California Breast Cancer Research Program Prevention Initiatives (CBCPI)

Gaps Supplement

Targeted Scans of the 2007 "Gaps" Document "*Identifying Gaps in Breast Cancer Research: Addressing Disparities and the Roles of the Physical and Social Environment*"

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Introduction

In 2007, the California Breast Cancer Research Program (CBCRP's) published *Identifying Gaps in Breast Cancer Research: Addressing Disparities and the Roles of the Physical and Social Environment,* i.e., the "Gaps" document. The Gaps document was part of CBCRP's launch of its Special Research Initiatives – a five-year effort to select and fund the research that would lead to the most progress in finding answers to the questions:

- *What role does the environment play in breast cancer?*
- *Why do some groups of women bear a greater burden of this disease than others?*

To select the research for its Special Research Initiatives CBCRP followed a carefully-crafted, two-year, publicly-accessible strategy development process. An initial step in the process was the 2007 Gaps report reviewing previous research. The 2007 Gaps was not a comprehensive review of all research on the environment-breast cancer connection or the reasons why some groups of women bear more of the burden of the disease. It was instead a review of existing research—gathered from a wide breadth of sources—pointed toward discovering research areas that show some connection with the disease, and recommending further investigations that are likely to make the most difference toward eliminating the death and suffering caused by breast cancer.

The following report, *Targeted Scans of the 2007 Gaps Document for Research Conducted between 2007 and 2012,* presents updated information about the findings and recommendations in the 2007 Gaps document. The targeted scans presented here were created as one component of the Science Assessment that will help to inform the Steering Committee, Strategy Advisors and CBCRP's Council in their efforts determining future research directions for the Prevention Initiatives.

The targeted scans presented are a snapshot of the research that has transpired since publication of the Gaps document in 2007. The scans are not a systematic review and update of the literature on each of the topics, but rather are provided to document any substantive progress on the research questions in the five years that have passed since the Gaps was published.

Notably, the chapters of the 2007 Gaps report summarized the evidence—from in vitro, animal, and human studies—for individual environmental agents in isolation from one another. There remain obvious shortcomings to this kind of analysis. However, the hope expressed in the 2007 Gaps remains, i.e., that the atomized organization of these chapters will, nevertheless, inspire the reader to consider the various ways in which these individual agents might interact with one another in a web of causality and, in so doing, reveal potential avenues of inquiry that would be

fruitful to pursue.

Methods

For each chapter in the 2007 Gaps document a PubMed search was conducted to identify any substantive change in the findings and research recommendations presented in the 2007 Gaps. The search was limited to the period between 2007 and 2012 and English language papers. As the scans were conducted sequentially, the time period covered by the scans may vary by months.

Search terms were identified by: (1) a review of the MeSH terms assigned to five papers deemed relevant to the topic that were cited in the 2007 Gaps chapter being scanned, and reflect a variety of journals, authors and publication dates; (2) a search of the MeSH database for "breast cancer" terms; and (3) identifying all the unique terms used in the 2007 Gaps chapter related to exposure and breast cancer health outcomes. This initial search strategy produced a pool of papers that were further culled using search terms that eliminated extraneous papers and zeroed in on the most relevant papers. Titles and abstracts were scanned for relevance. The papers included were generally not critiqued, but rather reflect the conclusions of the study authors.

Each scan was conducted by one of a team of eight scientists. References that were known to the reviewer but may not have been identified in PubMed were also incorporated into each scan.

The findings of the PubMed search were then compared to the "Summary and Future Directions for Research" section at the end of the 2007 Gaps chapter to assess whether the papers represented a significant change in the state of the science, i.e., one that would fundamentally shift the questions originally posed in the Gaps document.

Results

Results of the targeted scans are organized below according to order of the chapters in the 2007 Gaps document. Each chapter is organized by listing the topics in the "Summary and Future Directions for Research" section of the 2007 Gaps chapter adjacent to the finding of the scan, so that the 2007 and 2012 findings can be compared.

Section I: Exposures from the Physical Environment and Breast Cancer

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A. Secondhand Smoke

Abstract

Note: The targeted scan of this chapter differs methodologically from the other chapters in this report as it is based on a comprehensive review of the literature published in 2012.

The 2007 Gaps summary found that studies on both active smoking and secondhand smoking and breast cancer had noted discrepancies in their study results and did not pay attention to the timing of exposure. For example, whereas in 2006, a report by the Surgeon General concluded, "The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke and breast cancer," [1] a 2006 review of the evidence by the California Environmental Protection Agency found, "overall, the weight of evidence is consistent with a causal association between ETS [environmental tobacco smoke] exposure and breast cancer in younger, primarily pre-menopausal women." [2] A 2012 review was consistent with the Cal-EPA reveiw, finding "the most recent weight of the evidence has suggested a potentially casual role for active smoking and breast cancer, particularly for long-term heavy smoking and smoking initiation at an early age… Recent studies evaluating the possible modifying role of polymorphisms in genes involved in the metabolism of tobacco products, particularly NAT2, have contributed another dimension to these assessments, although to date that evidence remains equivocal."[3]

2007 Gaps Summary **Organized by topic in chapter summary with the actual language of the topic quoted**	**2012 Update Based on a Published Review (3)**
A 2006 review of the evidence by the California Environmental Protection Agency found, "overall, the weight of evidence is consistent with a causal association between ETS [environmental tobacco smoke] exposure and breast cancer in younger, primarily pre-menopausal women." [2] More research is needed to discern whether the disrepencies in study results are a function of methodological flaws related to study design or are a reflection of varying risks associated with differing times of exposure and/or subpopulations of susceptible individuals. The need for more cohort studies with full characterization of ETS/SHS exposures across time periods and settings is glaringly apparent. It is also critical to create a "clean" referent group in all these studies that includes lifetime never smokers with no ETS/SHS exposures for any time period or from any setting.	Active smoking is likely to pose a modest risk for breast cancer. There is also evidence of increased risk among women who intitiated smoking at an early age and/or who smoked heavily prior to a first full term pregnancy. As active smoking rates have declined in the population, secondhand smoke exposure has become a more important source of tobacco exposure and has been the subject of increasing policy restrictions on smoking in public places. [3]
It is very important not only to construct a full lifetime exposure profile for ETS/ SHS exposure, but also to examine the risks in the context of the hormonal milieu in which the exposure occurs. The provocative finding recently reported by Manjer and colleagues—of an increased risk of breast cancer associated with active smoking only among women with high levels of endogenous estrogens—deserves more attention.	

2007 Gaps Summary **Organized by topic in chapter summary with the actual language of the topic quoted**	**2012 Update Based on a Published Review (3)**
Consideration of genotypes both that affect the activation, detoxification, DNA repair, and cell cycle control/apoptotic processes in tobacco-related carcinogens, as well as estrogen metabolism, may help to reveal the mechanistic pathway by which smoking exposures may differentially influence risk during different time periods of life. While most of the studies to date have taken into account confounding by other known breast cancer risk factors, more attention to some covariates may be warranted.	
Given that both active and passive smoking are strongly correlated with alcohol consumption, this issue deserves further attention and highlights the importance of going beyond simple covariate adjustment to examining the potential for effect modification for this and other covariates. Elucidating the breast cancer risk associated with both active and passive smoking during early life may be particularly important in helping to provide the impetus to eliminate these exposures.	

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B. Environmental Chemicals/Pollutants

1. Air Pollutants, Fuels and Additives

Abstract

Most studies related to air pollutants, fuels and additives focus on how specific types of exposures impact DNA or hormones related to breast cancer risk. Human and animal-based cell studies focused on estrogen receptors and polymorphisms of certain gene types. A number of meta-analysis or summary studies provide further evidence for the connections between workplace and neighborhood exposure to air pollution and breast cancer risk, including a large population study in Europe that compared occupational exposures for both men and women for a number of difference cancers. There was overlap between this search and other topics, including cigarette smoke (since secondhand smoke is considered an air pollutant) and dietary intake e.g. smoked meats. Polycyclic aromatic hydrocarbons (PAHs) were considered a key gap in the 2007 scan and these were only marginally addressed in more recent research. The gap identified in research that considers neighborhood-level disparities and air pollutants is still there with few studies looking at any neighborhood level variables and air exposures.

Bullet point summary:

- Human and animals cell studies still dominated the research on exposure to certain types of air pollutants and breast cancer risk via DNA and other genotype changes.
- Little research still exists on neighborhood-level variables and disparities in exposure to air pollution as it relates to breast cancer risks.
- There was also a gap in literature that examined concentrations of various pollutants in indoor air quality, where women spend most of their time.
- Polycyclic aromatic hydrocarbons (PAHs) were identified as a key area for more research. A few studies have examined PAHs and other derivatives but there has not been a large push into this line of inquiry.

2007 Gaps Summary Organized by topic in chapter summary with the actual language of the topic quoted	2012 Update Targeted Scan
Additional study of the impact of the parent compounds, metabolites and combustion byproducts is critical. Primary research into these issues is needed to identify possible links to breast cancer.	Human Experimental Cell Culture: Diesel exhaust particles (DEPs) cause many adverse health problems, and reports indicate increased risk of breast cancer in men and women through exposure to gasoline and vehicle exhaust. This study clarifies previous work that isolated two nitrophenols from DEPs-3-methyl-4-nitrophenol (4-nitro-m-cresol; PNMC) and 4-nitro-3-phenylphenol (PNMPP)-and showed that they had estrogenic and anti-androgenic activities. First, comet assay was used to detect the genotoxicity of PNMC and PNMPP in a CHO cell line. At all doses tested, PNMC and PNMPP showed negative genotoxicity, indicating that they had no tumor initiating activity. These results clearly indicate that PNMC and PNMPP do not show genotoxicity but act as tumor promoters in an estrogen receptor α-predominant breast cancer cell line [1]. Animal Study: Environmental pollution with nitroaromatic compounds may pose health hazards. The study examined the tumorigenicity in female Sprague-Dawley rats of 2,7-dinitrofluorene (2,7-diNF) and 9-oxo-2,7-diNF administered by intraperitoneal (i.p.) and oral routes at 10 μmol/kg body weight, 3 times per week for 4 weeks. The preferential display of carcinogenicity and genotoxicity in the mammary gland by low doses of 2,7-diNF signifies its potential relevance for environmental breast cancer [2].
Methodological problems include inadequate dioxin and TCDD exposure assessment, lack of unexposed populations, and lack of preclinical markers to identify associations that may be obscured by disease latency. Work on identifying an appropriate biomarker is continuing. It may also be important to study specific congeners, rather than look at total dioxins.	Human Experimental Cell Culture: This study examined dioxin exposure & its known endocrine disrupting properties by examining the effect of 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) on estrogen synthesis in the breast cancer cells MCF-7. Results showed that TCDD increased the aromatase activity in a time- and dose-dependent manner. Further investigation indicated that TCDD slowed down the CYP19 mRNA degradation with concurrent activation of ERK. This demonstrates that TCDD might induce a post-transcriptional regulatory mechanism of gene expression in breast cancer cells [3]. Retrospective Cohort Study: 2,3,7,8-Tetrachlorodibenzo-para-dioxin (TCDD), a widespread environmental contaminant, disrupts multiple endocrine pathways. In 1996, the Seveso Women's

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	Health Study (SWHS), was initiated to examine health effects after a major exposure to TCDD on reproductive health of the women. A total of 833 women participated in the 2008 follow-up study. The adjusted hazard ratio (HR) associated with a 10-fold increase in serum TCDD for all cancers combined was significantly increased [adjusted HR = 1.80; 95% confidence interval (CI): 1.29, 2.52]. For breast cancer, the HR was increased, but not significantly (adjusted HR = 1.44; 95% CI: 0.89, 2.33). This all-female study adds to the epidemiologic evidence that TCDD is a multisite carcinogen [4].
It has been difficult to measure or estimate exposure to PAHs, since exposure occurs over a lifetime from multiple sources… Improvements in biomonitoring methods, additional ambient and personal air pollution monitoring, and refined modeling of relationships between environmental databases and individual exposure will improve future epidemiologic studies. [This mirrors other parts of the Gap Scan that call for more longituditional research and/or consideration of age and length of exposure]	Human Experimental Cell Culture: Diet and environmental exposures to aromatic and heterocyclic amines, and polycyclic aromatic hydrocarbons, are thought to be etiologic factors for breast cancer risk. This study quantified the major DNA adduct derived from one member of each of these classes of carcinogens in epithelial cell DNA isolated from human breast milk. The presence of ABP adducts was significantly associated with the use of hair coloring products (OR=11.2, 95% CI=1.1-109.2) but not tobacco usage and metabolic genotype can be a susceptibility factor [5]. Human Population-based Case-Control Study: This case-control study of breast cancer involved women, aged 35-79, residents of Erie and Niagara Counties. Cases had incident, primary, histologically confirmed breast cancer. Using lifetime residential histories, exposure to traffic emissions was modeled for each woman using her residence as a proxy. Higher exposure to traffic emissions at the time of menarche was associated with increased risk of premenopausal breast cancer (OR 2.05, 95% CI 0.92-4.54, p for trend 0.03); and at the time of a woman's first birth for postmenopausal breast cancer (OR 2.57, 95% CI 1.16-5.69, p for trend 0.19). Statistically significant associations were limited to lifetime non-smokers; there was a significant interaction between exposure at time of menarche and smoking for premenopausal women [7].
Better biological measures are needed and work is underway to develop new biomarkers. To better understand the role of PAHs in breast cancer risk, epidemiologists could identify and	Human Population-Based Case Control Study: The authors investigated lifetime passive cigarette smoke exposures, 36 variants in 12 carcinogen-metabolizing genes, and breast cancer risk among Ontario, Canada, women (for 920 breast cancer cases and 960 controls) who had never smoked (2003-2004). Significant interactions were observed between certain types of passive smoke exposure

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monitor susceptible subpopulations or highly-exposed workers over time, improving the exposure estimates.	and genetic variants in CYP2E1, NAT2, and UGT1A7. Although the results of this study were largely null, it is possible that premenopausal women exposed to passive smoke or carrying certain genetic variants may be at higher risk of breast cancer [8]. Population-based case-control study: Associations between detectable polycyclic aromatic hydrocarbon (PAH)-DNA adducts and breast cancer risk were examined in Long Island, New York among 1,053 cases and 1,102 controls. The presence of at least one variant allele in XPD was associated with a 25% increase in the odds ratio [OR, 1.25; 95% confidence interval (95% CI), 1.04-1.50] for breast cancer. This study suggests that the risk of breast cancer may be elevated among women with polymorphisms in NER pathway genes and detectable PAH-DNA adducts [9]. Human Population-Based Case Control Study: Another study suggests that there is no significant correlation between CYP1A1 M1/ CYP1A1 M2 polymorphism and occurrence of breast cancer in South Indian women [10]. Population-based case-control study: Between 1996 and 1997 a case-control study was conducted in Montreal, Quebec. Cases comprised 556 women, aged 50-75 years, with incident malignant breast cancer, and their controls were 613 women with other cancers, frequency matched for age, date of diagnosis and hospital. An expert team of chemists and industrial hygienists translated their job histories into exposure to about 300 agents. Certain occupational exposures appear to increase the risk of developing postmenopausal breast cancer & findings are consistent with the hypothesis that breast tissue is more sensitive to adverse effects if exposure occurs when breast cells are still proliferating [11]. Human Experimental Cell Culture: This study investigated the effects of five ClPAHs with three to five rings and the corresponding parent PAHs on the expression of CYP1A1 and 1B1 in human breast cancer MCF-7 cells. Results suggest that estrogenic action mediated ER signaling through AhR

2007 Gaps Summary Organized by topic in chapter summary with the actual language of the topic quoted	2012 Update Targeted Scan
	activation does not necessarily occur for every ligand that can activate AhR [12]. Population-based cohort study: This study presents up to 45 years of cancer incidence data by occupational category for the Nordic populations. The study covers the 15 million people aged 30-64 years in the 1960, 1970, 1980/1981 and/or 1990 censuses in Denmark, Finland, Iceland, Norway and Sweden, and the 2.8 million incident cancer cases diagnosed in these people in a follow-up until about 2005. The occupational variation in the risk of female breast cancer (the most common cancer type in the present series, 373,361 cases) was larger, and there was a tendency of physically demanding occupations to show SIRs below unity. Women in occupations which require a high level of education have, on average, a higher age at first child-birth and elevated breast cancer incidence. Women in occupational categories with the highest average number of children had markedly lower incidence. In male breast cancer (2,336 cases), which is not affected by the dominating reproductive factors, there was a suggestion of an increase in risk in occupations characterized by shift work. Night-shift work was recently classified as probably carcinogenic, with human evidence based on breast cancer research. In addition to the cancer data demonstrated in the present publication, the NOCCA project produced Nordic Job Exposure Matrix [13]. Findings from another case-control study suggest that some environmental chemicals are possible mammary carcinogens among male breast cancer patients in Europe. Petrol, organic petroleum solvents or polycyclic aromatic hydrocarbons are suspect because of the consistent elevated risk of male breast cancer observed in motor vehicle mechanics. Endocrine disruptors such as alkylphenolic compounds may play a role in breast cancer [14].
Other than PAHs, data on exposure to hazardous air pollutants, such as MTBE, acetaldehyde and 1,3-butadiene, are very limited. These exposures vary geographically in California.	Meta-Analysis: The metabolism of polycyclic aromatic hydrocarbons and other procarcinogens through CYP1B1 may well lead to their activation. Apart from the extensively studied Val432Leu polymorphism, three single nucleotide polymorphisms in CYP1B1 have been studied concerning their potential implication in terms of breast cancer risk: Arg48Gly, Ala119Ser and Asn453Ser. This meta-analysis suggests that CYP1B1 Arg48Gly, Ala119Ser and Asn453Ser polymorphisms are not associated

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	with breast cancer risk. Studies on Chinese populations are needed, to elucidate race-specific effects on East Asian populations, if any [15]. Population-based case-control study: p53 participates in cell cycle control, programmed cell death/apoptosis, and DNA repair, all pathways involved in carcinogenesis. TP53 variants may influence p53 function. Genotypes and haplotypes were determined using long-range PCR in a sample of 578 cases and 390 controls. These results suggest that cigarette smoking may influence breast cancer risk through interaction with p53 [16]. Human Population-Based Case Control Study: Cytochrome P4501A2 (CYP1A2) is involved in breast carcinogen activation [aromatic (AAs) and heterocyclic amines (HAs), polycyclic aromatic hydrocarbons (PAHs)]. 125 BC cases and 43 non-cancer controls were genotyped. They found that the -3860A variant, independently from environmental factors, as well as by interacting with fried foods (p=0.025) and indoor exposure to pollutants (p=0.050), reduced the risk of BC (p=0.025), whereas its interaction with coffee (p=0.045) increased the BC risk. This is the first study indicating that the -3860A variant, by decreasing CYP1A2 activity, modifies BC risk by interacting with environmental factors, thereby supporting the hypothesis that reduced CYP1A2 activity contributes to BC risk in different ways [17]. Human population-based case-control study: 250 breast cancer patients and the same number of healthy age-matched controls were analyzed for the polymorphism of CYP1A1*2 by polymerase chain reaction-restriction fragment length polymorphism. Results suggest a significant correlation between CYP1A1*2 expression and the occurrence of breast cancer.
It may be most useful to study air contaminants together, given that actual exposure is never limited to a single component. Future studies should also take into account that ambient concentrations of pollutants are not a good indicator of indoor where people	Environmental air quality study: 2009 household exposure study tested for multiple compounds hypothesized to affect breast cancer. The study analyzed indoor and outdoor air from 40 homes in industrial Richmond, California, and 10 in rural Bolinas, California, for 153 compounds, including particulates and endocrine disruptors. The researchers concluded, "indoor air quality is an important indicator of the cumulative impact of outdoor emissions in fence-line communities. Policies based on outdoor monitoring alone add to environmental injustice concerns in communities that host

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spend most of their time.	polluters" [21].
Finally, future research into the relationship between air pollutants and breast cancer should consider the significant potential confounding with neighborhood level disparities. Recent research suggests that disparities associated with ambient air toxics are affected by segregation and that these exposures may have health significance for populations across racial lines. These interactions between the physical environment and social disparities deserve additional research.	Critical Review/Summary Study: Key recurring themes in the growing scientific literature on breast cancer and environmental risk factors are: (a) the importance of understanding the effects of mixtures and interactions between various chemicals, radiation and other risk factors for the disease; and (b) the increasing evidence that timing of exposures matters, with exposures during early periods of development being particularly critical to later risk of developing breast cancer. A review of the scientific literature shows several classes of environmental factors have been implicated in an increased risk for breast cancer, including hormones and endocrine-disrupting compounds, organic chemicals and by-products of industrial and vehicular combustion, and both ionizing and non-ionizing radiation [19]. Population-based Case-Control Study: Participants were 787 Cape Cod, Massachusetts, women diagnosed with breast cancer between 1988 and 1995 and 721 controls. Telephone interviews asked about cleaning product use, beliefs about breast cancer etiology, and established and suspected breast cancer risk factors. Breast cancer risk increased two-fold in the highest compared with lowest quartile of self-reported combined cleaning product use (Adjusted OR = 2.1, 95% CI: 1.4, 3.3) and combined air freshener use (Adjusted OR = 1.9, 95% CI: 1.2, 3.0). Recall bias may influence higher odds ratios for product use among participants who believed that chemicals and pollutants contribute to breast cancer. Alternatively, the influence of experience on beliefs is another explanation, illustrated by the protective odds ratio for family history among women who do not believe heredity contributes "a lot" [20]. Environmental air quality study: This study compared an urban fence-line community (neighboring an oil refinery) and a nonindustrial community in an exposure study focusing on pollutants of interest with respect to breast cancer and environmental justice. The study analyzed indoor and outdoor air

2007 Gaps Summary Organized by topic in chapter summary with the actual language of the topic quoted	2012 Update Targeted Scan
	from 40 homes in industrial Richmond, California, and 10 in rural Bolinas, California, for 153 compounds, including particulates and endocrine disruptors. Eighty compounds were detected outdoors in Richmond and 60 in Bolinas; Richmond concentrations were generally higher. Indoor air quality is an important indicator of the cumulative impact of outdoor emissions in fence-line communities. Community-based participatory exposure research can contribute to science and stimulate and inform action on the part of community residents and policymakers [21].

