- Eskenazi B, Bradman A, Castorina R. 1999. Exposures of children to organophosphate pesticides and their potential adverse health effects. *Environ Health Perspect* 107 Suppl 3:409-419.
- Euling S, Herman-Giddens M, Lee P, Selevan S, Juul A, Sorensen T, et al. 2008. Examination of US puberty-timing data from 1940 to 1994 for secular trends: panel findings. *Pediatrics* 121 Suppl 3:S172-191.
- Ewing R, Schmid T, Killingsworth R, Zlot A, Raudenbush S. 2003. Relationship between urban sprawl and physical activity, obesity, and morbidity. *Am J Health Promot* 18(1):47-57.
- Fenton SE. 2006. Endocrine-disrupting compounds and mammary gland development: early exposure and later life consequences. *Endocrinology* 147(6 Suppl):S18-24.

Forman MR, Cantwell MM, Ronckers C, Zhang Y. 2005. Through the looking glass at early-life exposures and breast cancer risk. *Cancer Invest* 23(7):609-624.

Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. 2002. Relation of age at menarche to race, time period, and anthropometric dimensions: the Bogalusa Heart Study. *Pediatrics* 110(4): e43.

Garland M, Hunter DJ, Colditz GA, Manson JE, Stampfer MJ, Spiegelman D, et al. 1998. Menstrual cycle characteristics and history of ovulatory infertility in relation to breast cancer risk in a large cohort of US women. *Am J Epidemiol* 147(7):636-643.

Gladen BC, Ragan NB, Rogan WJ. 2000. Pubertal growth and development and prenatal and lactational exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene. *J Pediatr* 136(4):490-496.

Golding J. 1990. Children of the nineties. A longitudinal study of pregnancy and childhood based on the population of Avon (ALSPAC). *West Engl Med J* 105(3):80-82.

Golub MS, Collman GW, Foster PM, Kimmel CA, Rajpert-De Meyts E, Reiter EO, et al. 2008. Public health implications of altered puberty timing. *Pediatrics* 121 Suppl 3:S218-230.

Gouon-Evans V, Lin EY, Pollard JW. 2002. Requirement of macrophages and eosinophils and their cytokines/chemokines for mammary gland development. *Breast Cancer Res* 4(4):155-164.

- Graber JA, Brooks-Gunn J, Warren MP. 1995. The antecedents of menarcheal age: heredity, family environment, and stressful life events. *Child Dev* 66(2):346-359.
- Graber JA, Lewinsohn PM, Seeley JR, Brooks-Gunn J. 1997. Is psychopathology associated with the timing of pubertal development? *J Am Acad Child Adolesc Psychiatry* 36(12):1768-1776.
- Greiser CM, Greiser EM, Doren M. 2005. Menopausal hormone therapy and risk of breast cancer: a meta-analysis of epidemiological studies and randomized controlled trials. *Hum Reprod Update* 11(6):561-573.
- Grumbach MM, Styne DM. 2002. Puberty, ontogeny, neuroendocrinology, physiology, and disorders. In: Williams Textbook of Endocrinology (Larsen PR, Kronenberg HM, Melmed S, Plonsky KS, eds). Philadelphia: W.B. Saunders Co. 1115-1286.
- Guzman RC, Yang J, Rajkumar L, Thordarson G, Chen X, Nandi S. 1999. Hormonal prevention of breast cancer: mimicking the protective effect of pregnancy. *Proc Natl Acad Sci U S A* 96(5):2520-2525.
- Haslam SZ, Woodward TL. 2003. Host microenvironment in breast cancer development: epithelial-cell-stromal-cell interactions and steroid hormone action in normal and cancerous mammary gland. *Breast Cancer Res* 5(4): 208-215.
- Hayward C, Killen JD, Wilson DM, Hammer LD, Litt IF, Kraemer HC, et al. 1997. Psychiatric risk associated with early puberty in adolescent girls. *J Am Acad Child Adolesc Psychiatry* 36:255-262.
- Henderson BE, Feigelson HS. 2000. Hormonal carcinogenesis. *Carcinogenesis* 21(3):427-433.