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2. Persistent Organic Pollutants

Abstract

A substantial amount of research has been completed on persistent organic pollutants (POPs) and breast cancer that address the questions posed in the 2007 Gaps chapter. In particular, evidence that POPs contribute to a cocktail of estrogenic chemicals that act in concert to raise the risk of breast cancer is very strong. Nearly all of the chemicals that fall under the banner of persistent organic pollutants have been shown to display estrogenic qualities in cell culture studies and/or epidemiological studies. There is also a substantial body of evidence that developmental exposure to POPs alters mammary development, which may contribute to increased incidences of breast cancer. On the other hand, questions about the effect of POPs on lactation, the increased lethality of cancers associated with POPs, and the viability of using E-screen assays to assess internal exposure to xenoestrogens remain largely unanswered.

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Do POPs contribute to a cocktail of estrogenic chemicals that act in concert to raise the risk of breast cancer? Or, in practical terms, does the blood sera of women with breast cancer exhibit increased mitogenicity?	Human experimental cell culture: A study using transcriptional assays, competitive binding assays and bioluminescence resonance energy transfer (BRET) assays found that monohydroxylated PAHs elicit a biologically active response from ERβ in human breast cancer cells and potentially interfere with ERβ signaling pathways [1]. Human experimental cell culture: A study on the cellular effects of DDT, found that the chemical potentiates ER transcriptional activity, resulting in an increased expression of receptor target genes, including progesterone receptor, bcl-2, and trefoil factor 1 in a human MCF-7 breast cancer cell line [2]. Human epidemiological: A study of 50 women in Iran found that living next to factories that generate PAHs and dioxins – two xenoestrogens –was a major risk factor in premenopausal breast cancer (p=0.001, OR=4.8) [3]. Human experimental cell culture: Several studies found that TCDD altered estrogen receptor activity in MCF-7 breast cancer cell lines through a variety of mechanisms [4-9]. Review: In a review of the effect of environmental estrogens on mammary carcinogenesis, the authors note that "compounds with potent activity are mainly lipophilic organochlorine substances extremely resistant to biodegradation that accumulate in adipose tissue, a property that compensates their relatively weak affinity for ERs. The fact that most

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	investigations report an equipotent binding potency for ERa and ERb is suggestive of weak estrogen agonistic or antagonistic action depending on tissue ERa/ERb ratio [10]." Human experimental cell culture: E-SCREEN tests of triclosan, PFOS and PFOA found that all three compounds display estrogenic activity and that co-exposure to contaminants and 17-β estradiol produces anti-estrogenic effects [11]. Human epidemiological/Report: An analysis of human epidemiological studies found that environmental pollutants, including several POPs, were able to explain 38% of the variation in the rate of ER+ breast cancers and only 17% of the variation in rate of ER- cases, suggesting that the risk factors for the two types of cancer are different [12]. The results further expand on previous findings that ER+ breast cancers respond more strongly to estrogen than ER- breast cancers and many common environmental pollutants are EDCs. Human experimental cell culture: HBCD, a brominated flame retardant, displayed estrogen-like effects on MCF-7 cells in an E-screen assay [13]. Human experimental cell culture: A complex mixture of organochlorines and PCBs at environmentally relevant levels increased the proliferation of MCF-7 cells due to its estrogenic potential [14]. Human experimental cell culture: Findings from a study of the combinatory effects of PCBs on breast cancer cells suggest the possibility that PCB138 and 153 contribute to the action of

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	endogenous 17 β-estradiol on cell proliferation and apoptosis in the breast cancer cell line MCF-7 [15]. Human epidemiological**:** A study of 77 women found significantly higher levels of DDE and DDT in the patients with late onset of breast cancer and estrogen-independent cancer was more frequent in the patients exposed to numerous risk factors in which higher levels of HCB, gamma-HCH, DDD and DDT in adipose tissue were detected [16]. Human experimental cell culture: PBDE-71 behaved as a mild estrogen in a cell culture of MCF-7 human breast cancer cells [17]. Human experimental cell culture: A study of DDE in a human breast cancer cell line found that the chemical could increase breast cancer progression by opposing the androgen signaling pathway that inhibits growth in hormone-responsive breast cancer cells [18]. Human experimental cell culture: Dieldrin is one of several chemicals found to up-regulate VEGF expression in human breast cancer cells by an ER-dependent mechanism. Since VEGF increases capillary permeability and breast tumor angiogenesis *in vivo*, the physiological relevance of these findings is discussed [19].
Can bioassays such as the E-SCREEN test provide a measure of internal exposure to estrogen-like chemicals?	Body Burden/Methods: A study on the activity of xenoestrogens discussed the difficulties that may be encountered during the estimation of low doses *in vivo* [20]. High statistical power is required when the underlying dose-response curves are shallow. Through the use of large

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	sample sizes and numerous repeats, the experimental power of the E-Screen assay was sufficiently high to measure effect magnitudes of around 1-2% with reliability. However, such resources are usually not available for *in vivo* testing, with the consequence that the statistical detection limits are considerably higher. If this coincides with shallow dose-response curves in the low-effect range (which is normally not measurable *in vivo*), the limited resolving power of *in vivo* assays may seriously constrain low-dose testing.
Does exposure to POPs interfere with the ability to lactate? (Longer duration of breast-feeding affords increased protection against breast cancer.)	Review: A review of the effect of environmental estrogens on mammary development summarized findings that show DDT/DDE alters lactation in humans, which increases the risk of breast cancer [21]. Review: A review of reproductive disorders and EDCs summarizes the current evidence that EDC's, including DDT/DDE and PCBS, are able to reduce the duration of lactation [22]. The authors conclude that disruption of lactation by environmental contaminants is possible after both embryonic and adult exposures, but limited data in humans comprise a data gap and should be the subject of further research.
How do POPs exposures during crucial periods in early life – especially prenatal and pubertal – alter mammary gland development in girls?	Human epidemiological: A retrospective study of 112 women found that postpartum levels of PCB 203 were associated with a six fold increase in breast cancer risk before age 50 [23]. PCBs 167 and 187 were associated with a reduced risk, 0.2 and 0.4, respectively. Review: In a review of the effect of environmental estrogens on mammary development, the

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	authors note that "Differential effects xenoestrogens integrate a broad spectrum of modulations on gene signatures encoding for various proteins regulating, metabolism, milk production, terminal end bud maturation and apoptosis, cell cycle, proliferation and inflammation. These changes seem to rely on… the time of onset upon stimuli, with major consequence on susceptibility to carcinogenesis… [E]xposure to such compounds during critical periods of early development may play an important role in breast cancer susceptibility in adulthood [10]." Review: A review of perinatal environmental exposures and mammary development identifies TCDD, dieldrin, organochlorines, PCBs, PFOA, and PBDEs as chemicals that have been shown to delay mammary gland development, which, in the majority of cases, is related to long term development of carcinogen-induced tumors [24]. Review: Another similar review summarized findings that show DDT/DDE alter lactation and dioxin alters mammary gland development in humans, which increases the risk of breast cancer in both instances [21]. The review also shows that these findings are generally concordant with animal studies. Review: The authors suggest that the majority of epidemiological studies examining the relationship between environmental chemicals and breast cancer have not found strong evidence because they share common limitations including the inability to account for exposure in early life when the breast may be most vulnerable [25]. They present DDT as a

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	case study and suggest approaches for human studies that might advance our understanding of environmental stressors in the developmental origins of disease. Review: A review of environmental exposures and the mammary gland reports that one of the most important lessons learned from the literature is that early life vs. adult exposure to EDCs causes a more severe, permanent, or sensitive response in the rodent mammary gland [26]. The paper specifically discusses DDT, PFOA, and dioxin. Animal experimental: This study indicates that developmental exposure to the environmental contaminant dieldrin causes increased tumor burden in genetically predisposed mice [27]. Dieldrin exposure also altered the expression of BNDF and TrkB, novel modulators of cancer pathogenesis. Animal experimental: A study of two different strains of mice found that developmental PFOA exposure had inhibitory effects on mammary development in one strain and stimulatory effects in the other [28]. Review: Using a carcinogen induced rat mammary cancer model, the authors show that prenatal exposure to TCDD alters mammary gland differentiation and increases susceptibility for mammary cancer [29].
Do POPs exposures make breast cancer more lethal? And do the higher POPs body burdens in African	Human epidemiological: Results from a large population-based study did not find strong support for an association between detectable PAH-DNA adducts and survival among women

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American women explain their higher rates of breast cancer mortality?	with breast cancer, except perhaps among those receiving radiation treatment [30].
Finally, which are the most relevant POPs to study? As pointed out above, many studies have focused on the role PCBs and DDE may play in breast cancer development, yet resources may be better directed at other compounds in light of the fact that neither DDE nor most PCBs are estrogenic or mammary carcinogens.	Human epidemiological: A population based study of 224 Spanish women found that hat healthy women show a very different profile of organochlorine pesticide mixtures than breast cancer patients [31]. The most prevalent mixture of organochlorines among healthy women was the combination of lindane and endrin, and this mixture was not detected in any affected women. Breast cancer patients presented more frequently a combination of aldrin, dichlorodiphenyldichloroethylene (DDE) and dichlorodiphenyldichloroethane (DDD), and this mixture was not found in any healthy woman. Human epidemiological: A retrospective study of 146 women in Greenland found a significant association between serum PFC levels and the risk of breast cancer [32].

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3. Polybrominated Flame Retardants

Abstract

A substantial amount of research on PBDEs has been published since the 2007 gaps scan chapter, although very few results have a direct bearing on the role PBDEs may play in increasing the risk of breast cancer. Much of the published literature continues to describe the major sources of human exposure (dust, indoor air, diet) and environmental fate of various PBDE congeners. Generally, PBDE is a ubiquitous environmental chemical and is capable of bioaccumulation in humans, including in breast milk and mammary gland tissue. Of particular interest to CBCPI are studies showing that Californian women have some of the highest ever recorded internal concentrations of PBDEs, most likely due to strict state flammability standards. Published literature also continues to expand our understanding of the endocrine-disrupting properties of PBDEs, particularly of thyroid hormones. There is small amount of literature that shows PBDEs affect reproductive function, such as age at onset of puberty and menstrual function, and are carcinogenic *in vitro*, but there is a lack of epidemiological studies looking at the association between PBDE levels and cancer risk.

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What are the main routes of human exposure among both adults and children?	There was an enormous body of literature on routes of human exposure; representative studies for the most common routes are summarized below (with an emphasis on critical windows i.e. pregnancy, childhood etc and studies in California). <u>Total exposure</u> Review [1]: The review estimated total daily PBDE doses received by consumers in North America and Europe, along with the most important pathways and congeners, and derive PBDE elimination half-lives for chronic exposure. The study estimated distributions for all parameters (PBDE concentrations in exposure media, food consumption rates, etc.) and conducted a probabilistic exposure assessment. Results showed that Americans are exposed the most, likely due to stricter fire regulations, followed by consumers from the UK and Continental Europe. In the central quantiles of the exposure distributions derived, food is the dominant pathway; in the upper quantiles either food or oral and dermal exposure to dust. This reflects the lipophilic and persistent nature of PBDEs and their use in products for indoor-use. Review [2]: Being lipophilic and persistent organic compounds, PBDEs accumulate in lipid-rich tissues. Consequently, food items like fish from high trophic levels or lipid-rich oils have been found to contain relatively high concentrations of PBDEs, thus presenting an important exposure pathway to humans. The presence of PBDEs in various products of everyday use may lead to some additional exposure in the home environment. Dust seem to be an aggregate of the indoor source, and the ingestion of dust conveys the highest intake of BDE-209 of all sources, possibly also

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	of other PBDE congeners. The PBDE exposure through dust is significant for toddlers who ingest more dust than adults. Infants are also exposed to PBDEs via breast milk. <u>House Dust:</u> Human biomonitoring [3]: The highest concentrations of PBDEs ever reported in house dust were found in California and consequently, Californian's have elevated serum levels compared to other regions of the United States. This may be the result of the state's furniture flammability standards. Human biomonitoring [4]: This study used hand wipes to estimate exposure to PBDEs in house dust among toddlers and examined sex, age, breast-feeding, race, and parents' education as predictors of serum PBDEs. PBDEs were detected in all serum samples (geometric mean for SigmapentaBDE in serum was 43.3 ng/g lipid), 98% of the handwipe samples, and 100% of the dust samples. This study suggests that hand-to-mouth activity may be a significant source of exposure to PBDEs. Furthermore, age, socioeconomic status, and breast-feeding were significant predictors of exposure, but associations varied by congener. Specifically, serum SigmaBDE3 was inversely associated with socioeconomic status, whereas serum BDE-153 was positively associated with duration of breast-feeding and mother's education. Human biomonitoring [5]: The major objectives of this study were to investigate the maternal and fetal exposure to PBDEs on the basis of maternal and umbilical cord plasma samples and to study the extent of placental transfer for different PBDE congeners. The findings were also compared with previously observed PBDE levels

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	and patterns determined in placental tissue from the same individuals, and the relationship with the external exposure from house dust from the participants' homes was explored. PBDEs were detected in all maternal and umbilical cord plasma samples. The positive correlations for PBDEs for both maternal and umbilical cord plasma with house dust showed that domestic house dust is a significant source of human exposure to PBDEs in Denmark including *in utero* exposure. <u>Indoor Air</u> Human biomonitoring [6]: A study using personal air samplers found total personal air concentrations (particulate + vapor) of 469 pg/m3 for non-209 BDEs and 174 pg/m3 for BDE 209 in indoor air. Use of personal air concentrations increased estimates of inhalation exposure over those previously reported. Inhalation may account for up to 22% of the total BDE 209 exposure in U.S. adults. Levels of chemicals [7]: The distribution and fate of PBDEs in classrooms and computer rooms in 17 elementary schools in South Korea were described. Eight congeners (brominated diphenyl ether-28, -47, -99, -100, -153, -154, -183, and -209) in air, floor dust, and product surface dust were measured. The results indicate that both surface dust and floor dust may act as a secondary source of PBDEs in indoor environments after emission from facilities. <u>Dietary</u> Human biomonitoring [8]: This study determined the body burden of PBDEs in 100 California children, and evaluated associations with sociodemographic, household,

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	and dietary factors. Circulating levels of PBDEs were 10-to 1000-fold higher than similar aged populations in Mexico and Europe, 5-times higher than similar aged children across the U.S., and 2- to 10-fold higher than U.S. adults. Increased levels of higher-brominated congeners were associated with the recent purchase of new upholstered furniture or mattresses and consumption of pork. Concentrations of lower-brominated congeners increased with frequency of poultry consumption Levels of chemicals [9]: The objectives of this study were to provide updated measurements of PBDEs in US food, to estimate possible difference in levels from differing geographical regions, and to provide an improved estimate of current dietary intake. PBDE intake from food was estimated to range from 2.7 ng/kg/day for children 2 through 5 years of age to 0.8 ng/kg/day for women aged 60 years and older. This compares closely with the authors previous study where the intake estimate was 2.7 ng/kg/day for children 2 through 5 years of age and 0.9 ng/kg/day for women aged 60 years and older. The study did not find a decrease of PBDEs in food since the authors previous studies which they expected to find due to the declining use of PBDEs in the USA. These findings could be consistent with food contamination from depot sources of PBDEs. Levels of chemicals [10]: This study was conducted to measure the concentration of PBDEs in various food stuffs from Korea and to estimate levels of PBDE intake from food for the Korean population according to geographical location and age. Total dietary intake of PBDE for the average general population was 72.30ng/day (not detected (ND)=0) which was similar to other countries. In all food groups, the largest contribution to PBDE intake was from fish and shellfish (48.96ng/day). Total

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	PBDE consumed per kilogram of body weight was estimated to range from 2.70ng/kg/day for infants 1 through 2years of age to 0.85ng/kg/day for 65years and older and was highest in young children and decreased with increasing age.
How are the various PBDE congeners metabolized and excreted? What are their half-lives in humans? To what degree does Deca-BDE break down into more toxic congeners?	Review [1]: Median elimination half-lives for PBDEs in humans are in a range of 1-3 years except for BDE-153 with about seven years and BDE-209 with 4-7 days. Animal experimental [11] A fish model (Bhavsar et al. 2008, Environ. Sci. Technol., 42, 3724-3731) is used to predict the debromination of BDE-209 to more toxic lower-brominated PBDEs over a 15-year life period of piscivorous- and non-piscivorous lake trout (pLT, npLT). Estimated BDE-209, -99 and -47 concentrations were compared with human fish consumption guidelines developed using the draft U.S.EPA tolerable daily intakes. The model predicted that bioaccumulation of BDE-209 as well as BDE-47 and -99 due to dietary exposure to deca-BDE over the 15-year period would not be appreciable in pLT (generally unrestricted consumption advisory) and would be moderate in npLT (unrestricted to 2 meals/month advisory) even for worst-case scenarios. Human experimental [12]: A human ex vivo placenta perfusion system was used to study the kinetics and extent of the placental transfer of BDE-47, BDE-99 and BDE-209 during four-hour perfusions. The transport of BDE-47 and BDE-99 indicates *in utero* exposure to these congeners. The transport of BDE-209 was limited, however, possible metabolic debromination may lead to products which are both more toxic and transportable. Animal experimental [13]: To evaluate maternal transfer of decabromodiphenyl

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	ether (BDE-209), Sprague-Dawley rats were given daily oral doses of 5 mumol/kgb.w. BDE-209 in peanut oil from gestation day (GD) 7 to postpartum day (PD) 4. BDE-209 was increased temporally in maternal blood, placenta, fetuses and neonates. Furthermore, more BDE-209 was found in neonate whole-body samples obtained during lactational period (PD 4) than in that of fetal whole-body samples during pregnancy GD 15 and 21. Animal experimental [14]: Orally dosed BDE-47 was readily absorbed from the gut of chickens and was estimated to be 73% bioavailable. Cumulative tissue retention at 72 h was 60.2% of the dose. BDE-47 was deposited preferentially in lipophilic tissues, and the decreasing rank order of concentration on a wet weight basis was adipose tissue, skin, gastrointestinal tract, lung, carcass, muscle, liver, and kidney. When concentrations were adjusted for lipid content, the levels of BDE-47 in the principal edible tissues in chicken, that is, adipose tissue, skin, liver, and white and dark meat, were very similar to one another. Excretion of unbound metabolites in excreta was <1% of the dose, but bound radioactivity was a major component of excreta at >12% of the dose. Alkaline hydrolysis of bound material yielded a hydroxylated tetrabromo metabolite. The metabolic pathway of BDE-47 in chicken included mono-oxidation, mono-oxidation/debromination, and debromination. Animal experimental [15]: Between 25% and 50% of each of the dosed congeners (BDE-99, BDE-47) was retained in the rats with the liver being a minor depot (<1% of the dose). Fecal excretion accounted for 4-12% of the dosed congeners. A large percent of the dose (40-60%) was not recovered indicating that metabolic transformations may have occurred in the rats. Hydroxylated metabolites were

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	qualitatively identified in the feces and carcass by GC-MS. The relative congener distribution in each tissue was nearly identical to the congener distribution of the commercial mixture. Conclusions from the study suggest that the tetra- to hexa-BDEs present in commercial penta-BDE formulations are largely bioavailable, that bioavailability in the rat is not dependent on the degree of bromination, and that metabolism may occur to a large extent during a chronic exposure. Animal experimental [16]: In this work, pregnant Wistar rats were force-fed with 99.8% pure [14C]-Deca-BDE over 96 h at a late stage of gestation (days 16 to 19). More than 19% of the administered dose was recovered in tissues and carcasses, demonstrating efficient absorption of DBDE despite its high molecular weight and low solubility. The highest concentrations of DBDE residues were found in endocrine glands (adrenals, ovaries) and in the liver, with lower values recorded for fat. In all tissue extracts, most of the radioactivity was associated with unchanged DBDE. The use of high-grade purity [14C]-DBDE allowed quantification of several metabolites present both in maternal tissues and in fetuses. These biotransformation products accounted for 9-27% of the extractable radioactivity in tissues and 14% of that in fetuses. Animal experimental [17]: Pregnant Sprague-Dawley rats were given daily oral doses of 5mumol/kg b.w. BDE-209 in peanut oil during gestational and lactational period or during lactational period only. BDE-209 and its debrominated congeners were analyzed in several maternal tissues, offspring carcass and neonatal tissues. The occurrence of polybrominated diphenyl ethers (PBDEs) and their time profiles in maternal blood, placenta and fetuses/sucking pups indicated that BDE-209 and

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	its debrominated products can be transferred from mother to offspring via *in utero* or lactational exposure. Nona-BDEs were the predominant congeners in the analyzed pup tissues, and BDE-206 was the most abundant congener while BDE-197/204 was the major congener of octa-BDE.
What is the environmental fate of PBDEs, in particular Deca-BDE, which is still being produced and used in the U.S.?	There were 100+ studies on the environmental fate of PBDEs. PBDE contamination is widespread around the world, particularly in the marine environment where it tends to bioaccumulate and biomagnify. A brief cross-section of the literature is reported below. Environmental monitoring [18]: Accumulation of PBDEs at near part-per-million levels was measured in the surface sediments at the Sweetwater Recharge Facility in Tucson, Arizona, during 10-15 years of operation. Half-lives for loss of major PBDE congeners from sediments were decades or longer. Local agricultural soils amended with biosolids over a 20-year period showed similar accumulation of PBDEs. Environmental monitoring [19]: The occurrence of PBDEs has been studied in the atmosphere of four sites in the United Kingdom over a period of ten years. The concentrations have exhibited a sharp decrease after 2001-2003. This is evident in the urban sites of Manchester and London and at the semi-rural site of Hazelrigg. The average SigmaPBDE half-lives for these three sites were 3.4, 2.0 and 3.5 years respectively. SigmaPBDEs concentrations in the UK (in 2010 SigmaPBDEs < 10 pg m(-3)) are among the lowest reported in literature. Comparison of concentrations to estimated emissions and employment of PBDE profiles suggest that PBDEs in the UK atmosphere originate from primary emissions from products that contain mainly

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	the penta-BDE technical mixture. The detection of BDE-183 in the majority of samples hints that octa-bromodiphenylether has also been used extensively in the UK, however to a smaller extent than the penta- product. Environmental monitoring [20]: Polybrominated diphenyl ethers (PBDEs) concentrations and congener profiles were evaluated in four species of Antarctic fish (Chionodraco hamatus, Chaempsocephalus gunnari, Gymnoscopelus nicholsi,Trematomus eulepidotes) and in one Mediterranean species (Tuna, Thunnus thynnus). The GC/MS-ECNI analysis revealed that average sigmaPBDE concentrations in Antarctic fish species ranged from 0.09 ng g(-1)wet weight (wet wt) in G. nicholsi to 0.44 ng g(-1)wet wt in C. gunnari. In Mediterranean tuna they were two or three orders of magnitude higher (15 ng g(-1)wet wt). The results of this study confirm that PBDE contamination of the marine environment now occurs on a global scale. Review [21]: This review summarizes most available PBDE data in birds and emphasizes several specific aspects, i.e., inter-regional differences in PBDE contamination, the extent of BDE-209 contamination, differences in congener composition patterns between piscivorous and terrestrial-feeding birds, trophic biomagnification and temporal changes in PBDE contamination. A meta-analysis of PBDE congener profiles reveals distinctly different patterns between birds utilizing terrestrial and aquatic food webs. Terrestrial-feeding birds appear to exhibit heightened Deca-BDE contamination. Inter-regional comparisons reveal elevated PBDE burdens in North American aquatic birds compared to those from the rest of the world, likely related to greater Penta-BDE demand there. Examination of North

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	American and Chinese terrestrial birds also exhibited some of the highest BDE-209 concentrations ever reported in wildlife, and suggested that urban environments in general and some commercial activities (e.g., electronic recycling) may increase exposure of wildlife and humans to Deca-BDE. Summaries of temporal trend studies suggest that varying usage histories and regulations have influenced PBDE contamination patterns at different regions. As a consequence of continued usage of Deca-BDE around the world, significant increases in BDE-209 burdens have been observed in both North American and European birds. Environmental monitoring [22]: Ninety-six riverine runoff samples collected at eight major outlets in the Pearl River Delta (PRD), South China, during 2005-2006 were analyzed for 17 brominated diphenyl ether (BDE) congeners (defined as Sigma17PBDE). Fourteen and 15 congeners were detected, respectively, in the dissolved and particulate phases. The results showed that annual outflows of Sigma10PBDE and BDE-209 were estimated at 126 and 940 kg/year, respectively from the PRE to coastal ocean. Besides sedimentation and degradation, the majority of Sigma10PBDE and BDE-209 discharged into the PRE via riverine runoff was transported to the coastal ocean. Environmental monitoring [23]: The occurrence of the major components of the decabromodiphenyl ether (deca-BDE) flame retardant and other PBDEs was investigated in daily air particulate samples from 17th April to 20th May 2004 at a semi-rural site in north-west England. BDE-209 was found at between <0.49 and 100 pg m(-3) (median 13 pg m(-3)), and other higher-brominated PBDE congeners were also found, particularly the nona-BDEs (e.g. BDE-207: <0.042-79 pg m(-3),

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	median 2.5 pg m(-3)). Deca- and nona-BDEs dominated the median particulate sample congener profile: 60% BDE-209, 16% BDE-207, 6% BDE-208 and 4% BDE-206. Nona-BDEs were greatly enriched, relative to BDE-209, compared to the deca-BDE commercial mixture, which may suggest degradation of BDE-209 between source and sampling site, or release from older deca-BDE commercial mixtures, which may have contained higher proportions of nona-BDEs. Environmental monitoring [24]: Polybrominated diphenyl ethers are hydrophobic chemicals and can biomagnify in food chains. Little is known about the biomagnification of PBDEs in the Lake Michigan food web. Plankton, Diporeia, lake whitefish, lake trout, and Chinook salmon were collected from Lake Michigan in 2006 between April and August. Fish liver and muscle and whole invertebrates were analyzed for six PBDEs (BDE-47, 99, 100, 153, 154, and 209). Geometric means of Sigma PBDE concentrations in fish ranged from 0.562 to 1.61 µg/g-lipid. BDE-209 concentrations ranged from 0.184 to 1.23 µg/g-lipid in all three fish species. Sigma BDE-47, 99, and 209 comprised 80-94% of Sigma PBDE molar concentration. Within each fish species, there were no significant differences in PBDE concentrations between liver and muscle. The highest concentration of BDE-209 (144 µg/g-lipid) was detected in Diporeia.
Do workers with high levels of occupational exposures have higher-than-expected risks of cancer?	There is strong evidence that workers with occupational exposures have elevated body burden levels of PBDEs [25-30], but none of the occupational literature examines cancer outcomes.
Are body burden levels of PBDEs able to serve as early	Human epidemiological [31]: The goal of this study was to examine whether high

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indicators of breast cancer risk? Do they affect menstrual function, onset of puberty, development of mammary glands, or timing of menopause?	breast milk PBDE levels in reproductive-age females lead to interference with menstruation characteristics. The authors analyzed 15 PBDE congeners in 46 breast milk samples. Fifteen PBDE congeners (BDE-15, 28, 47, 49, 99, 100, 153, 154, 183, 196, 197, 203, 207, 208, and 209) were analyzed using a gas chromatograph equipped with a high resolution mass spectrometer. Women's age at menarche was not correlated with breast milk PBDE levels. Increased BDE-208 and 209 levels were significantly associated with the prolonged length of average and the longest menstrual cycle independent of age, pre-pregnant BMI, and parity. Higher concentrations of SigmaPBDEs and the higher brominated PBDEs from BDE-183 to 209, except 197, were significantly linked to women whose menstruation periods were still coming irregularly at the sampling time. Age-adjusted odds ratios (ORs) of BDE-153, 183, 207, 208, and SigmaPBDEs were significantly higher in women with length of average menstrual cycle >32 days, compared to the control. Women whose menstruation periods still came irregularly when they were 18 years old had higher age-adjusted ORs of BDE-207, 208, 209, and SigmaPBDEs than those whose periods came regularly at the same age. Human epidemiological [32]:The aim of this study was to examine how PBDEs in breast milk are associated with infant birth outcome and maternal menstruation characteristics. After maternal age, pre-pregnant BMI, and parity were adjusted, increased PBDEs in breast milk was related with decreased birth outcome, particularly for birth weight and length, chest circumference, and Quetelet's index of infants. No significant differences in PBDEs were found between the two groups of menstrual cycle length higher and lower than 30 days after the authors adjusted

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	for maternal age, pre-pregnant BMI, and parity. *In utero* exposure to low doses of PBDEs may result in lower birth weight and short or birth length. Human Epidemiological [33]: The authors analyzed the data from a sample of 271 adolescent girls (age 12-19 years) in the National Health and Nutrition Examination Survey (NHANES), 2003-2004 and estimated the associations between individual and total serum BDEs (BDE-28, -47, -99, -100, -153, and -154, lipid adjusted) and mean age at menarche. They also calculated the risk ratios (RRs) and 95% confidence intervals (CI) for menarche prior to age 12 years in relation to PBDE exposure. The median total serum BDE concentration was 44.7ng/g lipid. Higher serum PBDE concentrations were associated with slightly earlier ages at menarche. Each natural log unit of total BDEs was related to a change of -0.10 (95% CI: -0.33, 0.13) years of age at menarche and a RR of 1.60 (95% CI: 1.12, 2.28) for experiencing menarche before 12 years of age, after adjustment for potential confounders. Animal experimental [34]: This study evaluated neurobehavioral, hormonal, and reproductive effects in rat offspring perinatally exposed to a widely used pentabrominated commercial mixture, DE-71. Pregnant Long-Evans rats were exposed to 0, 1.7, 10.2, or 30.6 mg/kg/day DE-71 in corn oil by oral gavage from gestational day 6 to weaning. Mammary gland development of female offspring was significantly affected at PND 21. Animal experimental [35]:This study evaluated the effects of developmental exposure to low doses of PBDE-47 on the female reproductive system. Pregnant

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	Wistar rats were administered vehicle (peanut oil) or PBDE-47 [140 or 700 µg/kg body weight (bw)] on gestation day (GD) 6, or 5 mg 6-n-propyl-2-thiouracil (PTU)/L in the drinking water from GD7 through postnatal day (PND) 21. In female offspring sacrificed on PND38, there was a significant decrease in ovarian weight after exposure to PTU or 140 µg/kg PBDE-47. Alterations in folliculogenesis were apparent: a decrease in tertiary follicles and serum estradiol concentrations in the offspring exposed to either PTU or 700 µg/kg PBDE-47 was observed.
Are octa- and penta-BDEs carcinogenic? Basic cancer bioassays are needed.	Human Epidemiological [36]: The authors conducted a case-control study to evaluate the risk of breast cancer associated with adipose concentrations of polybrominated diphenyl ethers (PBDEs) among women undergoing surgical breast biopsies in the San Francisco Bay Area of California (n=78 cases; 56 controls). Adipose tissue was analyzed for the five major congeners of PBDEs. Unconditional logistic regression was used to estimate age- and race-adjusted exposure-specific odds ratios (ORs) and 95% confidence intervals (95% CI). Adipose levels of PBDEs were among the highest ever reported. Adjusted ORs for the highest compared with lowest levels of exposures were as follows: 0.56 (95% CI 0.19-1.68) for BDE-47; 1.19 (95% CI 0.35-4.10) for BDE-99; 0.91 (95% CI 0.33-2.53) for BDE-100; 0.52 (95% CI 0.19-1.39) for BDE-153; 1.67 (95% CI 0.44-6.29) for BDE-154; 2.04 (95% CI 0.45-9.20) for total BDEs. These results provide no evidence of an association between PBDE adipose concentrations measured at or near the time of diagnosis and breast cancer risk. Human cell line [37]: The authors used MCF-7 and MCF-7/ADR (multidrug-resistant MCF-7) breast cancer cell lines, the HeLa cervical cancer cell line, the OVCAR-3

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	ovarian cancer cell line, and the normal CHO (Chinese hamster ovary) cell line to assess the effects of PBDE-209 using cell viability, immunofluorescence, and flow cytometric assays. Western blot assays were used to detect changes in protein expression. To assess the effects of PBDE-209 on apoptosis, the authors used the protein kinase Cα (PKCα) inhibitor Go 6976, the extracellular signal-regulated kinase (ERK) inhibitor PD98059, and tamoxifen. The data demonstrate that PBDE-209 is able to promote proliferation of various cancer cells from the female reproductive system and normal ovarian CHO cells. Furthermore, it reduced tamoxifen, PKCα, and ERK inhibition-induced apoptosis. Finally, PBDE-209 up-regulated phosphorylation of PKCα and ERK1/2 proteins in tumor cells and in CHO cells.
How do PBDE congeners affect endocrine pathways that may play a contributory role in breast carcinogenesis? How do PBDEs contribute to the overall body burden of estrogenic and mitogenic synthetic chemicals, such as chlorinated persistent organic pollutants, pesticides, and pharmaceuticals, and, in so doing, are there	Animal experimental [38] This study evaluated the effects of BDE-99 on hormone homeostasis, as well as in urinary and serum biochemical parameters of adult male rats. Animals (10 per group) received BDE-99 by gavage at single doses of 0, 0.6 and 1.2mg/kg. Forty-five days after BDE-99 exposure, urine and serum samples were collected for hormonal and biochemical analysis.The hormonal analysis showed a significant decrease in testosterone and progesterone levels. Animal experimental [39]: This study employed immature rats as a developmental model to examine the potential involvement of BDE 47 in the induction of calbindin-D9k (CaBP-9k), which is a novel biomarker for screening estrogenic compounds. The results demonstrate that BDE 47 exposure results in increases in CaBP-9k mRNA and protein in the uteri of immature rats. The biochemical pathway for BDE 47-induced activity may involve the ER-mediated signaling pathway.

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important additive or synergistic effects?	Review [40]**:** Brominated flame retardants (BFR) are endocrine disrupters in experimental systems, both *in vitro* and *in vivo*. Although BFR effects on thyroid hormones are well confirmed, studies of effects on oestrogen/androgen systems are fewer but today growing in numbers. The effects of BFR on other hormone systems are still unknown. Hormonal effect levels in animals start from ca 1 mg/kg b.w., but there are exceptions: effects on spermatogenesis, suggesting hormonal causes, have been observed at a low dose (60 µg/kg b.w.) of a polybrominated diphenyl ether (PBDE) congener, BDE-99. It could be concluded that hormonal effects are of importance in risk assessment, and in some cases where effects are seen at low levels safety margins may be insufficient. *In vitro* assay [41]: The potential of BDE47 and its related hydroxylated analogsto modulate estrogen/thyroid/androgen receptor-(ER, TR, AR), mediated responses were investigated by use of reporter gene assays. Exposure to 1 or 10 muM, 4'-HO-BDE17 significantly up-regulated expression of Luc, whereas other four chemicals did not induce Luc expression under control of the ER. Anti-estrogenic potency was observed for 4'-HO-BDE17 (IC50=1.14 muM)>6-HO-BDE47 (IC50=2.65 muM)>2'-HO-BDE28 (IC50=9.49 muM)>BDE47 (IC50=21.11 muM). No anti-estrogenic effect of 4'-HO-BDE49 was observed. Both 4'-HO-BDE17, 4'-HO-BDE49 resulted in greater responses of Luc expression induced by T3. BDE47, 2'-HO-BDE28, 6-HO-BDE47 did not show any effect on the expression of Luc induced by 5 nM T3. 6-HO-BDE47 (IC50=0.34 muM)>4'-HO-BDE17 (IC50=1.41 muM)>BDE47 (IC50=3.83 muM)>2'-HO-BDE28 (IC50=29.22 muM) exhibited anti-androgenic potency, while 4'-HO-BDE49 did not show androgenic transcriptional activity.

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	In vitro assay [42]:This study tested estrogenicity using two assays: 3H-estradiol (3H-E2) displacement from recombinant ER-α and induction of reporter gene (ERE-luciferase) in cultured cells. Reporter gene activity was increased by DE-71 that had been subjected to microsomal metabolism. DE-71 did not displace E2 from ER-α, but all six of the OH-PBDE metabolites did. para-Hydroxylated metabolites displayed a 10- to 30-fold higher affinity for ER-α compared with ortho-hydroxylated PBDEs, and one produced a maximal effect 30% higher than that produced by E2. Coadministration of E2 and DE-71, or certain of its metabolites, yielded reporter activity greater than either chemical alone. *In vitro* assay [43]:The potential of BDE100 to modulate responses mediated by the estrogen (ER), thyroid hormone (ThR) or androgen receptors (AR) were investigated by use of transactivation reporter gene assays. The African green monkey kidney CV-1 cell transiently transfected with the constructed reporter gene plasmid ERE-TATA-Luc and pUAS-tk-Luc with luciferase (Luc) under control of the estrogen response (ERE), or thyroid hormone response (ThRE) elements were used to evaluate (anti)estrogen and thyroid effects of BDE100. The (anti)androgenic potency of BDE100 was also evaluated by use of MDA-kb2 cells, which were stably transfected with MMTV-luciferase. The assays displayed appropriate responses to known natural estrogen 17β-estradiol (E2), ThR ligand triiodothyronine (T3), and the AR agonist 5α-dihydrotestosterone (DHT). 10 or 50 muM BDE100 significantly up-regulated expression of Luc under control of the ER. Antiestrogenic potency was observed for BDE100 (IC50 = 6.21 muM). Co-exposure to 50 muM BDE100 significantly enhanced expression of Luc caused by 5 nM T3. BDE100 was

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	antiandrogenic at 10 and 50 muM with an IC50 of 28.60 muM BDE100. These results suggest that BDE100 can modulate the endocrine system in multiple ways by interfering with several hormonal signaling pathways simultaneously. Animal experimental [44]: The purpose of this study was to evaluate whether polybrominated diphenyl ethers (PBDE) at levels reported for human populations affect the thyroid state in pregnant sheep and lambs. Pregnant sheep were exposed to vehicle or BDE-47 (0.2, 2 and 20 µg/kg b.w.) from the 5th to 15th week of gestation by intravenous injections weekly. Thyroid hormone levels and BDE-47 content in the blood of sheep and lambs and adipose tissue were analyzed. The authors observed a significant decrease in total T(4) and T(3) in exposed lambs without any effect in pregnant sheep. The studies finding indicates that prenatal low-dose PBDE exposure results in PBDE storage in fat of offspring and can affect thyroid metabolism in the developing fetus. Human epidemiological [45]: The authors observed a positive association between the weighted sum of chemicals known to bind to transthyretin (SigmaTTR binders) and TSH levels. They also found positive associations between TSH and SigmaPBDE(5), SigmaOH-PBDE(4), BDE-47, BDE-85, 5-OH-BDE47, and 4'-OH-BDE49, and an inverse association with BDE-207. Relationships with free and total T(4) were weak and inconsistent. Results indicate that PBDE exposures are elevated in pregnant women in California and suggest a relationship with thyroid function. Human epidemiological [46]: This study meeasured the concentration of 10 PBDE congeners, free thyroxine (T4), total T4, and thyroid-stimulating hormone (TSH) in

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	270 pregnant women around the 27th week of gestation Serum concentrations of individual PBDE congeners with detection frequencies > 50% (BDEs 28, 47, 99, 100, and 153) and their sum (SigmaPBDEs) were inversely associated with TSH levels. Decreases in TSH ranged between 10.9% [95% confidence interval (CI), -20.6 to 0.0] and 18.7% (95% CI, -29.2 to -4.5) for every 10-fold increase in the concentration of individual congeners. Odds of subclinical hyperthyroidism (low TSH but normal T4) were also significantly elevated in participants in the highest quartile of SigmaPBDEs and BDEs 100 and 153 relative to those in the first quartile. Human epidemiological [47]: One hundred forty pregnant women > 34 weeks into their pregnancy were recruited into this study between 2008 and 2010. Serum was analyzed for a suite of PBDEs, three phenolic metabolites (i.e., containing an -OH moiety), and five thyroid hormones. PBDEs were detected in all samples and ranged from 3.6 to 694 ng/g lipid. Two hydroxylated BDE congeners (4 -OH-BDE 49 and 6-OH-BDE 47) were detected in > 67% of the samples. BDEs 47, 99, and 100 were significantly and positively associated with free and total thyroxine (T4) levels and with total triiodothyronine levels above the normal range. Associations between T4 and PBDEs remained after controlling for smoking status, maternal age, race, gestational age, and parity.
Does thyroid hormone disruption play a role in breast cancer risk?	There is substantial evidence that PBDEs affect thyroid hormone [45-47], but no papers explored the role of this disruption in breast cancer etiology.

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4. Pesticides

Abstract

While pesticides remain a fairly common research topic, breast cancer is rarely a risk or an outcome that is considered. Very little work has been published in the past five years on the 10 pesticides that Rudel et al identified as mammary carcinogens. Two studies were identified that provide evidence of gene-environment interactions involving pesticides and birth outcomes, and researchers found that organophosphates (OPs) cause epigenetic changes that could influence cancer risk. A few early life pesticide exposure studies were found. One study found pregnant women's exposure to atrazine in drinking water was associated with a higher prevalence of small-for-gestational age. Breast development could be affected by prenatal exposure according to a Danish study, but biological levels of pesticide metabolites were not related to precocious puberty in a Turkish study. A relatively high number of studies of mixtures were identified, including one that found different levels of OCs in BC cases and controls (Spain). Work on pesticide biomarkers, both methods and measures, is ongoing with some California specific data available. GIS work on pesticides has also been done in the state, but little has been published.