- Henderson BE, Pike MC, Casagrande JT. 1981. Breast cancer and the oestrogen window hypothesis. *Lancet* 2(8242):363-364.
- Heo M, Leibel RL, Fontaine KR, Boyer BB, Chung WK, Koulu M, et al. 2002. A meta-analytic investigation of linkage and association of common leptin receptor (LEPR) polymorphisms with body mass index and waist circumference. *Int J Obes Relat Metab Disord* 26(5):640-646.
- Hiatt R, Breen N. 2008. The social determinants of cancer: a challenge for transdisciplinary science. *Am J Prev Med* 35(2 Suppl):S141-150.
- Hodgson E, Rose RL. 2007. Human metabolic interactions of environmental chemicals. *J Biochem Mol Toxicol* 21(4):182-186.
- Hoffstedt J, Eriksson P, Mottagui-Tabar S, Arner P. 2002. A polymorphism in the leptin promoter region (-2548 G/A) influences gene expression and adipose tissue secretion of leptin. *Horm Metab Res* 34(7):355-359.
- Hong EJ, Ji YK, Choi KC, Manabe N, Jeung EB. 2005. Conflict of estrogenic activity by various phthalates between in vitro and in vivo models related to the expression of Calbindin-D9k. *J Reprod Dev* 51(2):253-263.
- Howard BA, Gusterson BA. 2000. Human breast development. *J Mammary Gland Biol Neoplasia* 5(2):119-137.
- Howdeshell KL, Peterman PH, Judy BM, Taylor JA, Orazio CE, Ruhlen RL, et al. 2003. Bisphenol A is released from used polycarbonate animal cages into water at room temperature. *Environ Health Perspect* 111(9):1180-1187.

- Hsieh CC, Trichopoulos D, Katsouyanni K, Yuasa S. 1990. Age at menarche, age at menopause, height and obesity as risk factors for breast cancer: associations and interactions in an international case-control study. *Int J Cancer* 46(5):796-800.
- Ingman WV, Wyckoff J, Gouon-Evans V, Condeelis J, Pollard JW. 2006. Macrophages promote collagen fibrillogenesis around terminal end buds of the developing mammary gland. *Dev Dyn* 235(12):3222-3229.
- Iyengar P, Combs TP, Shah SJ, Gouon-Evans V, Pollard JW, Albanese C, et al. 2003. Adipocyte-secreted factors synergistically promote mammary tumorigenesis through induction of anti-apoptotic transcriptional programs and proto-oncogene stabilization. *Oncogene* 22(41):6408-6423.
- Jasik CB, Lustig RH. 2008. Adolescent obesity and puberty: the "perfect storm". *Ann N Y Acad Sci* 1135:265-279.
- Jessani N, Humphrey M, McDonald WH, Niessen S, Masuda K, Gangadharan B, et al. 2004. Carcinoma and stromal enzyme activity profiles associated with breast tumor growth in vivo. *Proc Natl Acad Sci U S A* 101(38):13756-13761.
- John EM, Kelsey JL. 1993. Radiation and other environmental exposures and breast cancer. *Epidemiol Rev* 15(1):157-162.
- Kadlubar FF, Berkowitz GS, DeLongchamp RR, Wang C, Green BL, Tang G, et al. 2003. The CYP3A4*1B variant is related to the onset of puberty, a known risk factor for the development of breast cancer. *Cancer Epidemiol Biomarkers Prev* 12(4):327-331.

Kaplowitz PB. 2008. Link between body fat and the timing of puberty. *Pediatrics* 121 Suppl 3: S208-217.

Kariagina A, Aupperlee MD, Haslam SZ. 2008. Progesterone receptor isoform functions in normal breast development and breast cancer. *Crit Rev Eukaryot Gene Expr* 18(1):11-33.

Kelsey J, Bernstein L. 1996. Epidemiology and prevention of breast cancer. *Annu Rev Public Health* 17:47-67.

Knight CH, Sorensen A. 2001. Windows in early mammary development: critical or not? *Reproduction* 122(3):337-345.

Kotsopoulos J, Lubinski J, Lynch HT, Klijn J, Ghadirian P, Neuhausen SL, et al. 2007. Age at first birth and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *Breast Cancer Res Treat* 105(2):221-228.