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Biologic Evidence: Commonly used pesticides Known mammary carcinogens in common use, such as atrazine, simazine and dichlorvos, deserve closer scrutiny. The commonly-used herbicide 2,4-D and its phenolic metabolite, 2,4-DCP, also deserve further investigation. California's pesticide reporting program can pinpoint areas of intense use of these pesticides. Note: 10 Pesticides from Rudel RA, Attfield KR, Schifano JN, Brody JG. Chemicals causing mammary gland tumors in animals signal new directions for epidemiology, chemicals testing, and risk assessment for breast cancer prevention. Cancer. 2007 Jun 15;109(12 Suppl):2635-66. 1,2-Dibromo-3-chloropropane Atrazine Captafol Chlordane Clonitralid Dichlorvos Fenvalerate Nifurthiazole Simazine Sulfallate	Few of the pesticides on the Rudel mammary carcinogen list have been further researched in relationship to breast cancer. Groups such as Cancer Prevention Institute of California (CPIC-Reynolds), CHAMACOS and the California Environmental Health Tracking Program have applied GIS to pesticide use data (see Resources document for more information about these.) Atrazine: Review: A review found the causal relationship between atrazine exposure and breast cancer was "unlikely" based on a framework evaluating biological plausibility (animal) and epidemiological (human) evidence. Atrazine induces mammary tumors in aging SD rats by suppressing the luteinizing hormone surge (supporting persistent estrus and endogenous estrogen and prolactin.) However women who undergo reproductive senescence have low rather than elevated levels of estrogen and prolactin. Genotoxicity, estrogenicity, upregulation of aromatase gene expression or delayed mammary gland development were considered and none could account for the tumor response [1]. An *in vitro* study found that concentrations of atrazine can increase aromatase activity of human granulosa cells but not endothelial stromal cells and this effect is not elicited at the enzyme level [2]. Other: No studies were identified on fenvalerate and BC, but recent work was done on human uterine leiomyoma and myometrial cells. Sulfallate was the subject of a 2011 NTP report; no new mammary cancer information was included. Chlordane, while no longer in use, was the subject of research for other cancers, considering endocrine disruption and testicular germ cell tumor risk by hormone-metabolizing genes. Dichlorvos was examined in an epidemiologic study of men [3]. No new studies of 2,4-D and breast cancer were identified. Another chlorophenoxy herbicide,

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	diclofop-methyl was found to cause chromosomal aberrations (CA) in mouse bone-marrow cells and human peripheral lymphocytes CA and affect cell proliferation in the latter [4]. Another common pesticide, pentachlorphenol, was found to decrease tumor cell binding capacity and cell-surface protein expression of human natural killer cells [5].
Biologic Evidence: Genetic Future studies should also consider interactions between pesticide exposure and genes relevant in the biological pathways by which these chemicals influence breast cancer risk. Note: OP = organophosphate OC = organochlorine	No studies were found that are specifically related to breast cancer, however several address outcomes that may be related to BC risk. The gene-environment studies provide evidence that polymorphism in xenobiotic metabolizing genes can influence the relationship between prenatal exposure to pesticide and birth outcomes. Several studies looked at pesticides and gene expression and epigenetics. Gene-Environment: Among 306 mother-infant dyads, OP metabolite concentrations were associated with shortened gestation and reduced birth weight in this cohort, but the effects differed by race/ethnicity and PON1 genotypes [6]. A study found higher levels of OCs in pregnant women's maternal blood and cord blood in fetal growth restriction (FGR) cases as compared to controls. Looking at Glutathione S-transferase (GST- a polymorphic supergene family involved in OC detoxification) they found the genotypic distribution of GSTM1/GSTT1 was similar between cases and controls, but the frequency of GSTM1-/GSTT1- (null) genotype was significantly higher in cases. A significant association was seen between an OC metabolite and GSTM1- genotype with reduction in birth weight of 213 gram [7]. Gene Expression: Chlorpyrifos (an OP) modifies the expression of genes relevant for placental function. In human placental JEG-3 cells, it increased the expression of several trophoblast target genes (ABCG2, GCM1 and, even more significantly, βhCG mRNAs) in conditions where cell viability and morphology were not compromised [8].

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	Fonofos (an OP),was one of 3 pesticides associated with increased prostate cancer risk in Agricultural Health Study and the only one higher among those with a family history of prostate cancer. A study's findings suggest a role of base excision repair genetic variation in pesticide-associated prostate cancer risk [9]. Another study observed a significant interaction among chromosome variants, pesticide use, and risk of prostate cancer. OPs were the strongest modifiers of risk, although the biological mechanism is unclear [10]. Epigenetic: Three OPs (fonofos, parathion, and terbufos) induced methylation changes in the promoter regions of 712 genes as well as OP-specific methylation alterations, associated with numerous carcinogenesis-related genes. Further studies in other cell types and human samples are required, as well as determining the impact of these methylation changes on gene expression [11]. An epigenetic mouse study included *in utero* exposure to a mixture of permethrin and insect repellant DEET. It was the only compound tested that did not promote early-onset female puberty transgenerationally (F3 generation) [12].
Exposure Timing The biological impact of pesticide exposures at early developmental stages remains unknown. Animal studies, particularly of atrazine, indicate the importance of cellular events taking place many years before breast cancer develops. Pesticide use patterns at the time of diagnosis do not reflect conditions at the time that these cellular changes take place. This is especially problematic for many currently-used pesticides, which are not persistent. Future studies should focus on	In addition to the gene-environment and epigenetic studies above, several studies focused on prenatal pesticide exposure. Animal: The effects of neonatal exposure to low doses of endosulfan on the expression of proteins regulating uterine development and differentiation; striking decrease in Progesterone Receptor expression was detected in the prepubertal rats following each dose of endosulfan. DES treatment deregulated ERα and Hoxa10 uterine expression at each age [13]. Epidemiologic: One study found no evidence of an association between prenatal DDE (an OC metabolite) exposure and child growth during the first year of life [14]. An Indiana study

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pesticide exposures at biologically relevant time points (i.e. *in utero*, puberty, before childbirth).	modeling exposure to atrazine in drinking water among pregnant women found an association with increased prevalence of small-for-gestational-age, but not preterm delivery [15]. A Danish study's findings suggest that prenatal exposure to currently approved pesticides may cause earlier breast development in girls, because of higher androgen levels, which indirectly may increase estrogens through aromatization. In addition, lower serum Anti-Müllerian Hormone levels indicated a reduced pool of antral ovarian follicles [16]. A Turkish study of breast development among girls living in a greenhouse intensive area evaluated serum and adipose tissues for various pesticides. Only DDE was detectable. Among girls who had premature thelarche, basal luteinizing hormone (LH), stimulated LH, follicle-stimulating hormone, and the long axis of the uterus and both ovaries were significantly different between those with detectable and undetectable DDE levels. The presence and levels of pesticides were not related to precocious puberty [17].
Pesticide Mixtures The biologic impact of combined exposures remains unknown. New methods in epidemiology, analytical chemistry, and toxicology need to be developed to explore real-life mixtures. Evidence from *in vitro* studies indicates that effects of pesticides can be cumulative and additive. Studies should focus on commercial formulations,	Some recent mixture work has focused on endocrine disrupting (ED) chemicals, including pesticides. One paper showed that nonmonotonic responses and low-dose effects were common in studies of natural hormones and ED chemicals. They concluded that when nonmonotonic dose-response curves occur, the effects of low doses cannot be predicted by the effects observed at high doses [18]. *In vitro*: A study of a mixture of three azole fungicides found androgen receptor antagonistic effects were close to the predicted additive effect, the inhibition of testosterone production was close to additive, whereas the estradiol production inhibition was over-estimated when assuming additivity. These and other studies show that weak endocrine disrupting compounds, like parabens and azole fungicides, give rise to combination effects when they occur in mixtures [19].

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including the inert ingredients, and not just the active ingredients.	Animal: A study looking at sexual development in rat offspring found that a mixture of low doses of five environmentally relevant endocrine disrupting pesticides (mancozeb et al) caused adverse developmental toxicity effects in rats and that additive mixture effect predictions were in good agreement with the observed effects [20]. Epidemiologic: Looking at real-life mixtures, a Spanish study compared the profiles of organochlorine pesticide mixtures in breast cancer cases and controls. They found a combination of aldrin, DDE and DDD in multiple cases, but not in controls; and a combination of lindane and endrin in multiple controls, but not in cases [21]. A study comparing pesticide plantworkers vs. controls, found a significant, but biologically irrelevant, increase in chromatid breaks. While genomic frequency of translocations was significantly elevated, the distribution of DNA damage appeared random. Translocation yield correlated with years spent in pesticide production, thus multiple pesticide exposure may pose a risk to genome integrity, and however other groups of chromosomes should be considered [22]. One paper posited that PBTK models could be useful as tools to assess combined tissue doses of the mixture of pesticide residues in food, and that they could help predict potential interactions including thresholds for such effects [23].
Epidemiologic Evidence in High Risk Populations Environmental epidemiology needs to be integrated with disparities research. Hispanic women in California experience a 42% lower risk of breast cancer than do non-Hispanic white women. Reproductive patterns probably explain part of this difference. Among	The epidemiologic studies specific to cancer identified were primarily in men, with occupational studies in pesticide applicators, plant workers or farmers. While some research on effects of pesticides on those living in agricultural areas is being done, none directly focuses on breast cancer. A review of occupational exposure to pesticides and cancer noted that every major functional

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Hispanic farmworkers, the intense physical activity required by farm labor may also have a protective effect. Hispanic women living in intensely agricultural areas and/or working as farmworkers need to be compared to Hispanic women without such exposures. Simply comparing rates of breast cancer among women of all races among counties with varying pesticide use patterns may blur important associations within and among subpopulations. Interactions between reproductive history and pesticide exposure deserve further investigation.	class of pesticides (insecticides, herbicide, fungicides, and fumigants) has been associated with an array of cancer sites. Specific chemicals, such as OC, OP, and carbamates and phenoxy acid and triazine herbicides, have been observed but not every chemical in these classes was found to be carcinogenic in humans. Twenty-one pesticides identified subsequent to the last IARC review showed significant exposure-response associations in studies of specific cancers, but these observations need to be evaluated and replicated. The reviewer called for a multidisciplinary expert review and evaluation of these pesticides and their potential to produce cancer in occupational settings [24]. A 15-20 year occupational follow-up of pesticide applicators in the Agricultural Health Survey (AHS) found little evidence of an association between cumulative lifetime use of dichlorvos (DDVP) and risk of any cancer at this stage of follow up, but the population was primarily male [3].
Exposure Measures: Biomarkers	A prospective study of pregnant women in a province where organophosphates are intensively applied half of the year was reported. Of the several potential OP exposure biomarkers measured, cholinesterases were significantly depressed during the spraying season and cortisol increased very significantly in the first trimester of pregnancy during spraying season versus non-spraying season [25]. A review summarized mean serum/milk ratios from 13 studies to aid comparison between human POPs exposure studies. They suggest that more studies are needed to allow a valid comparison between analysis of breast milk and serum samples for a broader range of POPs [26]. A pilot using a multi-residue laboratory method to measure non-persistent and persistent pesticides in breast milk in women residing in an agricultural region and an urban area in

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	California found that neonates and young children may be exposed to persistent and non-persistent pesticides (and PCBs) via breast milk [27]. CHAMACOS published recently on organophosphate metabolite levels in house dust, children's urine, and blood and urine of women and newborns in the Salinas Valley. They were recently funded by CBCRP to study decreasing teens' exposure to endocrine-disrupting chemicals [28, 29]. Another study looked at cancer risk from food contaminant exposures for children and adults in California [30]. Women are at risk of occupational pesticide exposure. Ongoing surveillance has shown that females who did not handle pesticides are over-represented among farmworker pesticide illness and injury cases. Females working on fruit and nut crops appeared more exposed to off-target pesticide drift and to fungicides and fumigants compared to males [31].

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5. Solvents and Industrial Chemicals

Abstract

Limited research has been conducted on the relationship between solvents and breast cancer since the 2007 Gap document. There have been a handful of large human cohort studies, but the results are inconsistent. Many of the additional questions from the 2007 document remain outstanding and additional research is still needed on the basic questions of exposure and toxicology before the issue of breast carcinogenicity can be adequately addressed.

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"There are thousands of other organic solvents and industrial chemicals, some of which have not been adequately tested for carcinogenicity or endocrine disruption or other potential effects that might impact breast cancer risk."	Human Case-Control: A case-control study of Inuit populations of Greenland & Canada investigated exposure to persistent organic pollutants (POPs) and perfluorinated compounds (PFCs). They found significant association between serum PFC levels and the risk of BC [1]. Review/Commentary: A PubMed search of 30 years of literature on methyl isocyanate and its role in cancer etiology found both animal and human epidemiological data to support further research into specific mechanisms of carcinogenicity after exposure [2]. Population-Based Cohort Study: A study of 24,697 postmenopausal women in a Danish cohort found that, among non-smokers, higher concentrations of GA-Hb as a result of acrylamide exposure were associated with a higher hazard rate of breast cancer specific mortality especially among those with estrogen receptor positive tumors [3]. Human Case-Control/Follow-Up: This study reexamined exposure data from tetrachloroethylene- contaminated drinking water in Cape Cod, Massachusetts. New water distribution modeling software helps strengthen evidence for elevated breast cancer risk for highly exposed women, with minimization of misclassification by using the latest technology [4].
"We lack information on the levels of exposure and relative contribution of various sources to our body burden. The fact that no one is exposed to just one of these chemicals at a time highlights our lack of understanding of possible additive effects, interactions or synergies."	Pilot survey study: A pilot survey study of Vietnamese nail salon workers in Alameda County, CA found that most workers are concerned about their health from exposure to workplace chemicals. The findings highlight a critical need for further investigation into the breast cancer risk of nail salon workers due to routine use of carcinogenic and endocrine-disrupting chemicals, and specific concerns of immigrant women in this workforce [5]. Human Population-Based Case Control Study: A retrospective study of 63,982 female workers from 1973-1997 were studied to observe the effects of a variety of solvent exposure in Taiwan.

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	Female workers with exposure to trichloroethylene and/or mixture of solvents, first employed prior to 1974, may have an excess risk of breast cancer [6]. Human Experimental Cell Culture: Food-borne phytochemicals (PC) as well as synthetic chemicals (SC) were tested alone and in combination to test their estrogenic or anti-estrogenic properties. The tested PCs and SCs appeared to act as (full) agonists for the estrogen receptor & interacted in mixtures and with estradiol in an additive way [13].
"Further work is needed in exposure assessment, toxicology, and susceptibility to make future epidemiologic studies more useful. One of the most promising lines of research would be an on-going study of a large number of exposed women workers, with government ensuring access to this population. There is an on-going Agricultural Health Study; we need something like this for industrial workers."	Review/Commentary: This updated literature review on the effects of Dichloromethane (methylene chloride) on cancer risk agreed that population-based case-control studies of incident disease with robust exposure assessments including detailed occupational information are key to better understanding these relationships [7]. Human Population-Based Case Control Study: The CECILE study out of France did case-control examinations of breast cancer risk across a variety of occupations. They found increased risks for textile workers, rubber and plastics product makers, and in women employed for more than 10 years as nurses and as tailors/dressmakers. These findings also focus on night-shift work, solvents and endocrine disrupting chemicals and require further studies with detailed assessment of occupational exposures [8]. Human Population-Based Case Control Study: This cohort study in Poland found little to no evidence of a relationship between organic solvent exposure and increased risk for breast cancer. They find that the associated risk might be limited to hormone receptor-negative tumors [9]. Human Population-Based Case Control Study: This cohort study in Italy followed 797 women for benzene exposure in shoe factory work. The study moderately supports the hypothesis that

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	benzene represents a risk factor for breast cancer [9]. Meta-Analysis: Inconsistent relationships between ethylene oxide and breast cancer risk were tested in a combined examination of cohort studies of over 19,000 workers. Authors found no statistically significant relationship between exposure and increased risk beyond EPA recommended exposure guidelines from the 2006 draft IRIS risk assessment [11]. Human Population-Based Case Control Study: Data from Child Health and Development Studies cohort (N = 112) were tested to see if exposure to polychlorinated biphenyls (PCBs) measured during the early postpartum period predict increased risk of maternal breast cancer diagnosed before age 50. The net association of PCB exposure, estimated by a post-hoc score, was nearly a threefold increase in risk [12].
"For nonylphenol and nonylphenol ethoxylate, work is needed to determine how exposure to these compounds disrupts the endocrine system, including determining the toxicologically active form(s) and the pharmacokinetics and toxicokinetics of nonylphenols and metabolites. Other congeners in this group may also be of concern, but no data were identified, making this another area for possible study."	Few studies examined any new or updated information on nonylphenol and nonylphenol ethoxylate with specific attention to breast cancer with one cell culture study and one animal study summarized below. Human Pilot Case Control Study: Endocrine disrupting effects of Phytoestrogens and xenoestrogens may be multifactorial when components from both the diet and the environment act at the same point in steroid metabolism [14]. Human Experimental Cell Culture: A study examining the genotoxicity of Nonylphenol polyethoxylates (NPEOs) in a human breast adenocarcinoma cell line, with a focus on markers for DNA damage. The authors found that cells that generated γ-H2AX (phosphorylation of histone H2AX) formed DSBs, the worst type of DNA damage, thus causing the NPEOs to act as a tumor initiator and promoter. The results indicated therefore that attention should be paid to degradated short chain NPEOs and their genotoxicity [15].

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"While formaldehyde and acetaldehyde are important indoor toxicants, little is known about the toxicology of many terpenoid oxidation products. Several reaction pathways involving ozone and reactive compounds that are present in the formulation of household products are still not well characterized and deserve further attention."	No articles were found related to "terpenoid oxidation products." Literature searches in this line mainly resulted in articles related to breast cancer treatment or drug improvements rather than exposure concerns.

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6. Water Contaminants

Abstract

Although there has been a substantial amount of research on many of the common environmental contaminants found in water, little research has been devoted to the impact of those chemicals in the context of human exposure through drinking water. Several human epidemiological studies looked at the indirect effects of water disinfection by-products on breast cancer risk, via pathways such as shortened menstrual cycles, but the results were largely inconclusive. In general, the conclusions discussed in the 2007 Gaps chapter remain accurate and the questions posed remain unanswered.

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How does childhood exposure to MX, a direct-acting mutagen, affect breast cancer induction? Oxidative metabolism is known to detoxify MX, but oxidative enzyme systems (such as liver CYP2E1) are not fully active in early life.	No research
What is the total mutagenicity of finished drinking water? Mixtures of chlorination by-products, triclosan, pesticides, and gasoline additives, for example, may exhibit toxic effects that are complex and not predicted from the effects of single compounds.	Experimental Human Cell Line: A complex mixture of organochlorine pesticides encouraged proliferation of breast cancer cell lines *in vitro* [1]. Experimental Human Cell Line: Oxidative stress response of human breast cancer cell line was found to be much more sensitive than cytotoxicity response in drinking water samples. Also, chlorination of drinking water actually increased oxidative stress, most likely due to disinfection by-products [2]. Human Epidemiologic: Breast cancer is significantly associated with consumption of fish from water contaminated by various industries, including PCBs and heavy metals [3].
What are the indirect effects of water disinfection by-products on breast cancer risk, via pathways such as shortened menstrual cycles? These pathways may be important for women living in large urban areas, where trihalomethane levels in drinking water are high. San Francisco, for example, has a history of high trihalomethane levels and, on this basis, received a grade of "poor" for drinking water quality from the Natural Resources Defense Council in 2003.	Environmental monitoring: The effluent from a chlorination wastewater treatment plant has significantly higher 17β-estradiol equivalent quantity (EEQ) levels than upstream water, although the effluent did not significantly impact the quality of downstream samples. Similarly, chlorination significantly increased the concentration of trihalomethanes in plant effluent, but this was not reflected in downstream samples [4]. Human Epidemiologic: A cross-sectional study found that exposure to drinking water disinfection by-products (DBPs)--in particular, total trihalomethanes (TTHMs)—did not have an adverse effect of exposure on fetal growth. An association of TTHM with small for gestational age births was seen only for average residential concentrations above the current

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	regulatory standard [5]. Human Epidemiologic: A cross-sectional study found no evidence of an increased time to pregnancy among women who were exposed to higher levels of disinfection by-products [6]. Human Epidemiologic: A cross-sectional study of pregnant women in Crete found no evidence for an increased risk of LBW, SGA and preterm delivery at the relatively low level exposure to THMs and particularly brominated THMs in drinking water[7]. Human Epidemiologic: A study in New South Wales found that mothers' exposures during pregnancy to total trihalomethane as well as to chloroform and bromodichloromethane were associated with SGA [8]. Review: A review of the epidemiology of disinfection by-products in drinking water showed that there appears to be good epidemiological evidence for an association between chlorination by-products, as measured by THMs, in drinking water and bladder cancer, but the evidence for other cancers including breast cancer appears to be inconclusive and inconsistent [9]. Furthermore, there appears to be some evidence for a relationship between chlorination by-products and SGA and IUGR and, to a lesser extent, pre-term delivery, but evidence for other outcomes such as LBW, stillbirth, congenital anomalies and semen quality appears to be inconclusive and inconsistent. Human Epidemiologic: A cross-sectional study found that residential THM exposure during pregnancy is not associated with birth weight, SGA, LBW, or preterm delivery in Spain despite the high THM levels in some areas and the extensive exposure assessment [10]. Human Epidemiologic: A study of 90,848 women in Taiwan found no evidence of an increased risk of TLBW, SGA, and preterm delivery at the relatively low concentrations of

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	total trihalomethanes (TTHMs) in Taiwan's drinking water. Maternal TTHMs exposure was estimated from the TTHMs concentration for the municipality of residence at birth [11].
What can data on water contaminants available through the Safe Drinking Water Act reveal about breast cancer risk in different geographic areas? These data have been underused in breast cancer studies. Together with databases mandated by California's Proposition 65, they provide a means to reconstruct historical exposures to water-borne carcinogens. Tools for GIS computer mapping, already developed for use in the Cape Cod Breast Cancer and Environment Study, are also available for these studies.	Human Epidemiologic: An update on of the Cape Cod study found slightly elevated breast cancer risk for highly exposed women, with strengthened exposure assessment and minimization of misclassification by incorporation of more sophisticated flow estimates in the exposure assessment method [12].
How many chemicals identified by Rudel as mammary gland carcinogens in animals are found in California's drinking water? And are they associated with elevated breast cancer risk?	Water Quality Reports: Rudel identifies 216 chemicals as mammary gland carcinogens in animals. Based on water quality reports from three large water utilities (LA, SF, Oak) only acrylamide was detected in 2011[13-15]. (Note: CBCPI science assessment staff are in the process of identifying how many chemicals actually screened.)
Is PCE-contaminated drinking water associated with elevated breast cancer rates in California, as it is in Cape Cod?	No research
What potential human exposures may be associated with the growing use of reclaimed wastewater in California?	Experimental Human Cell Line: Treated waste water (TWW) and soil irrigated with TWW up-regulated cell proliferation and tumor-related proteins in MCF-7 breast cancer cells [16].

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7. Hormones in Food

Abstract

A number of advances have been made in testing for residues of the veterinary growth hormones that are used in cattle production, but there is still little information about differences in hormonal activity of tissues from treated versus untreated animal foods. Despite these advances, such testing is still experimental and not used for regulatory or other routine screening, with one article noting a lack of laboratory capacity in the U.S. Most meat hormone studies continued to focus on zeranol. Research on human breast and breast cancer cells are suggestive that this estrogenic compound and it's metabolites could pose a risk for initiation and or progression of breast cancer, including long-term exposure of low levels. The relationship between pubertal development and zeranol (or the related mycotoxin) was also addressed in two limited studies.

A number of hormonal products are used in dairy production, too. Methods have been also been developed to quantify hormone levels in milk, and while differences have been found between pregnant and non-pregnant cows, no large studies were found examining differences between milk from treated vs. untreated cows. Use of these products may pose a risk for women in the dairy industry.

Very little additional research into the relationship between milk product consumption and IGF-1 levels was identified, but a meta-analysis and the new introduction of milk into the diet of Mongolian children provide additional evidence. Again, no studies with data on differences between treated vs. untreated dairy products were found.

Calls for increased understanding of and oversight of hormones in animal based foods included 1) establishing a regulatory database with relevant and updated reliable "state-of-the-art" information about the levels of natural and xenobiotic "hormones" in common food commodities of animal origin; 2) evaluating hormones in food using all facts about the actual total dietary intake of "hormones", e.g. from meat (products), poultry, milk, dairy products, eggs and fish (products) taking into account also the effects of various methods of food production and/or of "household" cooking; and 3) analyzing along the whole food chain downstream (tracking) from primary production to the consumer and upstream (tracing) from the consumer to primary production, accounting for inorganic as well as organic residues and contaminants, to assess and prioritize vulnerable food chain steps.

2007 Gaps Summary Organized by topic in chapter summary with the actual language quoted	2012 Update Targeted Scan
Biologic Effects of Hormones in Meat It is difficult to distinguish between endogenous and exogenous hormones in meat and to determine how they affect human hormone levels.	Veterinary hormones are still widely used in animal production in the U.S. Most of the research has focused on the growth hormone zeranol in cellular models **Zeranol (Z):** an implant used in beef production, it is closely related to zearalenone (Zea), a mycotoxin common in grains, which can 'carry-over' from feed to animal tissues, milk and eggs (it has also been included in bust-enhancing dietary supplements). Zeranol is expected to be extensively and rapidly absorbed from the intestinal lumen *in vivo* and reach the portal blood both as aglycones and as glucuronide and sulfate conjugates in humans [1] Zea and its metabolites are able to adopt molecular conformation, which sufficiently resembles 17β-estradiol to allow it to bind to oestrogen receptors (ERs) in target cells exerting estrogenic (agonist) actions. Review of both suspected as triggering factor for precocious pubertal development at least in prepubertal exposed girl [2] Zeranol (and DES) showed estrogenic effects by inhibiting oncosuppresor miR-34b expression and by restoring the protein levels of the miR-34b targets cyclin D1 and JAG1 in MCF-7 cells [3]. A study of uterotropic activity in ovariectomized female mice found that Z displayed a much higher binding affinity for human ERα and ERβ than Zea did. They propose that Z and Zea are less potent than 17β-estradiol because 17β-estradiol could bind to the receptor pocket without significantly changing its conformation, while Z or Zea require considerable conformational alterations upon binding to the ERs [4]. Hepatic microsomes from five species generate catechol metabolites of α-ZAL and ZAN, the highest amounts formed by human liver, followed by rat, mouse, steer and swine. The microsomal extracts and the individual catechols of α-ZAL, ZAN, E2 and E1 were found to induce oxidative DNA damage [5]. Z enhanced the mitogenic activity of leptin and increased aromatase expression in human normal breast pre-adipocytes. (-)-gossypol counteracted Z- and leptin-induced cell proliferation and aromatase expression. Z may increase estrogen biosynthesis in obese

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	individuals by increasing aromatase expression and estrogen production, promoting cell sensitivity and increase breast cancer cell growth [6]. Leptin enhanced the sensitivity of MCF-7 Adr cells to zeranol and increased cell growth. Exposure to zeranol may lead to initiation of transformation of normal breast cells to breast preneoplastic cells [7]. Growth of MCF-10A exposed to 0.2, 1 and 5% Z-containing serum (ZS) treatment for 3 weeks was 1.3, 1.75 and 1.8-fold faster compared to that of the control sera. ZS increased cyclin D1 and decreased p53 expression at the mRNA and protein levels in MCF-10A compared to the controls. More importantly, treatment of 1% Z-containing sera for 21 days stimulated MCF-10A cells anchorage-independent colony formation in soft agar which illustrates its capability of inducing human normal breast epithelial cell neoplastic transformation. These results suggest that long-term exposure of low levels of Z and its metabolites contained in beef products might be a potential risk factor in human breast cancer initiation and development [8]. In a study of proteomic effect of a low level dietary compound on potential breast cancer, the protein disulfide isomerase (PDI) was up-regulated 5-fold in the HBEC exposed to zeranol. PDI has been shown to be up-regulated in a variety of cancerous tissues, although this is the first reported up-regulation of PDI in breast tissue [9]. **Trenbolone** is a human as well as veterinary pharmaceutical. It is used in beef production is an implant (and when used illicitly by bodybuilders is associated with increased diabetes risk). H295R cell bioassay estradiol production was significantly affected by changes in concentrations of trenbolone, cyproterone, and ethynylestradiol. Exposures with individual pharmaceuticals showed the possible secondary effects that drugs may exert on steroid production. Results from binary mixture exposures suggested the possible type of interactions that may occur between drugs and the joint effects product of such interactions. Dose-

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	response results indicated that although two chemicals may share a common mechanism of action the concentration effects observed may be significantly different [10]. No studies were identified on the other implants used in beef feedlots: 17β-estradiol, testosterone and progesterone. **Roxarsone** (ROX) is an arsenic compound widely used in the poultry industry as a feed additive to prevent coccidiosis, stimulate growth, and to improve tissue pigmentation. Resulting manure contains ROX and metabolites arsenate, arsenite As(III), monomethylarsonic acid, and dimethylarsinic acid [11]. Little is known about the potential human health effects. One study found ROX exhibits a higher angiogenic index than As(III) at lower concentrations in human endothelial cells. Increased endothelial nitric oxide synthase (eNOS) activity was observed for ROX but not for As(III)-induced angiogenesis. However, As(III) caused more rapid and pronounced phosphorylation of eNOS. The two compounds have different and often opposite effects on angiogenic gene expression [12]. **Ractopamine**: A β(2)-agonist, hormonal growth feed additive used in pork production; U.S. banned in 2006, but it is still in use in other countries [13].
Exposure: Meat & Dairy	Advances are being made in chemical composition analysis, including analysis of estrogens in complex samples. However, the work is being done only in a very limited and fragmented way and its application to regulation and policy is unclear. One researcher calls for gathering and evaluating comprehensive data about the actual total dietary intake of "hormones", e.g. from meat (products), poultry, milk, dairy products, eggs and fish (products) taking into account the effects of various methods of food production and different cooking techniques [14]. The Proceedings of HVDA-2010, the 6th International Symposium on Hormone and Veterinary Drug Residue Analysis (June 2010, Belgium) were not available. **Human Exposure:** A cross-sectional analysis among 163 girls, aged 9 and 10 years found Zea in urine in 78.5% of the girls, and that urinary levels were predominantly associated with beef

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	and popcorn intake. Girls with detectable urinary Zea levels tended to be shorter and less likely to have reached the onset of breast development [15]. Women working on Pennsylvania dairy farms milked (71%) and fed (61%) routinely; 28% of the respondents administered veterinary obstetric drugs [16]. One product label includes a warning that women of childbearing age should exercise extreme caution when handling [17]. New methods for detecting Ractopamine have been developed for animal tissue and human urine [18)]. **Hormones in Animal Tissues (Meat & Eggs)** The analysis of residues in meat producing animals has known a tremendous evolution during the past 35-40 years. In the future, it can be foreseen that this evolution will proceed in the direction of the use of more and more sophisticated and expensive machines [19]. New methods permit the simultaneous determination and confirmation of trace residues of 24 different growth promoters and metabolites. Ranges of progesterone and testosterones in Irish beef imports were reported in one abstract, but were not related to the use of veterinary growth hormones [20]. The WHO evaluates toxicological and residue data on veterinary drug residues in food, but in this time frame only melengestrol was addressed and no data were presented in the abstract [21, 22]. Dutch scientists found that US beef has higher levels of 17α- and 17β-estradiol than EU beef, but that Dutch hen's eggs had the highest levels and were likely the major dietary source for average consumers [14]. **Hormones in Dairy** A variety of hormones, including follicle stimulating hormone, gonadotropin releasing hormones, progesterone and prostaglandin [17, 23] are administered to dairy cattle at

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	specific times to induce ovulation. Estimates of up to 1/3 of U.S. dairy cows are injected with rBGH. Recently a lab developed and validated methods for quantification of six sex hormones in milk [pregnenolone, progesterone, estrone (E_1), testosterone (T), androstenedione (A) and dehydroepiandrosterone (DHEA)]. Differences between milk from pregnant and non-pregnant cows were confirmed [24] Some work has also been done on levels of phytoestrogens in milk, which do not appear to differ with cow diet. Recent research sought to characterize E_1 and estrone sulfate (E_1S) concentrations in milk from a large number of individual cows, in skim and fat fractions of milk, and in retail milk. 55% of E_1 and 14% of E(1)S was associated with the fat fraction. Estimated total E_1 intake from three servings of whole milk was 68 ng/day, which represents 0.01% to 0.1% of daily production rates in human beings [25].
Biologic Evidence: Hormones in Milk & IGF-1 Levels Evidence for an overall increase in the hormonally activity of cows' milk does not currently exist. Studies cited here offer evidence of a positive association between IGF-1 levels in humans with milk consumption; however, more information is needed about the effect of IGF-1 levels in milk on the levels in humans. It is also important to evaluate differences in human response to treated and untreated milk, as well as responses to milk from dairy cow by pregnancy status and stage.	Little research was identified that addressed this topic and no studies addressed differences in IGF-1 levels or other human responses to treated versus untreated milk products. Milk has been associated with early menarche and with acceleration of linear growth in adolescence. NHANES data show a positive relationship between milk intake and linear growth in early childhood and adolescence, but not middle childhood, a period of relatively slow growth. IGF-I is a candidate bioactive molecule linking milk consumption to more rapid growth and development, although the mechanism by which it may exert such effects is unknown [26]. A meta-analysis of current evidence suggests that milk consumption may increase the circulating IGF-I level [27]. After a month of drinking whole milk, 10-11 y.o. Mongolian children had significantly higher plasma levels of IGF-I and IGF-I/IGFBP-3 than before [28].

2007 Gaps Summary Organized by topic in chapter summary with the actual language quoted	2012 Update Targeted Scan
Policy While governments in Canada and the EU have banned the use of rBST, consumers concerns about human health are driving change in the U.S. Following a few other large producers (Tillamook, some Safeway and Kroger plants), California Dairies Co., which supplies about 10% of U.S. milk, is eliminating rBST in the milk it handles by mid-2007. Kroger will finish eliminating rBST from milk it processes and sells by early 2008.	In the U.S. five hormonally active growth promoters are still legal in livestock production as ear implants (17β-estradiol, testosterone, progesterone, trenbolone and zeranol) and one as a feed additive (melengestrol acetate) in the U.S. [14, 13]. A 2010 article stated that no adequate regulatory database with relevant and updated reliable "state-of-the-art" information about the levels of natural and xenobiotic "hormones" in common food commodities of animal origin exists, and suggested that there is no adequate laboratory operation in the U.S. to analyze for residue of "hormones" in food animals or any of their products [14]. One researcher calls for chemical analysis along the whole food chain downstream (tracking) from primary production to the consumer and upstream (tracing) from the consumer to primary production to ensure food safety and quality. Such testing would take into account inorganic as well as organic residues and contaminants, the use of nitrite in meat products, the incidence of veterinary drugs, as well as a Failure Mode and Effect Analysis system to assess and prioritize vulnerable food chain steps [29]. Manure (and potentially urine) with excreted veterinary pharmaceuticals could contaminate water sources [11].

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Hormonally Active Compounds in Food Equipment, Containers and Other Confounders The use of equipment and containers with hormonally active compounds, such as plastics with the potential to leach phthalates, is an additional factor that may confound research on the role of food and should be considered in future studies.	Food additives, contaminants and compounds formed in cooking are not addressed here, including dioxins, furans, heterocyclic amines, hexachlorobenzene, nonylphenols, polycyclic aromatic hydrocarbons (PAHs), PCBs, pesticides and phthalates. Of note, however, in a 2004 report, 13% of lactating dairy cows were treated with insecticides permethrin, pyrethrin, coumaphos, and dichlorvos by daily or every-other-day coat sprays [30]. Among dairy cattle feed additives approved by FDA are acrylamide-acrylic acid resin, anhydrous ammonia, formaldehyde [31]. The Food Animal Residue Avoidance Databank (FARAD) is a congressionally-mandated risk-management program that is supported by the USDA. The program is maintained by a consortium of universities, including University of California- Davis (UCD). FARAD's primary mission is to prevent or mitigate illegal or harmful residues of drugs, pesticides, biotoxins and other chemical agents that may contaminate foods of animal origin [23]. Some endogenous and supplemental nutrients, particularly in milk, may also affect breast cancer risk, including calcium, casein (protects IGF-1 from digestion) and vitamin D (potentially protective, addressed in another chapter.)

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8. Metals

Abstract

Much of the recent literature on metals and breast cancer has focused on potential mechanisms of carcinogenicity. The estrogenic activity of select compounds was highlighted in the 2007 Gaps Document, and recent literature further supports carcinogenicity by several mechanisms, including endocrine disruption. Several new retrospective studies have found associations between higher levels of metals and risk of breast cancer or tumor size, but there is still a need for high quality prospective and occupational studies of breast cancer risk.

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"Given that there is widespread exposure to several metals that are likely to cause other types of cancer in humans and that these compounds are estrogenic, more breast cancer studies of cadmium, chromium, lead, and nickel are warranted."	Much of the recent literature on metals and breast cancer has focused on potential mechanisms of carcinogenicity. The estrogenic activity of select compounds was highlighted in the 2007 Gaps Document, and recent literature further supports carcinogenicity by several mechanisms, including endocrine disruption. **Estrogenicity** Human Biomonitoring: Blood samples from 252 healthy, premenopausal women were assessed for cadmium, lead, and mercury exposure and patterns of reproductive hormones. Authors found decreases in mean FSH with increasing levels of cadmium, and increases in mean progesterone with increasing levels of lead. Findings support the hypothesis that environmentally relevant levels of these metals are associated with modest hormone changes in healthy women [1]. Human *in vitro* and Animal *in vivo*: Cd, Cr, and Pb compounds were listed in the Gaps document as estrogenic using E-screen assay systems. A follow-up study showed Pb and Cu to be estrogenic both *in vitro* and *in vivo*. However, Cd compounds were only shown to be estrogenic *in vitro*. The authors emphasized an integrated approach of both *in vitro* and *in vivo* assays for EDCs [2]. Review/Commentary: The Gaps document states that the association between arsenic and breast cancer has been "inconsistent across studies." Davey et al. observed a concentration-dependent inhibition of estradiol *in vivo* and *in vitro* [3]. In addition, newer evidence reveals a non-monotonic dose-response (lower concentrations induced cell proliferation while higher concentrations or longer treatment periods induced apoptosis) [4]. Human Cell Culture: The Gaps document states that, "the association between breast cancer and other metals like arsenic, cobalt, and mercury has been inconsistent across studies." One recent study showed that mercuric chloride proliferated human breast cancer cells, and that

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	mercuric chloride exhibits the estrogen-like effect through binding and activating ER [5]. Human Experimental Cell Culture: The Gaps document indicates that metals act through an estrogen receptor (ER)-dependent mechanism, particularly in proliferating in ER-positive human breast cancer cell lines. (Breast cancer can be classified as either ER positive or ER negative, depending on the presence or absence of ER-α). One recent study confirms this association and additionally details the actual mechanism by which this takes place [6]. Human Experimental Cell Culture: Very limited studies have been produced on the role played by Cd on estrogen receptor-negative human breast cancer cells [7], and the Gaps document does not mention this as a potential mechanism. Benbrahim-Tallaa et al. found that low doses of cadmium malignantly transforms normal human breast epithelial cells through a mechanism not requiring ER-α into a basal-like cancer phenotype. The authors conclude that, "direct cadmium induction of a malignant phenotype in human breast epithelial cells strongly fortifies a potential role in breast cancer" [8]. The basal phenotype is clinically associated with a higher risk of relapse after treatment and lower survival rates [9]. **Other Mechanism** *In vitro*: Candeias et al. used a biochip to detect the effects of cadmium on DNA base and nucleotide repair pathways and found cadmium chloride to be a potent inhibitor of these processes, characterizing cadmium as a "very potent DNA repair poison" [10]. **Protective Metals** Review: The 2007 Gaps Document mentions that dietary zinc may have a protective effect against development of breast cancer. This review article examines the biological plausibility and mechanisms involved in zinc (II) intake and protection against breast cancer. They also note that per NHANES data, 12% of Americans do not receive adequate zinc (II), and that this deficiency could disrupt the function and signaling of molecules involved in DNA replication and repair, and affect the anti-tumor gene p53 [11].

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	Review: Although studies have indicated that selenium exposure may have an inverse association with certain cancers, there has not been conclusive evidence that selenium is protective against breast cancer. There is limited evidence for an inverse association between zinc and breast cancer (from case-control studies), but more prospective studies are needed to confirm this finding [12]. **Interactive Effects** Animal Study: The Gaps document mentions that selenium has been associated with protective effects in tumor development in mice infected with MMTV. In a follow-up study to the one mentioned in Gaps, cadmium was shown to interfere with this protective effect, and also to interact with Zn, Cu, and Cr to contribute to mammary tumor formation. The authors concluded that effective breast cancer risk reduction should reduce the exposure to Cd (and other Se-antagonistic elements) in addition to "assuring and adequate dietary intake of Se through prudent food choices or supplementation" [13]. Human Case Control: Metal analysis in blood samples of 50 cancer patients with 150 controls in Kuwait found that levels of Cu, Zn, and Se were significantly lower in breast cancer patients, as compared to controls, and the level of Cd was significantly higher. Abnormalities in metal concentration were also associated with micronucleated lymphocytes (a marker for genotoxicity) [14]. Review: The Institute of Medicine in their report Breast Cancer and the Environment summarized the evidence on metals: "All told, the evidence available for metals as risk factors for breast cancer indicates biologic plausibility for increased risk of breast cancer in association with exposure to certain metals, particularly cadmium and possibly arsenic, but metals are unlikely to be a major risk factor at environmentally relevant doses. Much of the evidence is from *in vitro* studies using concentrations of metals that are considerably higher than would occur in humans from environmental exposures" [15].