Kovacs M. 1992. Children's Depression Inventory manual. North Tonawanda, NY: Multi-Health Systems, Inc.

Krishnan AV, Stathis P, Permuth SF, Tokes L, Feldman D. 1993. Bisphenol-A: an estrogenic substance is released from polycarbonate flasks during autoclaving. *Endocrinology* 132(6):2279-2286.

Lambe M, Hsieh C, Trichopoulos D, Ekblom A, Pavia M, Adami HO. 1994. Transient increase in the risk of breast cancer after giving birth. *N Engl J Med* 331(1):5-9.

Lamminen T, Huhtaniemi I. 2001. A common genetic variant of luteinizing hormone; relation to normal and aberrant pituitary-gonadal function. *Eur J Pharmacol* 414(1):1-7.

- Land CE, Tokunaga M, Koyama K, Soda M, Preston DL, Nishimori I, et al. 2003. Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950-1990. *Radiat Res* 160(6):707-717.
- Lawson JS. 1999. The link between socioeconomic status and breast cancer--a possible explanation. *Scand J Public Health* 27(3):203-205.
- Lee JM, Appugliese D, Kaciroti N, Corwyn RF, Bradley RH, Lumeng JC. 2007. Weight status in young girls and the onset of puberty. *Pediatrics* 119(3): e624-630.
- Lee RE, Cubbin C. 2002. Neighborhood context and youth cardiovascular health behaviors. *Am J Public Health* 92(3):428-436.
- MacMahon B, Trichopoulos D, Brown J, Andersen AP, Aoki K, Cole P, et al. 1982a. Age at menarche, probability of ovulation and breast cancer risk. *Int J Cancer* 29(1):13-16.
- MacMahon B, Trichopoulos D, Brown J, Andersen AP, Cole P, deWaard F, et al. 1982b. Age at menarche, urine estrogens and breast cancer risk. *Int J Cancer* 30(4):427-431.
- Maffini MV, Soto AM, Calabro JM, Ucci AA, Sonnenschein C. 2004. The stroma as a crucial target in rat mammary gland carcinogenesis. *J Cell Sci* 117(Pt 8): 1495-1502.
- Magnusson CM, Roddam AW, Pike MC, Chilvers C, Crossley B, Hermon C, et al. 2005. Body fatness and physical activity at young ages and the risk of breast cancer in premenopausal women. *Br J Cancer* 93(7):817-824.

- Massart F, Parrino R, Seppia P, Federico G, Saggese G. 2006. How do environmental estrogen disruptors induce precocious puberty? *Minerva Pediatr* 58(3):247-254.
- Matthews JB, Twomey K, Zacharewski TR. 2001. In vitro and in vivo interactions of bisphenol A and its metabolite, bisphenol A glucuronide, with estrogen receptors alpha and beta. *Chem Res Toxicol* 14(2):149-157.
- McClintock MK, Conzen SD, Gehler S, Masi C, Olopade F. 2005. Mammary cancer and social interactions: identifying multiple environments that regulate gene expression throughout the life span. *J Gerontol B Psychol Sci Soc Sci* 60 Spec No 1:32-41.
- McElroy JA SM, Trentham-Dietz A, Hampton JM, Newcomb PA. 2006. Cadmium exposure and breast cancer risk. *J Natl Cancer Inst* 98(12):869-873.
- Miyoshi K, Meyer B, Gruss P, Cui Y, Renou JP, Morgan FV, et al. 2002. Mammary epithelial cells are not able to undergo pregnancy-dependent differentiation in the absence of the helix-loop-helix inhibitor Id2. *Mol Endocrinol* 16(12): 2892-2901.
- Moos RH. 1990. Conceptual and empirical approaches to developing family-based assessment procedures: resolving the case of the Family Environment Scale. *Fam Process* 29(2): 199-208; discussion 209-111.
- Morello-Frosch R, Jesdale BM. 2006. Separate and unequal: residential segregation and estimated cancer risks associated with ambient air toxics in U.S. metropolitan areas. *Environ Health Perspect* 114(3):386-393.

- Morland K, Wing S, Diez Roux A, Poole C. 2002. Neighborhood characteristics associated with the location of food stores and food service places. *Am J Prev Med* 22(1):23-29.
- Morris JJ, Seifter E. 1992. The role of aromatic hydrocarbons in the genesis of breast cancer. *Med Hypotheses* 38(3):177-184.
- Muraoka-Cook RS, Shin I, Yi JY, Easterly E, Barcellos-Hoff MH, Yingling JM, et al. 2006. Activated type I TGFbeta receptor kinase enhances the survival of mammary epithelial cells and accelerates tumor progression. *Oncogene* 25(24):3408-3423.
- Mustanski BS, Viken RJ, Kaprio J, Pulkkinen L, Rose RJ. 2004. Genetic and environmental influences on pubertal development: longitudinal data from Finnish twins at ages 11 and 14. *Dev Psychol* 40(6):1188-1198.
- Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. 2006. Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA* 295(13):1549-1555.
- Olea N, Pulgar R, Perez P, Olea-Serrano F, Rivas A, Novillo-Fertrell A, et al. 1996. Estrogenicity of resin-based composites and sealants used in dentistry. *Environ Health Perspect* 104(3):298-305.
- Ong KK, Ahmed ML, Dunger DB. 1999. The role of leptin in human growth and puberty. *Acta Paediatr Suppl* 88(433):95-98.
- Ouyang F, Perry MJ, Venners SA, Chen C, Wang B, Yang F, et al. 2005. Serum DDT, age at menarche, and abnormal menstrual cycle length. *Occup Environ Med* 62(12):878-884.

Page-McCaw A, Ewald AJ, Werb Z. 2007. Matrix metalloproteinases and the regulation of tissue remodelling. *Nat Rev Mol Cell Biol* 8(3):221-233.

Park SK, Kang D, McGlynn KA, Garcia-Closas M, Kim Y, Yoo KY, et al. 2008. Intrauterine environments and breast cancer risk: meta-analysis and systematic review. *Breast Cancer Res* 10(1):R8.

Pathak DR. 2002. Dual effect of first full term pregnancy on breast cancer risk: empirical evidence and postulated underlying biology. *Cancer Causes Control* 13(4):295-298.

Pathak DR, Osuch JR, He J. 2000. Breast carcinoma etiology: current knowledge and new insights into the effects of reproductive and hormonal risk factors in black and white populations. *Cancer* 88(5 Suppl):1230-1238.

Paukku K, Silvennoinen O. 2004. STATs as critical mediators of signal transduction and transcription: lessons learned from STAT5. *Cytokine Growth Factor Rev* 15(6):435-455.

Perez Mayorga M, Gromoll J, Behre HM, Gassner C, Nieschlag E, Simoni M. 2000. Ovarian response to follicle-stimulating hormone (FSH) stimulation depends on the FSH receptor genotype. *J Clin Endocrinol Metab* 85(9):3365-3369.

Pike MC, Spicer DV, Dahmouch L, Press MF. 1993. Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. *Epidemiol Rev* 15(1):17-35.

Pukkala E, Kesminiene A, Poliakov S, Ryzhov A, Drozdovitch V, Kovgan L, et al. 2006. Breast cancer in Belarus and Ukraine after the Chernobyl accident. *Int J Cancer* 119(3):651-658.

- Quinlan RJ. 2003. Father absence, parental care, and female reproductive development. *Evol Hum Behav* 24(6):376-390.
- Radloff L. 1977. The CES-D scale: A self-report depression scale for research in the general population. *Appl Psychol Meas* 1:385-401.
- Ramji DP, Foka P. 2002. CCAAT/enhancer-binding proteins: structure, function and regulation. *Biochem J* 365(Pt 3):561-575.
- Ramos JG, Varayoud J, Sonnenschein C, Soto AM, Munoz De Toro M, Luque EH. 2001. Prenatal exposure to low doses of bisphenol A alters the periductal stroma and glandular cell function in the rat ventral prostate. *Biol Reprod* 65(4):1271-1277.
- Reynolds CR, Kamphaus RW. 2002. The clinician's guide to the Behavior Assessment System for Children (BASC). New York, NY: Guildford Press.
- Reynolds P, Hurley S, Goldberg DE, Anton-Culver H, Bernstein L, Deapen D, et al. 2004. Active smoking, household passive smoking, and breast cancer: evidence from the California Teachers Study. *J Natl Cancer Inst* 96(1):29-37.
- Rogol AD. 1998. Leptin and puberty. *J Clin Endocrinol Metab* 83(4):1089-1090.
- Romans SE, Martin JM, Gendall K, Herbison GP. 2003. Age of menarche: the role of some psychosocial factors. *Psychol Med* 33(5):933-939.
- Rosenfield PL. 1992. The potential of transdisciplinary research for sustaining and extending linkages between the health and social sciences. *Soc Sci Med* 35(11):1343-1357.

Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. 2002. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 288(3):321-333.

Routledge EJ, White R, Parker MG, Sumpter JP. 2000. Differential effects of xenoestrogens on coactivator recruitment by estrogen receptor (ER) alpha and ERbeta. *J Biol Chem* 275(46):35986-35993.

Rudland PS. 1993. Epithelial stem cells and their possible role in the development of the normal and diseased human breast. *Histol Histopathol* 8(2):385-404.

Russo IH, Russo J. 1996. Mammary gland neoplasia in long-term rodent studies. *Environ Health Perspect* 104(9):938-967.

Russo J, Balogh GA, Russo IH. 2008. Full-term pregnancy induces a specific genomic signature in the human breast. *Cancer Epidemiol Biomarkers Prev* 17(1):51-66.

Russo J, Calaf G, Russo IH. 1993. A critical approach to the malignant transformation of human breast epithelial cells with chemical carcinogens. *Crit Rev Oncog* 4(4):403-417.

Russo J, Russo IH. 2008. Breast development, hormones and cancer. *Adv Exp Med Biol* 630:52-56.

Saelens BE, Sallis JF, Frank LD. 2003. Environmental correlates of walking and cycling: findings from the transportation, urban design, and planning literatures. *Ann Behav Med* 25(2):80-91.

- Schedin P, O'Brien J, Rudolph M, Stein T, Borges V. 2007. Microenvironment of the involuting mammary gland mediates mammary cancer progression. *J Mammary Gland Biol Neoplasia* 12(1):71-82.
- Seagroves TN, Krnacik S, Raught B, Gay J, Burgess-Beusse B, Darlington GJ, et al. 1998. C/EBPbeta, but not C/EBPalpha, is essential for ductal morphogenesis, lobuloalveolar proliferation, and functional differentiation in the mouse mammary gland. *Genes Dev* 12(12):1917-1928.
- Selevan SG, Rice DC, Hogan KA, Euling SY, Pfahles-Hutchens A, Bethel J. 2003. Blood lead concentration and delayed puberty in girls. *N Engl J Med* 348(16):1527-1536.
- Shore RE, Hildreth N, Dvoretzky P, Andresen E, Moseson M, Pasternack B. 1993. Thyroid cancer among persons given X-ray treatment in infancy for an enlarged thymus gland. *Am J Epidemiol* 137(10):1068-1080.
- Sivaraman L, Medina D. 2002. Hormone-induced protection against breast cancer. *J Mammary Gland Biol Neoplasia* 7(1):77-92.
- Smedley BD, Syme SL. 2001. Promoting health: intervention strategies from social and behavioral research. *Am J Health Promot* 15(3):149-166.
- Sonnenschein C, Soto AM. 1998. An updated review of environmental estrogen and androgen mimics and antagonists. *J Steroid Biochem Mol Biol* 65(1-6): 143-150.
- Sonnenschein E, Toniolo P, Terry MB, Bruning PF, Kato I, Koenig KL, et al. 1999. Body fat distribution and obesity in pre- and postmenopausal breast cancer. *Int J Epidemiol* 28(6):1026-1031.

Sternlicht MD, Kouros-Mehr H, Lu P, Werb Z. 2006. Hormonal and local control of mammary branching morphogenesis. *Differentiation* 74(7):365-381.

Stingl J, Eirew P, Ricketson I, Shackleton M, Vaillant F, Choi D, et al. 2006. Purification and unique properties of mammary epithelial stem cells. *Nature* 439(7079):993-997.