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"Occupational studies to monitor breast cancer incidence rates in occupations with exposures to cadmium, chromium, lead, and nickel, along with better characterization of exposures to these metals by job type and task."	Human Occupational Study: 69 male workers occupational exposure to As and Pb, and exposed to Cd environmentally via tobacco smoke were analyzed for biological markers of tumor formation. There was a strong positive correlation between blood concentrations of Cd and CEA, the marker of abnormal cellular differentiation. Significant correlations were also found between As, Cd, and Pb and other tumor markers (serum TPS and/or TPA concentrations) in exposed workers [16]. Population-Based Cohort Study: 586 women who were previously diagnosed at baseline were cases along with 438 newly diagnosed women; each case had 8 matched controls. The study sought to find which occupations were most at risk for having incident and prevalent breast cancer. Of all the occupations analyzed, the associations with women who work with metals (pipeline workers, welders, metal component installers, surface treatment of metals) did not indicate any positive association with breast cancer among women in this industry [17]. Human Case-Control: A study conducted in eight European countries included 104 cases and 1901 controls to assess occupations and breast cancer among men. This study did not find an increased incidence of male breast cancer among metal processors, men employed in metal manufacturing, or welders [18].
"A prospective study evaluating biological levels of these metals in blood or urine and the associated breast cancer risk. Metals are easily measured in blood or urine. Due to their persistence, a single biological measurement is likely to be representative of exposure levels over a relatively long period of time."	Unfortunately, most of the epidemiological literature on the association metals and breast cancer is still conducted retrospectively. However, the papers below use different biological media to assess metal content, produce associations to tumor size and disease progression, or analyze different metals than those mentioned in Gaps. Human Case Control/Biomonitoring: Different patterns of hair minerals were observed in breast cancer patients (n= 40) compared to normal controls (n= 144). Breast cancer patients had low calcium, magnesium, iron, copper, manganese, and zinc, whereas they had high arsenic, sodium, and potassium compared with the normal controls [19]. Human Case Control and Animal Study: Using blood samples from both male mice and human

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	cancer patients (compared to matched controls), Majumder et al.'s results indicated that copper is "linked to both tumor growth and drug resistance" in chemotherapy treatments. Blood serum of tumor-bearing mice contained higher amounts of copper than healthy mice. Analysis of patients with breast, colon or lung cancer (n=22) showed that the serum copper contents were higher in patients not responding to chemotherapy when compared to patients whose tumors responded to treatment. The copper levels in serum of healthy volunteers were lower than in cancer patients irrespective of their response to chemotherapy [20]. The Gaps document did not specifically look at copper in its analysis or the effects of potential heavy metal burden on disease progression and treatment outcomes. Human Case Control: Measured urinary concentrations of strontium in 240 invasive breast cancer patients and 246 age-matched controls. Women in the highest tertile of strontium showed 124% increased risk of breast cancer, compared to the lowest tertile after adjustment for other potential risk factors. This association was particularly strong for HER2 positive breast cancer (HER2 over-expression has been shown to result in increased invasiveness, tumourigenicity, and proliferation) [OR (95% CI): 10.92 (3.53-33.77)], and only occurred among premenopausal women [21]. Human Case Control: Higher levels of Pb were found in blood and head hair samples of newly diagnosed patients with breast cancer in Nigeria (n=12) than in cancer-free controls (n=12) from the same area. Pb levels in hair samples were directly correlated with the volume of tumors, and Pb was in the highest concentration of all the metals tested. Pb was thought to exert harm by interfering with the protective effects of Se, whose levels were also significantly reduced in cases vs. controls [22]. Human Case Control: The study was carried out on 100 female patients: 75 with breast cancer and 25 with benign breast diseases. The results showed a significant increase in urine and tissue cadmium concentrations and urine copper concentration in cancerous patients compared to controls. Lead had no significant difference between groups but it was generally

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	high in the tissue samples, while zinc had no significant difference between studied groups [23]. **Breast Tissue Analysis for Metal Content** The Gaps document highlights similar studies of this kind, but mentions that they are limited in their power due to small sample sizes (n~ 22). The findings in the studies below are worth mentioning, since their sample sizes are larger than those mentioned in the Gaps document. Although somewhat conflicting in their results, all studies showed significantly elevated levels of cadmium compared to controls. Human Experimental Cell Culture: A study of 67 breast cancer samples and 16 matched non-cancer breast tissues were examined for metal concentration. Authors reported significantly higher concentrations of cadmium and aluminum in cancerous tissue, but they did not observe a statistically significant difference for nickel [24]. Human Experimental Cell Culture/Biomonitoring: Average concentrations of Cd, Co, Cr, Cu, Fe, Mn, K, Ca, and Zn were noted to be significantly higher in malignant tissues (n=53) compared with benign tissues (n=61) [25]. Pasha et al. also analyzed plasma samples of breast cancer patients for selected trace metals compared to controls and found significantly different trace metal profiles for cancer patients, notably higher Cd, Cr, Cu, Ni, Pb, and Zn concentrations [26]. These findings are interesting because the Gaps document reveals inconsistent evidence for cobalt and a protective effect for zinc; it is unclear whether these biological levels are causal or the result of disease state or treatment. Human Cell Culture: Samples taken from the central regions of cancerous tissues generally had different concentration levels of xenobiotics and trace elements than normal tissues. The levels of lead, cadmium and zinc, copper and magnesium were all significantly higher in cancerous tissues as compared to the unaffected cells of 50 cancer patients [27]. Human Case Control: Strumylate et. al. analyzed the Cd concentration in breast tissue, urine,

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	and blood of 57 breast cancer and 51 benign tumor patients. The data showed higher concentrations of cadmium in breast tumor and urine of cancer patients. Cancer patients with positive estrogen receptors (ERs) had significantly greater concentration of breast tissue Cd compared to patients with negative ERs [28].
"Since the existing human evidence of a relationship between exposure to metals and breast cancer is weak, a prospective case-control study of breast cancer that accounts for environmental exposures to potentially carcinogenic metals by all major pathways (air, water, or diet) is needed."	Human Ecological Study: Pan et al. analyzed correlations between Cd concentrations in topsoil (considered to be the most representative of dietary exposure through food) and incidence of breast cancer in European countries. They showed general increase of cancer incidence with increasing Cd concentrations in topsoil and stream water. Authors admit that the correlation could have been confounded by factors not controlled for in the study (e.g. diet, exercise, differences in water treatment methods, etc.) [29]. **Proximity/Environmental Justice Considerations** Human Exposure Study: Although issues of environmental justice were not raised in this particular chapter of the Gaps document, it is important to note that heavy metal exposure was found to be significantly more prevalent in indoor and outdoor air in an urban fence-line community than a non-industrial community in California [30]. Human Population-Based Case Control Study: Pan et al. conducted an analysis on the relationship between breast cancer risk and residential proximity to industrial sources of metal exposure in Canada [31]. The study used data from 2343 cases with breast cancer and 2467 controls. Adjusted odds ratios showed a statistically significant increase for residing near steel mills and thermal power plants in premenopausal women, petroleum refinery and pulp mills in postmenopausal women, and for 10 or more years of residing near thermal power plants.

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9. Exposures from Polyvinyl Chloride

Abstract

Since 2007 there has been very little research on the association between exposures related to PVC and breast cancer. Two human biomonitoring studies detail the increased burden of phthalates associated with occupational exposures to PVC, but otherwise, all of the conclusions and questions from the 2007 Gaps chapter reflect the most up to date science on this topic.

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"Elucidation of the portion of body burden levels of these compounds that is attributable to the PVC life cycle is a necessary step towards reducing such exposures."	Human biomonitoring: Human biomonitoring of 156 workers from eight industries occupationally expose to phthalates found that DEHP intake estimates based on three DEHP metabolites combined were 0.6–850 μg/kg/day, with the two highest geometric mean (GM) intakes in polyvinyl chloride (PVC) film manufacturing (17 μg/kg/day) and PVC compounding (12 μg/kg/day). Levels were ~2–6-fold higher than in German adults and children, but that of platelet donors highly exposed to DEHP leaching from PVC materials used during apheresis [1]. Human biomonitoring: A study of occupational exposure to diisononyl phthalate (DiNP) in polyvinyl chloride processing operations found Creatinine-adjusted MCiOP urinary concentrations ranged from 0.42-80 μg/g in PVC film and from 1.11-13.4 μg/g in PVC compounding. Occupational exposure to DiNP associated with PVC film manufacturing tasks were substantially higher (sixfold to tenfold) than adult general population exposures; however, all daily intake estimates were less than 25% of current United States or European acceptable or tolerable daily intake estimates [2].
"Research aimed at investigating the risk of breast cancer associated with PVC plastics focusing on these individual compounds – considering the toxicokinetic properties of each, the probably timing of exposures in relationship to critical periods of breast and brain development, and the latency of breast cancer – could be fruitful."	It is likely that research on the individual compounds was conducted since 2007, but there was no such research done in the context of PVC exposure and breast cancer risk.
"…examining potential breast cancer risks in communities living near industrial sources of these exposures may allow for a more comprehensive evaluation of breast cancer risks associated with all exposures originating from PVCs."	No research

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10. Bisphenol A

Abstract

There has been an enormous amount of new research on BPA since the 2007 Gaps document. The research has documented that BPA is a ubiquitous environmental chemical and human exposure from a variety of sources is constant and largely unavoidable. There is also a strong body of evidence supporting the endocrine disrupting properties of BPA, as well as animal evidence of an effect of pre-natal exposure resulting in mammary cancer in adult animals; however, a direct link to increased risk of human breast cancer has yet to be established. Despite the large amount of information available on BPA sources, understanding of how these sources contribute to human exposures remains poor. Several animal studies have demonstrated that low dose BPA exposure affects the development of the mammary gland, mammary histogenesis, gene and protein expression in the gland, and the development of mammary cancers. These results are also consistent with the effects of low dose BPA exposure on mammary epithelial cells in culture. In order to replicate these animal studies epidemiologists must collect information about prenatal and neonatal exposures and relate them to adult breast cancer incidence-something that would take decades to conduct. [1]

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New biomonitoring methods and data from NHANES may help establish better reference ranges.	Human biomonitoring [2]: Nationally representative data on urinary levels of BPA from NHANES 2005/06 were used to estimate daily BPA intakes, and sources of exposure, and personal characteristics. Median daily intake for the overall population is approximately 34 ng/kg-day. Median daily intakes for men are statistically significantly higher than for women; there is a significant decrease in daily BPA intake with increasing age. Gender- and age-specific median intakes differ from the overall population by less than a factor of 2. Although estimates of daily BPA intake have decreased compared to 2003/04 NHANES, it is premature to draw conclusions regarding trends at this time, as there is no indication that BPA use declined from 2003 to 2006. On the basis of assessment of urinary BPA and questionnaire data from 2005/06 NHANES, consumption of soda, school lunches, and meals prepared outside the home--but not bottled water or canned tuna--was statistically significantly associated with higher urinary BPA. (Paper from 2003/04 data is less detailed.)
The potential of BPA to hasten the onset of breast development in girls needs to be explored.	Review [3]: Review of BPA and adverse health outcomes in humans, especially children. Two studies report weak associations between urinary BPA concentrations and delayed onset of breast development in girls.
Conduct occupational studies to identify groups at high risk for exposures, paying special attention to women of childbearing age.	Human Epidemiological [4]: This study examined associations between urinary BPA concentrations in workers at epoxy resin factories and laboratory parameters for health status via spot urine checks and blood samples. Samples analyzed for liver function, glucose homeostasis, thyroid function and cardiovascular diseases. The 28 participants were workers in two semiautomatic epoxy resin factories. The average urinary BPA concentration was 55.73±5.48 ng/ml (geometric mean ± geometric SD) (range 5.56-1934.85 ng/ml). BPA feeding operators showed the highest concentrations, over 10 times those of the crushing and packing and office workers. Higher BPA concentrations were associated with clinically abnormal concentrations of FT3, FT4, TT3, TT4, thyroid-stimulating hormone, glutamic-

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	oxaloacetic transaminase and γ-glutamyl transferase. Workers with higher BPA concentrations showed higher FT3 concentrations (linear trend: $p<0.001$). Conclusion: Higher occupational BPA exposure, reflected in urinary concentrations of BPA, may be associated with thyroid hormone disruption.
Document the degree to which body-burden levels change over time, i.e., how representative of lifetime exposures are a single or a few body-burden measurements?	Braun et al collected urine samples from 137 women before and during pregnancy. Urinary BPA concentrations were variable before and during pregnancy, but the magnitude of variability was biomarker specific. The authors conclude that because BPA levels were more variable during pregnancy, more than one sample is needed to classify BPA concentrations [5].
Conduct a body-burden study to examine age of puberty and amount of BPA in umbilical cord blood at birth, or BPA in urine of young children (a current aim of epidemiological studies by the Breast Cancer and Environment Research Centers, jointly funded by the National Institute of Environmental Health Sciences and the National Cancer Institute).	Methodological/Human Biomonitoring. BPA in paired human maternal and umbilical cord blood serum samples were measured. The results demonstrated that total BPA concentrations in human maternal serum at mid-pregnancy and at delivery ranged from <0.026 ng/mL to 10.425 ng/mL (median 0.548 ng/mL, n=12) and <0.026 ng/mL to 3.048 ng/mL (median 1.461 ng/mL), respectively. Results for matching umbilical cord blood serum BPA concentrations were in the range of <0.026-2.569 ng/mL (median 1.823 ng/mL). The concentrations measured in this study agreed well with BPA levels in human serum reported internationally. Only 2 mid-pregnancy serum samples out of 12 contained quantifiable amounts of conjugated BPA, indicating that BPA-glucuronide is not abundant in either human maternal or umbilical cord blood serum [6]. Since 2007 there have been several studies that have looked at BPA in umbilical cord blood from termed infants (32-41 weeks of gestation) reporting a median of 1ng/ml for unconjugated BPA levels[7-10].

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Elucidate major factors that determine body-burden levels in humans. While it is assumed that oral ingestion from contaminated food and drink is the main route of exposure in humans, this is mostly based on models and speculation, not real data. Welshons and colleagues have emphasized the importance of considering inhalation and transdermal exposures through bathing with contaminated water.	Human Biomonitoring [11]: Diet is thought to be a major route of exposure to BPA. Study looked at urinary BPA patterns in five individuals over a 48-h period of fasting (bottled water only). Personal activity patterns were recorded with a diary to investigate non-dietary routes of exposure. Given patterns found in day 1 and the subsequent decline to lower levels in day 2, hypothesize that BPA exposures in these individuals were diet-driven. On day 2, non-dietary sources may still be present, such as from dust. Another hypothesis is that small reservoirs of BPA from past exposures are released from storage (lipid reservoirs, e.g.) and excreted. Review [12]: Review of food and non-food sources of BPA, and evaluation of their contribution to human exposure. Food sources here include epoxy resins, polycarbonate and other applications, such as paperboard and polyvinylchloride materials. Non-food sources include exposure through dust, thermal paper, dental materials, and medical devices. These authors conclude that total exposure to BPA is several orders of magnitude lower than the current tolerable daily intake of 50µg/kgbw/day, but the authors judgments in making that conclusion may be open to debate. Concentrations in consumer products [13]: Study estimated exposure of non-breast-fed infants to polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/F), polychlorinated biphenyls (PCB), organochlorine pesticides (OCP), and bisphenol A (BPA) and its chlorinated derivatives through consumption of commercial infant foods with largest shares of the market in 22 European Union countries. Overall, the estimated dietary exposure to BPA via commercial baby foods was lower than the tolerable daily intake (TDI) of 50 µg kg(-1) body weight (bw). Findings indicated that the dietary exposure of 0-9-month-old infants through the products investigated here does not exceed the maximum TDI of 4 pg WHO-TEQ (toxic equivalents) kg(-1) bw. However, exposure to more than 2 pg WHO-TEQ kg(-1) bw day(-1) might occur for 0-4-month-old infants consuming 'starting' hypoallergenic formula. Considering the importance of early development and the vulnerability of infants and

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	children, it is essential to determine their dietary exposure to contaminants in order to decide which efforts of risk reduction should receive highest priority. Concentrations in consumer products [14]: Paper currencies from 21 countries (N = 156) were analyzed for BPA, which was measured in 19 mm punches taken from three spots on the paper currencies. BPA was found in all paper currencies at concentrations ranging from 0.001 to 82.7 µg/g (mean 4.94; median 1.02) and the concentrations in samples taken from the middle portion of the currencies were higher than those taken from peripheral portions. They also examined the transfer of BPA from thermal receipt paper to currencies by placing currencies in contact with thermal receipt papers for 24 h in a wallet. Concentrations of BPA dramatically increased after 24 h of contact with thermal receipt papers, suggesting that thermal receipt paper is an important source of BPA in paper currencies. The estimated daily intake of BPA through dermal absorption from handling paper currencies was on the order of a few nanograms per day. Human Biomonitoring [15]: While oral uptake of BPA is considered as the major route of exposure, the contribution of skin penetration has been a recent area of focus as it could be an important contributor to exposure. This study found that the systemic exposure to BPA via the skin contributes in a negligible way to total systemic BPA exposure. Concentrations in consumer products [16]: 4-Nonylphenol (NP) and bisphenol A (BPA) are phenolic substances used in high volumes by the industry. This study investigated possible sources of NP and BPA exposure from food, by analyzing their levels in a Swedish food market basket, based on the Swedish per capita food consumption. In food, BPA levels above LOQ (2 ng/g fresh weight) were found in fish, meats, potatoes, and dairy products. The study documented that food is a source of BPA and NP in the general Swedish population. The results indicate that there is a continuous source of exposure to NP and BPA that is high

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	enough for free NP and BPA to be detected in some consumers.
Further investigate BPA pharmacokinetics in humans, especially in infants and children. (The process by which a drug is absorbed, distributed, metabolized, and eliminated by the body.)	Human Pharmacokinetic [17]: Study of placental transfer and conjugation of bisphenol A (BPA). Human placentae obtained from healthy term singleton pregnancies were utilized in a dual recirculating model of ex vivo placental perfusion. The transfer percentage for antipyrine and BPA were 25.5 +/- 1.13% and 27.0 +/- 1.88%, respectively, and the transfer index for BPA was 1.1 +/- 0.09 after 180 minutes of perfusion. Only 3.2 +/- 1.6% of BPA in the fetal compartment was in the conjugated form. The researchers conclude that BPA at low environmentally relevant levels can transfer across the human placenta. Human Biomonitoring [18]: Using 20 study participants, this study assessed the relative concentration of BPA in blood, urine, and sweat. BPA was found to differing degrees in each of blood, urine, and sweat. In 16 of 20 participants, BPA was identified in sweat, even in some individuals with no BPA detected in their serum or urine samples. They conclude that biomonitoring of BPA through blood and/or urine testing may underestimate the total body burden of this toxicant. Sweat analysis should be considered as an additional method for monitoring bioaccumulation of BPA in humans. Induced sweating appears to be a potential method for elimination of BPA. *In Vitro* Experimental [19]: This study found interspecies differences between humans and rodents with respect to absorption, distribution, and excretion of BPA. These differences between human and rodent ABC transporters may have important implications for interspecies extrapolation used in risk assessment. Human Biomonitoring [20]: This study examined exposure of adult humans to BPA and the relationship between the serum and urinary pharmacokinetics of BPA. Blood and urine samples were collected approximately hourly over a 24-h period from 20 adult volunteers

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	who ingested 100% of one of three specified meals comprising standard grocery store food items. The volunteers' average consumption of BPA, estimated from the urinary excretion of total BPA was 0.27 µg/kg body weight (range, 0.03-0.86), 21% greater than the 95th percentile of aggregate exposure in the adult U.S. population. Serum (TOT)BPA concentrations ranged from less than or equal to limit of detection (LOD, 1.3 nM) to 5.7 nM and were, on average, 42 times lower than urine concentrations. **Studies of health impacts not categorized in 2007 Gaps:** Human Cell Line [21]: This study investigated toxic effects of BPA concentrations close to levels found in serum of pregnant women on human cytotrophoblasts (CTB). Their findings suggest that exposure of placental cells to low doses of BPA may cause detrimental effects, leading *in vivo* to adverse pregnancy outcomes such as preeclampsia, intrauterine growth restriction, prematurity and pregnancy loss. Human Cell Line [22]: Study explores effect of BPA on the EGFR-STAT3 pathway in breast cancer. Treatment with BPA (1 µM) in the presence of AG1478 for 48 h resulted in the stimulation of cell growth in MCF-7 cells, similar to that of the BPA alone treatment. BPA increases STAT3 expression, which is a major factor in the pathway of BPA-induced proliferation, and STAT3 activation contributes to BPA-induced breast cancer cell proliferation. However, EGFR mediates negative signaling for BPA-induced breast cancer cell proliferation. Human Cell Line [23]: This study examines *in vitro* BPA's effects on proliferative capacities of the human trophoblastic cell line, JEG-3. First researchers show that JEG-3 cells express the specific BPA receptor, namely estrogen-related receptor □1 (ERR□1). Secondly, demonstrate that BPA did not exert any cytotoxic action in JEG-3 cells up to 10−6 M. Moreover [3 H]-thymidine incorporation experiments revealed that BPA significantly reduced cell proliferation. The results also showed that BPA induced JEG-3 apoptosis capacity as reflected

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	by DNA fragmentation experiments. Human Cell Line [24]: The molecular mechanisms by which early memory of BPA exposure is imprinted in breast progenitor cells and then passed onto their epithelial progeny are not well understood. This study examined epigenetic changes in breast epithelial cells treated with low-dose BPA; and the effect of BPA on the ERα signaling pathway and global gene expression profiles. Researchers identified 170 genes with similar expression changes in response to BPA. Functional analysis confirms that gene suppression was mediated in part through an ERα-dependent pathway. As a result of exposure to BPA or other estrogen-like chemicals, the expression of lysosomal-associated membrane protein 3 (LAMP3) became epigenetically silenced in breast epithelial cells. These results suggest that the *in vitro* system developed in laboratory is valuable tool for exposure studies of BPA and other xenoestrogens in human cells. Individual and geographical differences may contribute to altered patterns of gene expression and DNA methylation in susceptible loci. Combination of this exposure model with epigenetic analysis and other biochemical assays can give insight into the heritable effect of low-dose BPA in human cells. Human Cell Line [25]: Authors recently demonstrated that ERRc (estrogen related receptor c) binds strongly to bisphenol A (BPA) thus retaining ERRc's high basal constitutive activity. Based on report that BPA accumulates in the human maternal–fetal placental unit, authors hypothesize that a large amount of ERRc might exist in the human placenta. Placenta was found to express ERRc extremely highly. Among the three ERRc protein isoforms, placenta exclusively expresses the type-1 isoform, which possesses additional 23-mer amino- acid residues at the N-terminus of the ordinary ERRc. This N-terminal elongation was found to elevate by approximately 50% the basal constitutive activity of ERRc, as evidenced in the luciferase reporter gene assay. The present results suggest that BPA accumulates in the placenta by binding to ERRc.

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	Human Cell Line [26]: Study examines mechanisms by which BPA induces cell proliferation, and the occurrence of bioremediation by treatment with laccase. BPA promotes human cancer cell proliferation via ERa-dependent signal transduction pathways. Similar to 17b-estradiol, BPA increases the phosphorylation of both extracellular regulated kinase and AKT. Specific inhibitors of these kinase completely block the BPA effect on cancer cell proliferation. High BPA concentrations (i.e., 0.1 and 1 mM) are cytotoxic even in ERa-devoid cancer cells, indicating that an ERa-independent mechanism participates to BPA-induced cytotoxicity. On the other hand, BPA oxidation by laccase impairs the binding of this environmental estrogen to ERa loosing at all ERa-dependent effect on cancer cell proliferation. Moreover, the laccase-catalyzed oxidation of BPA reduces the BPA cytotoxic effect. Thus, laccase appears to impair BPA action(s), representing an invaluable bioremediation enzyme. Human Cell Line [27]: Cell culture and mouse models used to examine whether the loss of BRCA1 (breast cancer susceptibility gene) function could affect BPA-mediated cell proliferation. *In vitro* they found that loss of BRCA1 enhances BPA-induced ER signaling. Their data suggest that loss of BRCA1 function may enhance BPA effects via estrogen related pathways. Human Cell Line [28]: To investigate the usefulness of a human-derived cell line, authors determined the transcriptional changes induced by BPA in Ishikawa cells at various doses and time points by comparing the response of approximately 38,500 human genes and ESTs between treatment groups and controls. Gene ontology analysis indicated that BPA results in changes to multiple molecular pathways affecting various biological processes particularly associated with cell organization and biogenesis, regulation of translation, cell proliferation, and intracellular transport; processes also affected by estrogen exposure in the uterus of the rat. These results indicate that Ishikawa cells are capable of generating a biologically relevant estrogenic response after exposure to chemicals with varied estrogenic activity, and offer an

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	in vitro model to assess this mode of action.
Consider BPA effects in context of mixtures.	Animal experimental [29]: Study looks at effects of plasticizers and their mixtures on estrogen receptor and thyroid hormone functions, including BPA. They found that tested plasticizers and phenols elicited endocrine-disrupting potential that can be mediated via interference with the estrogen and TH systems. Moreover, the observed mixture effect stresses the importance of considering the combined effect of the compounds for risk assessment of human health.
BPA exposures may be curtailed by regulatory action before we figure out if there is a breast cancer connection. If so, documenting past and persistent exposures may become critically important to studying and understanding BPA's health effects.	From google news -- In October, 2011 Governor Jerry Brown signed into law a bill known as the Toxin-Free Infants and Toddlers Act (AB 1319). Starting in 2013, the law will prohibit the use of BPA at levels above 0.1 parts per billion (ppb) in any bottle or cup intended for use by a child age 3 or younger. It also will require manufacturers to use the least toxic alternative when replacing BPA in containers intended for infants and toddlers Review/Report [30]: Given that US National Toxicology Program expressed concern for adverse effects of current level of exposure to BPA on developmental toxicity in 2008, the French Food Safety Agency (AFSSA) reviewed toxicity of doses below 5 mg/kg bw/day (the no observed adverse effect level set by different regulatory bodies). The working group concludes that toxicity studies conducted thus far in compliance with international standards do not demonstrate a hazard to human health. Report [31]: Author conducts a critical examination of the historical process by which BPA's safety has been defined and the ways the assumption has been tested and challenged by scientific research. Though scientific understanding of BPA expanded dramatically over the past 10 years, its 20-year-old safety standard, based on a threshold-dose model, has remained

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	fixed. Review [32]: NIH and US EPA convened expert panel of scientists in field of endocrine disruption, particular with knowledge and research on BPA. Panels charged with reviewing the published literature and reports in five areas, and compile a report and recommendations. Though review was published in 2007, the data for this study were derived from studies conducted by the National Toxicology Program in the 1980's.

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C. Compounds in Personal Care Products

Abstract

Research on the health effects of chemicals in personal care products has varied by chemical since the 2007 Gaps chapter. New methods for analysis of human exposure indicate that personal care products are a significant source of parabens and phthalates, but little has been done on UV filters and solvents. Since 2007 several new medical concepts, like the developmental origins of health and disease and epigenetics, have contributed to our understanding of the role of endocrine disruptors in the etiology of disease and the milieu of estrogenic compounds in personal care products may have a role in these mechanisms.

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Parabens "Given the significant role of estrogen and endocrine disruptors in breast cancer, widespread use of cosmetic products among a potentially vulnerable population of young women, and mildly suggestive toxicological data, it is logical to include parabens in the research agenda to explore etiologic factors that contribute to this disease. Future research should combine both toxicologic and epidemiologic methods, with more attention focused on exposure assessment, particularly historical exposures, given the long latency period for breast cancer. In summary, the hypothesis remains controversial and further research is needed to shed light on this question."	Review: The ability of parabens to be absorbed systemically from topical application to human subjects has been confirmed; the importance of dermal exposure has been further implicated[1]. Human Experimental Cell Culture: Intact paraben esters can be measured in human breast tissue; the authors note that it remains to be established if environmental chemicals with estrogenic properties contribute a functional component to the breast cancer disease process and propose a new approach to functionality research would be to build a profile of the distribution of multiple chemicals within and across single breasts from different locations and lifestyles[2]. Report/review: The hypothesis that paraben exposure from personal care products is related to breast cancer continues to be refuted by industry and their paid consultants [3, 4]. Human Experimental Cell Culture: While parabens were reported in the 2007 Gaps to have received the most attention as a culprit ingredient in underarm cosmetics, a 2012 study by Sappino et al used a well-established normal human mammary epithelial cell model to explore the hypothesis that antiperspirants contribute to breast cancer. They concluded that the results do not formally identify aluminium as a breast carcinogen, but challenge the safety ascribed to its widespread use in underarm cosmetics [5].
Phthalates "Despite the lack of human health studies, toxicologic evidence exists suggesting a possible link between phthalates and breast cancer. Cosmetic products have been shown to contain varying forms and amounts of phthalates and the presence of phthalates in urine and breast milk indicates that these compounds are bioavailable and remain in the body after	Human Experimental: Empirical data demonstrate that avoidance of phthalate exposure through avoidance of fragrances and hair gels, and careful selection of personal care products and changes in diet can reduce one's daily exposure to these compounds [6]. Human Epidemiologic/Reports: There have been significant advances in cumulative risk assessment methods in general [7], for phthalates in particular [8], and specifically for the anti-androgenic effects of phthalates [9, 10]. These methodological improvements demonstrate that many children are exposed to phthalates at levels of concern [9, 10].

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environmental exposure. Future research is needed to examine the role of phthalates in mammary carcinogenesis, taking into account individual exposures levels and their sources of exposure in order to plan for future risk-reduction efforts. Since phthalates are widely used in the cosmetics industry, including in nail polish, hair products, fragrances, and skin creams, future research should include studies of hairdressers, nail care workers, perfume counter technicians, makeup artists, and other occupational groups who routinely handle many of these products."	Human Case Control: A case control study among Mexican women showed for the first time a difference between various phthalate metabolites and increased breast cancer risk. The authors conclude that the various sources and levels of exposure to relevant phthalates present in cosmetics and other personal care products deserve further assessment, particularly at critical windows of exposure, such as adolescence. Also, the biological mechanisms warrant clarification [11]. Human Bio-Monitoring Methods: A 2011 by Hsu et al study is the first example demonstrating that the signal mining strategy SMAIT (signal mining algorithm with isotope tracing) can effectively and systematically discover urinary exposure makers for toxic di-isononyl phthalate esters (DINPs) [12].
Solvents "In summary, few human studies exist on the influence of organic solvents in cosmetic products on breast cancer, despite the mammary carcinogens widely used in these products. Because of the widespread use of potential mammary carcinogens in many nail and hair care products, organic solvents should become a high priority for the breast cancer research agenda. Future research should include studies of cosmetologists; particularly nail salon workers who have daily exposures to these volatile chemical compounds. These studies should focus on valid and reliable exposure assessment methods that take into account individual historical exposures. While biomonitoring methods exist to indicate recent exposure to some solvents, air monitoring may be more reflective of the current levels	Human Case-Control: A study of painters found low levels of toluene exposure can cause genetic damage, and this is related to oxidative stress, age, and time of exposure [13].

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of exposures, which may differ greatly from past exposures, given the dramatic changes in this industry in recent decades. Air monitoring may also help distinguish the source of exposure, i.e. workplace exposure as opposed to second hand smoke at home or outdoor air pollution. Identifying the source of organic solvent exposure can help with interventions to reduce levels of exposure for both workers and consumers of cosmetics. Breast cancer research related to nail salon worker exposures may be particularly of interest, as this type of business did not exist 40 to 50 years ago, workers are often younger, and it could indicate if infant and young girls are at increased risk from using nail products."	
UV Filters "Given the suggestive evidence of hormonal activity, further research is warranted into how these compounds act in humans and their role in breast cancer etiology. Greater attention should be paid to 4-MBC because of its common use and higher *in vivo* effect."	Review: A 2011 review of the carcinogenic potential of nanomaterials concluded, "no reliable conclusions can currently be drawn about exposure to nanoparticles and their release from products. Firstly, there are substantial deficits in information about the processing of nanomaterials in products and preparations. Secondly, there are only a small number of studies on nanoparticle release, and reliable techniques for measuring and monitoring nanomaterials in different environmental media are still being developed which is both complex and costly."[14] Experimental Animal: In 2012 Sharma et al demonstrated that sub-acute oral exposure to zinc oxide nanoparticles in mice leads to an accumulation of nanoparticles in the liver causing oxidative stress mediated DNA damage and apoptosis. The authors recommend that there is a need for a complete risk assessment of any new engineered nanoparticle before its arrival into the consumer market [15].

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	Non-Human Mechanistic: A 2009 study indicates that nano-sized titanium dioxide has the potential to convert benign tumor cells into malignant ones through the generation of reactive oxygen species in the target cells [16].
Estrogenic Properties and Hormonal Effects Among Compounds in Personal Care Products "While there are some noticeable differences among parabens, phthalates, and solvents with respect to their chemical properties and their purpose in products, they share very common characteristics of potential concern – estrogenic properties, other hormonal effects, and absorption into breast tissues. Curiously, there have been no systematic research efforts to examine their effects in human populations that are vulnerable to such exposures. The lack of epidemiologic studies appears to be mainly due to study design limitations (i.e. difficulties in conducting exposure assessment) and minimal resources, rather than lack of a clear rationale for further exploring these environmental links. Finding a population that is not exposed to parabens, phthalates, or solvents would be extremely difficult; therefore future studies may be best focused on *in vitro* and animal models, and longitudinal biomonitoring to compare relatively higher and lower exposures, such as the BCERC study. Reliance solely on animal studies has been criticized as providing insufficient evidence. However, evidence from these studies that indicates early-life exposures stimulate effect, when adult	Review: The developmental origins of health and disease (DOHaD) hypothesis has been expanded beyond nutrition to endocrine disrupting chemicals (EDCs) including compounds in personal care products[17], an issue that was not addressed in the 2007 Gaps chapter. Review: The science related to epigenetic mechanisms, an issue not covered in the 2007 Gaps chapter, has been greatly expanded with many ongoing studies attempting to elucidate the pathophysiological effects of gene-environment interactions[18]. Review: Phthalates (and other EDCs in personal care products) may act as "obesegens"[17, 19, 20]. Review: Parabens and phthalates can now be easily measured in the urine; testing can evaluate what exposures are occurring and monitor the effectiveness of avoidance procedures and policies[6]. Experimental Animal: An animal study found triclosan altered female reproductive development and the uterine response to exogenous estrogen, suggesting that triclosan augments estrogen action and that there is the potential for triclosan to alter estrogen-dependent function [21]. Review: Researchers at NIEHS recommend that animal bioassays for the carcinogenic health impacts of EDCs should be extended beyond 2 years and exposure should begin *in utero* [22]. Human Bio-Monitoring Methods: GC "time of flight" mass spectrometry has been proved to be a rapid and efficient technique for the screening and confirmation of anthropogenic contaminants in human breast adipose tissues. The method allows for screening for pre-

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exposures do not, should be heeded."	selected chemicals as well as for non-targeted screening, i.e., the discovery of compounds that are not included in the lists of target analytes [23].
Policy "Industry scientists are working on estimating exposure to personal care products as part of their safety assessments. Most effective would be to require more extensive testing before these products are marketed, similar to the system used for drugs. Such testing would be useful not just for synthetic compounds, but also for natural components of personal care products. For example, tea tree and lavender oils were recently suspected of causing breast growth in young boys and found to have estrogenic and anti-androgenic activity in human cell lines. Different interest groups, including industry and nonprofit organizations, have sought to influence the regulation of compounds in personal care products. Public policy appears to have been driven more by interest groups than by human health evidence, especially given the lack of human studies in this area. Often, the lack of scientific endeavors has been spun as a lack of supporting evidence for the link between the compounds and breast cancer, a misinterpretation that needs to be clarified with policy makers. Given that research has been trailing policy changes, it is imperative that more resources be dedicated to conducting human health studies on this issue to inform	Review; Human Experimental Cell Culture: The European Union has taken regulatory action to reduce human exposure to some parabens in cosmetic products and food [1, 2]. Human Epidemiologic/Reports: Combining exposures through improved methods of cumulative risk assessment allows for prioritization of policy goals based on the relative contribution of various exposures to risk [9]. Review: Public and private investment in research on low dose exposures, mixtures, and the timing of chemical exposures, as well as the development of health tracking and bio-monitoring programs designed to link data from pollution surveillance systems with disease registries were recommended as directions for breast cancer policy [24]. Levels of Chemicals in Consumer Products: A study by Dodson et al was the first to look for a large and varied suite of EDCs in consumer products including personal care products. Important policy issues identified included the limitations of rating the safety of consumer products based on the product label; unsafe product substitutions of better recognized EDCs with other, less recognized EDCs; the need to look at cumulative effects of multiple exposures; and the need for full and accurate disclosure on product labels for study and risk evaluation and to allow for informed consumer choice [25].

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sound public policy and better serve the public's interest."	

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D. Pharmaceuticals

Abstract

There has been a substantial amount of research on the association between pharmaceuticals and breast cancer since the 2007 Gaps Chapter, but only modest advancements in our general understanding of the topic. A single meta-analysis of five case-control studies found that antibiotic use is associated with a slightly elevated risk of breast cancer; however, additional research is likely needed to confirm this association. Research since 2007 generally confirms the conclusion that antidepressants do not increase the risk of breast cancer. While 7 studies indicate that statins are associated with a lower risk of breats cancer or have a chemopreventive effect on breast cancer tumor development, two new meta-analyses found that there was no association between statin use and breast cancer risk. The association between antihypertensive drugs and breast cancer remains inconclusive. In accordance with the original document, new research further implicates aspirin use in the chemoprevention of breast cancer, although the effect of other NSAID drugs is inconclusive. Substances continue to be considered one at a time. Finally, little to no research has been conducted on the relationship between breast cancer and the additional medications identified as areas for future research in the 2007 document.

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There is inconclusive evidence on the association between antibiotic use and breast cancer risk.	Meta-analysis [1]: Five case-control studies were eligible at the ever-use versus never-use analysis (13 069 cases and 73 920 controls). Antibiotic ever-use was associated with slightly elevated breast cancer risk (pooled OR = 1.175, 95%CI: 0.994-1.387). No publication bias became apparent. Meta-regression showed a borderline dose-response effect implicating the number of antibiotic prescriptions. Antibiotic use seems associated with slightly elevated breast cancer risk. The underlying nature of the association remains elusive, as it may be direct or due to secondary associations, that is, causal or confounding. At any case, this is a finding with potentially important public health implications, which should be further examined in the literature. Human Case Control [2]: A total of 3099 breast cancer cases and 12,396 matched controls were included. The incidence of breast cancer was higher in subjects who had more antibiotic prescriptions during the 1-15 years prior to the index date (RRs = 1.50, 1.63, 1.71 and 1.79 for the four quartiles, respectively, p-trend = 0.0001). Similar results were found when a number of units were considered. There was no effect of the timing of antibiotic exposure on breast cancer risk. Similar patterns of increased risk of breast cancer were detected for the specific antibiotic classes. A dose-dependent increase in breast cancer risk was observed in association with the antibiotic exposure up to 15 years in the past. However, the lack of temporal trends and the absence of class-specific effects suggest a non-causal relationship.
No strong evidence pointing to a significant role of antidepressant drugs in breast cancer development.	Meta-analysis [3]:The overall risk of breast cancer did not increase among AD users [adjusted odds ratio (aOR) 1.02; 95 % CI 0.96-1.08]. Those who took tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs) were not at increased risks of breast cancer. In subgroup meta-analyses, null associations were consistent across the type of AD, funding sources, the number of adjusted variables, medication dose, the ascertainment of exposure, and methodological quality. In subgroup analyses based on exposure duration, a marginal association was observed for the use of SSRIs < 1-2 years (aOR 1.10; 95 % CI 1.02-1.19). However, this effect was attenuated over time and those using SSRIs for more than 1-2 years had no elevated breast cancer risk. These results support the lack of a clinically meaningful association between AD use and the development of breast cancer and provide considerable reassurance. Given that the

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	data collected to date do not support changing the current prescribing patterns for ADs, the important benefits of AD therapy must be considered. Review [4]: The epidemiological and preclinical studies compiled in this review indicate a predominantly inhibitory action of antidepressants on cancer prognosis. Although some reports suggest an association of antidepressants with an increased risk of cancer, these differences may rely on the type of cancer and the antidepressant tested. As a future direction, it will be necessary to perform further studies examining these two parameters. Additionally, studies have clearly shown that the direct action of antidepressants on tumor cells is oncostatic. Interestingly, antidepressants seem to exert their control of cancer progression through a mechanism involving the modulation of the cell cycle and apoptosis in tumor cells. Review [5]: Both the pre-clinical and clinical data are mixed in terms of showing an association between AD use and breast and ovarian cancer. The possibility that ADs may exhibit a bi-phasic effect, whereby short-term use and/or low dose antidepressants may increase the risk of breast and ovarian cancer, warrants further investigation. Industry affiliations were significantly associated with negative conclusions regarding cancer risk. Human Experimental Cell Culture [6]: Multidrug resistance (MDR) is the main obstacle in breast cancer chemotherapy, a reversal reagent with high reversal effect but low toxicity is the hotpot issue at present. The antidepressant fluoxetine (FLX) is a new highly effective chemosensitizer; however, the possible mechanism of FLX in reversal of MDR is unclear. In this study, the effect of FLX on MDR mediated by apoptosis was researched in resistant/sensitive breast cancer cells. Findings indicated that by synergism with anticancer drugs, FLX modulation of apoptosis via targeting p53 and Bcl-2 expression, FLX reverse the breast cancer cell's resistance and enhance the chemosensitivity to ADM and PTX. Human Case Control [7]:In this large population-based case-control study, no conclusive evidence of breast cancer risk associated with the use of SSRIs was found even after assessing

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	the degree of serotonin reuptake inhibition and duration of use. Results do not support the serotonin-mediated pathway for the prolactin-breast cancer hypothesis. Human Epidemiologic [8]: The use of antidepressants or NSAIDS was not related to breast cancer mortality in long-term breast cancer survivors. In these women, however, antidepressants may increase the risk of all-cause mortality. Human Case Control [9]: Study of breast cancer recurrence nested in the population of female residents of Denmark who were diagnosed with non-metastatic estrogen-receptor positive breast cancers between 1994 and 2001 and who took tamoxifen for at least one year. About the same proportion of recurrent cases (37 of 366) and matched controls (35 of 366) received at least one prescription for citalopram or its s-stereoisomer while taking tamoxifen (adjusted odds ratio = 1.1, 95% confidence interval = 0.7, 1.7). Breast cancer patients taking other SSRIs were also at no increased risk of recurrence (adjusted odds ratio = 0.9, 95% confidence interval = 0.5, 1.8). Human Epidemiologic [10]: To characterize whether some selective serotonin reuptake inhibitor (SSRI) antidepressants reduce tamoxifen's effectiveness by inhibiting its bioactivation by cytochrome P450 2D6 (CYP2D6). Paroxetine use during tamoxifen treatment is associated with an increased risk of death from breast cancer, supporting the hypothesis that paroxetine can reduce or abolish the benefit of tamoxifen in women with breast cancer. By contrast, no such risk was seen with other antidepressants. Human Case Control [11]:The association between use of antidepressant medications and breast cancer risk was null (OR = 0.89, 95%CI 0.78-1.01). When stratified by type of antidepressant, use of selective-serotonin reuptake inhibitors (SSRIs) resulted in a similar risk overall (OR = 0.85, 95%CI 0.72-1.00) and among former and currents users. There were no associations between other types of antidepressant classes and breast cancer risk. In assessing risks among the five most commonly used antidepressants, no association with fluoxetine, sertraline, venlafaxine, or

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	buproprion hydrochloride was detected. There was a reduction in breast cancer risk of 36% (OR = 0.64, 95%CI 0.45-0.92) among users of paroxetine hydrochloride.
No strong evidence pointing to a significant role of statin drugs in breast cancer development.	Meta-analysis [12]: A comprehensive search for studies published through November 2006 was performed. Twenty case-control studies (100 129 incident cancer cases) were combined to obtain a pooled odds ratio using an inverse variance method. A funnel plot did not suggest a significant absence of unpublished data. The studies were significantly heterogeneous (P<0.01), thus a random effects model was used. The pooled OR and 95% confidence intervals for statin users and cancer were as follows: any cancer 0.71 (0.56-0.89), breast cancer 0.86 (0.60-1.23), colon cancer 0.89 (0.82-0.97), lung cancer 0.75 (0.50-1.11), and prostate cancer 0.74 (0.45-1.20). In this meta-analysis of case-control studies, a significant association between statin usage and any cancer was found, but when stratified by cancer type, only the association with colon cancer remained. On the basis of these results, randomized control trials with longer follow-up times than previously used are warranted. Meta-analysis [13]: A total of 24 (13 cohort and 11 case-control) studies involving more than 2.4 million participants, including 76,759 breast cancer cases contributed to this analysis. No evidence of publication bias and evidence of heterogeneity among the studies were found. Statin use and long-term statin use did not significantly affect breast cancer risk (RR = 0.99, 95 % CI = 0.94, 1.04 and RR = 1.03, 95 % CI = 0.96, 1.11, respectively). When the analysis was stratified into subgroups, there was no evidence that study design substantially influenced the effect estimate. Sensitivity analysis confirmed the stability of these results. Cumulative meta-analysis showed a change in trend of reporting risk of breast cancer from positive to negative in statin users between 1993 and 2011. The meta-analysis findings do not support the hypothesis that statins' have a protective effect against breast cancer. More randomized clinical trials and observational studies are needed to confirm this association with underlying biological mechanisms in the future. Systematic review [14]: Eighteen studies on the effects of statin use on breast cancer risk do not