Stokols D, Fuqua J, Gress J, Harvey R, Phillips K, Baezconde-Garbanati L, et al. 2003. Evaluating transdisciplinary science. *Nicotine Tob Res* 5 Suppl 1: S21-39.

Suzuki A, Sugihara A, Uchida K, Sato T, Ohta Y, Katsu Y, et al. 2002. Developmental effects of perinatal exposure to bisphenol-A and diethylstilbestrol on reproductive organs in female mice. *Reprod Toxicol* 16(2):107-116.

Titus-Ernstoff L, Longnecker MP, Newcomb PA, Dain B, Greenberg ER, Mittendorf R, et al. 1998. Menstrual factors in relation to breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 7(9):783-789.

Tokunaga M, Land CE, Tokuoka S. 1991. Follow-up studies of breast cancer incidence among atomic bomb survivors. *J Radiat Res (Tokyo)* 32 Suppl: 201-211.

TREC (Transdisciplinary Research on Energetics and Cancer). 2008. Available: <http://cancercontrol.cancer.gov/trec/> [accessed 31 March 2009].

Tremblay L, Frigon JY. 2005. Precocious puberty in adolescent girls: a biomarker of later psychosocial adjustment problems. *Child Psychiatry Hum Dev* 36(1):73-94.

Trichopoulos D, Lagiou P, Adami HO. 2005. Towards an integrated model for breast cancer etiology: the crucial role of the number of mammary tissue-specific stem cells. *Breast Cancer Res* 7(1):13-17.

- Vasiliu O, Muttineni J, Karmaus W. 2004. In utero exposure to organochlorines and age at menarche. *Hum Reprod* 19(7):1506-1512.
- Verla-Tebit E, Chang-Claude J. 2005. Anthropometric factors and the risk of premenopausal breast cancer in Germany. *Eur J Cancer Prev* 14(4):419-426.
- Vihko R, Apter D. 1984. Endocrine characteristics of adolescent menstrual cycles: impact of early menarche. *J Steroid Biochem* 20(1):231-236.
- Weiderpass E, Braaten T, Magnusson C, Kumle M, Vainio H, Lund E, et al. 2004. A prospective study of body size in different periods of life and risk of premenopausal breast cancer. *Cancer Epidemiol Biomarkers Prev* 13(7): 1121-1127.
- Wicha MS. 2008. Cancer stem cell heterogeneity in hereditary breast cancer. *Breast Cancer Res* 10(2):105.
- Windham GC, Bottomley C, Birner C, Fenster L. 2004. Age at menarche in relation to maternal use of tobacco, alcohol, coffee, and tea during pregnancy. *Am J Epidemiol* 159(9):862-871.
- Wiseman BS, Werb Z. 2002. Stromal effects on mammary gland development and breast cancer. *Science* 296(5570):1046-1049.
- Wolff MS, Britton JA, Boguski L, Hochman S, Maloney N, Serra N, et al. 2008. Environmental exposures and puberty in inner-city girls. *Environ Res* 107(3):393-400.

- Wolff MS, Collman GW, Barrett JC, Huff J. 1996. Breast cancer and environmental risk factors: epidemiological and experimental findings. *Annu Rev Pharmacol Toxicol* 36:573-596.
- Wu T, Buck GM, Mendola P. 2003. Blood lead levels and sexual maturation in U.S. girls: the Third National Health and Nutrition Examination Survey, 1988-1994. *Environ Health Perspect* 111(5):737-741.
- Xie JW, Haslam SZ. 2007. Extracellular matrix, Rac1 signaling, and estrogen-induced proliferation in MCF-7 breast cancer cells. *Breast Cancer Res Treat*.
- Xue F, Michels KB. 2007. Intrauterine factors and risk of breast cancer: a systematic review and meta-analysis of current evidence. *Lancet Oncol* 8(12):1088-1100.
- Yen IH, Kaplan GA. 1998. Poverty area residence and changes in physical activity level: evidence from the Alameda County Study. *Am J Public Health* 88(11):1709-1712.
- Zacharewski TR, Meek MD, Clemons JH, Wu ZF, Fielden MR, Matthews JB. 1998. Examination of the in vitro and in vivo estrogenic activities of eight commercial phthalate esters. *Toxicol Sci* 46(2):282-293.