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	lend strong support for a strong association between statin use and breast cancer risk. Data for any effects of statins on cancer prognosis and secondary prevention are lacking; with the exception of consistent evidence that statins are associated with reduced risk of advanced/aggressive prostate cancer. Statins appear safe in relation to cancer risk but any chemopreventive effect in humans remains to be established and should not be recommended outside the context of clinical trials. It is encouraging that numerous trials are ongoing. The prospect of reducing the incidence and burden of some of the most prevalent cancers with safe, affordable and tolerable medication that already reduces the risk of the leading cause of death and cardiovascular disease warrants further exploration in clinical trials and observational studies of prognosis and survival. Prospective Cohort [15]: A nationwide, population-based prospective cohort study of all female residents in Denmark diagnosed with stage I-III invasive breast carcinoma who were reported to the Danish Breast Cancer Cooperative Group registry between 1996 and 2003 (n = 18,769) was conducted. Women were followed for a median of 6.8 years after diagnosis. Prescriptions for lipophilic and hydrophilic statins were ascertained from the national electronic pharmacy database. Simvastatin, a highly lipophilic statin, was associated with a reduced risk of breast cancer (adjusted 10-year risk difference = -0.10, 95% confidence interval = -0.11 to -0.08) recurrence among Danish women diagnosed with stage I-III breast carcinoma, whereas no association between hydrophilic statin use and breast cancer recurrence was observed. Human epidemiologic [16]: A retrospective study of 703 women showed significant reduction in breast cancer recurrence among patients who used ACE-inhibitors/ARBs (hazard ratio (HR) = 0.57; 95% CI: 0.37-0.89; p = .013) or statins (HR = 0.43; 95% CI: 0.26-0.70; p < .001). After adjusting for multiple variables, the use of ACE-inhibitors/ARBs (HR = 0.49; 95% CI: 0.31-0.76; p = .002) and statins (HR = 0.40; 95% CI: 0.24-0.67; p < .001) remained significant and an additive effect was found on those who used both drugs (HR = 0.30 95% CI: 0.15-0.61; p = .001). No association was found regarding overall survival. The use of ACE-inhibitors/ARBs, statins, and the combination of both were all associated with a reduced risk of breast cancer recurrence. This

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	observation should prompt further exploration. Randomized-Control Trial [17]: A perioperative window trial of fluvastatin was conducted in women with a diagnosis of DCIS or stage 1 breast cancer. Patients were randomized to high dose (80 mg/day) or low dose (20 mg/day) fluvastatin for 3-6 weeks before surgery Proliferation of high grade tumors decreased by a median of 7.2% (P = 0.008), which was statistically greater than the 0.3% decrease for low grade tumors. Paired data for CC3 showed tumor apoptosis increased in 38%, remained stable in 41%, and decreased in 21% of subjects. More high grade tumors had an increase in apoptosis (60 vs. 13%; P = 0.015). Serum CRP did not change, but cholesterol levels were significantly lower post statin exposure (P < 0.001). Fluvastatin showed measurable biologic changes by reducing tumor proliferation and increasing apoptotic activity in high-grade, stage 0/1 breast cancer. Effects were only evident in high grade tumors. These results support further evaluation of statins as chemoprevention for ER-negative high grade breast cancers. Human Cell Line [18]: In this study, the effects of lovastatin acid and lactone on breast cancer MDAMB231 and MDAMB468 cells were evaluated using a combination of proteomic and metabonomic profiling techniques. The combination of proteomics and metabonomics enabled us to identify several key targets essential to the antitumor activity of lovastatin. The results imply that lovastatin has the potential to reduce the growth of breast cancer cells. Animal *in vivo* [19]: This study is the first report on the preventive effects of fluvastatin in experimental breast cancer *in vivo*. In this experiment, the antineoplastic effects of fluvastatin in the chemoprevention of N-methyl-N-nitrosourea-induced mammary carcinogenesis in female rats were evaluated. Fluvastatin at higher concentrations suppressed tumor frequency by 63% and tumor incidence by 33% in comparison with the controls. After fluvastatin treatment, immunohistochemical analysis of tumor cells showed a decrease in vascular endothelial growth factor receptor-2 expression by 86% and an increase in caspase-3 by 8.5%. Fluvastatin in both treated groups significantly increased the parameters of serum lipid metabolism and significantly

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	decreased femur compact bone thickness and body weight in animals. These results suggest that fluvastatin and other statins should be further evaluated for tumor-preventive characteristics. Retrospective cohort [20]: Via electronic pharmacy records from the Kaiser Permanente Northern California Cancer Registry on 2,141 female patients listed in 2003 as incident cases of breast malignancy. Breast cancer patients with exposure to statins have proportionately fewer ER/PR-negative tumors that are of lower grade and stage. Although the data set cannot address whether statins affect the incidence of breast cancer, it was shown that statin use may influence the phenotype of tumors. This suggests a new potential strategy for breast cancer prevention, that of combining statins with agents that prevent ER-positive cancer (tamoxifen, aromatase inhibitors). Human Case-Control [21]: Cases of incident invasive breast cancer in women 50 years of age or older and diagnosed from 1995-2001 were identified from population-based cancer registries in Wisconsin, Massachusetts, and New Hampshire. Overall, breast cancer cases were not more likely than controls to have ever used statins. Ever use of lipophilic statins as a group (simvastatin, lovastatin, and fluvastatin) and ever use of the hydrophilic statin pravastatin were also not associated with breast cancer risk. Ever use of fluvastatin was associated with a decreased risk of breast cancer (odds ratio [OR], 0.5; 95% confidence interval, 0.3-0.8) but the magnitude of the ORs did not vary across categories of duration of use.
Somewhat inconclusive evidence on the effect of antihypertensive drugs.	Meta-analysis [22]: Patients randomly assigned to receive Angiotensin-receptor blockers (ARBs) had a significantly increased risk of new cancer occurrence compared with patients in control groups (7.2%vs 6.0%, risk ratio [RR] 1.08, 95% CI 1.01-1.15; p=0.016). When analysis was limited to trials where cancer was a prespecified endpoint, the RR was 1.11 (95% CI 1.04-1.18, p=0.001). Among specific solid organ cancers examined, only new lung-cancer occurrence was significantly higher in patients randomly assigned to receive ARBs than in those assigned to receive control (0.9%vs 0.7%, RR 1.25, 1.05-1.49; p=0.01). No statistically significant difference in cancer deaths was observed (1.8%vs 1.6%, RR 1.07, 0.97-1.18; p=0.183). This meta-analysis of randomized

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	controlled trials suggests that ARBs are associated with a modestly increased risk of new cancer diagnosis. Systematic Review [23]: To investigate the association between angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) and disease progression and survival in cancer patients. ACEI/ARB use was protective against breast cancer recurrence (HR 0.60, 95% CI 0.37-0.96). Review [24]: A recent meta-analysis of RCTs found a significant increase in the risk of cancer with ARBs when compared with control, eliciting a safety review by the Food and Drug Administration. Subsequently, more robust meta-analyses have refuted these findings, demonstrating no association between any of the currently used antihypertensive agents and cancer. Despite the complex methodology of these meta-analyses, the randomized trials used for analysis are fraught with inconsistencies, including the availability of cancer outcomes, a brief time to follow-up as compared with the latency of cancer, and heterogeneous use of antihypertensive agents. The medical literature has long hypothesized potentially carcinogenic effects of antihypertensive agents, but to date there is no convincing evidence that any of the individual antihypertensives in clinical use, at the dosages and duration tested, lead to higher rates of cancer. Prospective Cohort [25]: Compared with women who reported no use of antihypertensive medications (AHTs), women who had used calcium channel blockers (CCB) within the past two years had a 1.6-fold increased risk of breast cancer (95 % confidence interval (CI): 1.0-2.5), and in particular, recent users of immediate-release CCBs had a 2.4-fold increased risk (95 % CI: 1.3-4.5). Neither ever nor recent use of any other type of AHT was associated with breast cancer risk. While the observed association between immediate-release CCBs and breast cancer risk is based on a small sample size and needs to be interpreted cautiously, this result is consistent with others in the literature.

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	Prospective Cohort [26]: The association between hypertension, antihypertensive (AH) medication use, and breast cancer in a large prospective study, the California Teachers Study (CTS), was investigated. Use of AH medication for >/=5 years, when compared with no use, was associated with a modest increased risk of invasive breast cancer (RR = 1.18, 95%CI 1.02-1.36). This increased risk appeared to be confined to estrogen receptor (ER)-positive tumors (RR = 1.21, 95%CI 1.03-1.43) and pre-/peri-menopausal women (RR = 1.58, 95%CI 1.11-2.25. Human Case-Control [27]: Digoxin was the sole cardiac glycoside prescribed to subjects during the study period. There were 324 breast cancer cases (5.8%) and 2,546 controls (4.6%) with a history of digoxin use at least 1 year before their index date (adjusted odds ratio (OR): 1.30; 95% confidence interval: 1.14 to 1.48). The breast cancer OR increased modestly with increasing duration of digoxin exposure (adjusted OR for 7 to 18 years of digoxin use: 1.39; 95% confidence interval: 1.10 to 1.74). The association was robust to adjustment for age, receipt of hormone replacement therapy, coprescribed drugs, and confounding by indication. A comparison of screening mammography rates between cases and controls showed no evidence of detection bias. These results suggest that digoxin treatment increases the risk of invasive breast cancer among postmenopausal women. Human Case-control [28]:The risk of developing breast cancer among patients taking both aspirin and an ACE inhibitor decreased as the ACE inhibitor dose increased. Among patients receiving between 28 and 364 cumulative defined daily doses (cDDDs) of aspirin, the adjusted odds ratios (ORs) were 0.97 (0.90-1.06), 0.91 (0.82-1.03), and 0.79 (0.68-0.92) for women taking ACE inhibitors for 0-27, 28-364, and more than 365 cDDD, respectively. Among women receiving more than 365 cDDD of aspirin, the adjusted ORs were 0.91 (0.80-1.03), 0.81 (0.70-0.94), and 0.81 (0.71-0.92) as the ACE inhibitor dose increased, respectively. The findings of this nationwide analysis support the hypothesis that ACE inhibitors enhance the antitumor effect of cyclooxygenase inhibitors on breast cancer.

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Suggestive evidence implicating aspirin use in the chemoprevention of breast cancer	Seventy-three studies of NSAID's, Aspirin and other selective COX2-inhibitors were identified. Only reviews and meta-analyses studies are shown here to help consolidate the findings. Meta-analysis [29]: A total of 33 studies (19 cohort studies, 13 case-control studies, and 1 randomized controlled trial [RCT]) that included 1,916,448 subjects were identified. The relative risks from individual studies were pooled using a random-effects model, heterogeneity, and publication bias analyses. In a pooled analysis of all studies, aspirin use was associated with reduced risk for breast cancer (odds ratio [OR] = 0.86, 95% confidence interval [CI] = 0.81, 0.92). In the subgroup analysis by study design, results were similar except for RCT (OR = 0.98, 95% CI = 0.87, 1.09). In conclusion, this meta-analysis indicated that regular use of aspirin may be associated with reduced risk of breast cancer. More RCT were needed to confirm this association in the future. Meta-analysis [30]: This review included cohort-studies and case-control-studies from 2001-2005, which evaluated the association between aspirin and breast cancer risk. The authors identified 10 studies which met the inclusion criteria. The combined estimate of the RR was 0.75 (95%CI: 0.64, 0.88) using the random effects model. The combination of frequency and duration of aspirin use resulted in a significant dose-response-relationship between aspirin use and breast cancer risk. The results of the meta-analysis support the current evidence that aspirin may reduce breast cancer risk. Moreover, a dose-response-relationship seems to exist. However, results have to be interpreted carefully, as exposure categories were defined very heterogeneously among the studies weakening the validity of the pooled estimates. Meta-analysis [31]: A total of 38 studies (16 case-control studies, 18 cohort studies, 3 case-control studies nested in well-defined cohorts, and 1 clinical trial) that included 2 788 715 subjects were identified. The results of these studies suggest that overall, NSAID use was associated with reduced risk for breast cancer (relative risk [RR] = 0.88, 95% confidence interval [CI] = 0.84 to 0.93). Specific analyses for aspirin (RR = 0.87, 95% CI = 0.82 to 0.92) and ibuprofen (RR = 0.79, 95% CI = 0.64 to 0.97) yielded similar results. Future research should include careful

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	evaluation of the biologic mechanisms involved in the relationship between NSAIDs and breast cancer. Meta-analysis [32]: Overall 26 studies with 528,705 participants were included. The RR of NSAIDs use and the incidence of breast cancer was 0.94 (95% CI: 0.88-1.00) with random effects model. A slight reduction of breast cancer by taking aspirin and ibuprofen was both observed with pooled RR of 0.91 (95% CI: 0.83-0.98) and 0.81 (95% CI: 0.67-0.97), respectively. These results indicate that NSAIDs use is associated with a slight decrease for the development of breast cancer with a marginally statistical significant difference. The associations are slightly more obvious in aspirin and ibuprofen use. Systematic Review [33]: Fifteen case-control studies show that regular use of aspirin reduces the long-term risk breast cancer (OR 0·81, 95% CI 0·72–0·93, psig=0·0002, phet=0·003) and the risk of distant metastasis. Results of methodologically rigorous studies are consistent with those obtained from randomized controlled trials, but sensitivity is particularly dependent on appropriately detailed recording and analysis of aspirin use.
Other medications that have not been subjects of epidemiological studies on their relationship to breast cancer may also warrant further investigation. These include medications that supplement thyroid hormones; anti-seizure medications such as Dilantin; steroidal drugs, including those used to treat asthma and those used and abused by young female athletes; and Ritalin, for its possible impact later in life after use in childhood.	Case-control [34]: The two cohorts were: (1) earlier cohort: 78,118 female members who received prescriptions in 1969-1973, of whom 2,467 developed breast cancer, and (2) later cohort: 3,289,408 female members who received prescriptions in 1994-2006 of whom 24,528 developed breast cancer. In the later cohort furosemide, and metronidazole showed statistically significant but very small increases in relative risk (ranging from 1.07 to 1.13). Of these, only furosemide showed increased risk in the earlier cohort: 2-year lag relative risk 1.66 (95% confidence interval 1.23-2.24) or as low as 0.97, assuming uncontrolled positive confounding. Griseofulvin showed significant increases in the later cohort: relative risk for three or more prescriptions 1.48 (1.08-2.03) or as low as 1.23 assuming uncontrolled positive confounding and non-significant increases were noted in the earlier cohort. These findings are limited by their inconsistency across the two cohorts and an inability to directly control for most established breast cancer risk factors. Although inconclusive, these findings suggest a need for more research

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	on furosemide and griseofulvin.

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E. Infectious Agents

Abstract

Generally, there have been no major shifts or revelations in infectious disease research with regards to its role in breast cancer since the 2007 report. The majority of the recent literature in this area focuses on the causative role of HPVs in breast cancer. Based on this scan of the literature, the hypothesis remains controversial and HPV DNA sequencing and detection depends largely on the methods used. Similarly mixed results were found for many of the other infectious diseases that have been studied in recent years.

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"Infectious and immunologic conditions predisposing to or protecting against breast cancer are plausible but have not been well studied. In this effort, we have reviewed available evidence for only a few of the infectious agents that could be relevant to breast cancer development. Many common infectious agents, including Helicobacter pylori and all classes of parasites, have been rarely considered as they might associate with breast cancer risk."	Human Epidemiologic/Reports: A review of 74 female populations around the world with cancer registries examined correlations between BC and microbial cancers (i.e. cervical, liver, and stomach due to their established causal associations with HPV, hepatitis virus, and *H. pylori* respectively). They found an inverse relationship between the two rates with a hyperbolic association. Authors hypothesize that BC etiology may have an appreciable link with microbial exposures (and/or immunological responses to them), the lack of which, especially in early life, may elevate BC risk [1]. Human Experimental Cell Culture: Human breast cancer cell lines were experimentally infected with genes from *Schistosomiasis japanicum* parasite. Results showed enhanced migration and proliferation of cancer cells through binding to the cell's receptor and causing up-regulatory expression [2]. **General Review Articles:**[1] Review: A 2008 review stated that, "The precise role that viruses play in tumorigenesis is not clear, but it seems that they are responsible for causing only one in a series of steps required for cancer development… Based on current research, substantial, but not conclusive, evidence that HPV, EBV and MMTV may be involved in breast cancer" [3]. Review: Describes that studies based on PCR detection techniques are subject to false-positive and false-negative results, particularly for HPV, and encourage immunohistochemical techniques in addition. Authors cite unpublished data that correlate low levels of p53 protein and the presence of HPV with noninvasive ductal carcinoma [4].

[1] These three review articles provided a review of the current state of the literature on this topic, and are worth reviewing for more in-depth information on this topic.

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	Report/Book Chapter: In order to explain the eightfold difference in breast cancer incidence between Western and Asian populations, Lawson put forth a hypothesis that is a combination of viral infection and shifting dietary patterns. "Oncogenic viruses such as MMTV and high-risk HPVs may initiate some breast cancers in most populations. Furthermore, dietary patterns are suggested to determine circulating sex hormone levels, which in turn promote the replication of the hormone-dependent viruses MMTV and HPV. In addition, diet and hormones promote growth of both normal and malignant cells" [5].
"As a first step, associations of relevant markers of infections and microbial exposure should be examined in a study population with adequate exposure variation. The diversity of the California population with respect to race/ethnicity, socioeconomic status, and immigration status would be important to ensuring appropriate heterogeneity. However, the very low prevalence of some of the infectious exposures of interest (e.g. parasites) might support an international or other multicenter study design. To the extent that serologic (e.g. antibodies) markers are available for exposures of interest, these studies should be designed to rely upon these measurements for exposure classification." "Future studies should pursue interactive links between infectious agents and environmental contaminants. Research should also examine the role of chronic infectious disease in altering pubertal timing and circulating hormone levels in ways that might	Human Epidemiologic: A prospective cohort of 100 births to determine "exposure" of newborn infants to colostrum and breast milk. This study also included a review of the breastfeeding practices of 87,000 Australian mothers. They found near universal exposure to breast milk, regardless of whether or not they were fully breastfed. This challenges the assumption that human milk borne viruses cannot be associated with breast cancer [6]. **Role of Immune System:** Human Bio-Monitoring: Blood samples were analyzed from 103 cases and 103 matched controls for the presence of allergen-specific IgE. Authors found a positive correlation between serum IgE, allergic history, and breast cancer. This suggests an IgE-mediated allergic response among women with breast cancer (hypothesis is that the immune system can enhance the inflammatory response and favor malignant transformation). Further studies should investigate whether this should be considered a risk-marker in susceptibility in development of breast cancer [7]. Review: Review explains immunosuppression mechanism as potentially protective against breast cancer development, and implicates a subgroup of human endogenous retroviruses (HERV-K) [8]. These HERV-K sequences can be activated by other viral infections, and reports suggest a potential role in breast cancer pathogenesis. These include a study that found 7-fold higher concentrations of HERV-K RNA in plasma when compared to healthy controls [9].

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lower breast cancer risk."	
"Although an infectious etiology for breast cancer remains elusive, the field of infectious disease oncology is only in its infancy. With the advent of translational medicine modalities in research, there is an historic opportunity to integrate basic science, immuno-epidemiology and clinical trial disciplines. New technologies, such as DNA and protein microarrays, have potential to identify molecular signatures and gene expression profiles associated with different cancers. The UC campuses have been in the vanguard of this movement, and are well equipped to assist in this challenge. The human immune system has co-evolved with infectious agents. The adaptive and homeostatic features of this extraordinary system enable the vast majority of hosts to escape the long-term consequences of infection, including cancer. Through our own cross-talk, the cross-talk of the host-pathogen ecosystem may be revealed. The future of this branch of breast cancer research may well hold the clues to our past."	The majority of the recent literature in this area seemed to focus on the causative role of HPVs in breast cancer. Based on this review, the hypothesis remains controversial and HPV DNA sequencing and detection depends largely on the methods used. Therefore, the evidence has been summarized and grouped by association and large-scale reviews. **HPV:** *Positive Associations* Human Case Control: 130 samples (79 cases, 51 controls) were analyzed for HPV infection in northern Iran. HPV was found to increase the risk of breast cancer (OR: 14.25, P=0.019) and high-risk HPV genotypes (16 and 18) were the predominant type [10]. Human Case Control: A Mexican study with 51 cases and 43 controls were analyzed, and found 29.4% of cases carry HPV-DNA, while it was completely absent in the controls [11]. Human Tissue and Sequence Analysis: Researchers used PCR and histology with light microscopy techniques to "unambiguously" demonstrate the presence of high-risk HPV in breast cancer specimens and breast cancer cell lines. They also found similar oncogenic characteristics of HPV-associated breast cancer with cervical cancer, i.e. that putative koilocytes are present [12]. Human Tissue and Sequence Analysis: Koilocytes are known to be the precursors of some HPV-associated cervical cancer, and were found in fixed normal and malignant specimens investigated by histology plus immunohistochemistry. The authors of this study concluded that HPVs may be causally associated with breast cancer. The presence of HPV E6 and koilocytes was demonstrated in the normal breast skin and lobules of some women who had cosmetic breast surgery, indicating HPV infection prior to carcinogenesis [13].

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	Human Tissue and Sequence Analysis: In a cohort of 113 Syrian breast cancer patients, 61% of samples were HPV positive. Expression of the E6 onco-protein of high-risk HPVs correlated with Id-I overexpression, which is an important regulator in BC metastasis, in the majority of invasive breast cancer samples [14]. *Negative Associations* Human Case Control: Two retrospective case-control studies in China found a low frequency of HPV infection in both patients and controls [15;16]. Human Tissue Analysis: In a population of Mexican breast cancer patients, analysis of 118 samples of breast epithelial tissues found no evidence of HPV DNA sequences [17]. Similarly in 81 samples of Swiss breast cancer patients, no HPV DNA was found [18]. Human Tissue Analysis: In a Japanese study, authors found that HPV was present in 21% of breast carcinomas, and was absent in normal breast tissue of cancer patients. However, they concluded that the low viral load of HPV in malignant tissues suggests that a correlation is unlikely [19]. Human Bio-Monitoring: Prospective samples of 252 patients with both blood and breast tissues samples of Indian women from different geographic regions did not find any evidence of HPV DNA by real-time or conventional PCR [20]. *Reviews* Systematic Review: 29 primary studies were analyzed and found overall significantly higher HPV DNA prevalence in breast cancer samples. Review of 9 case-control studies also showed breast cancer to be associated with HPV [21]. Meta-Analysis: A meta-analysis of 10 case-control studies also showed significant increase in

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	breast carcinoma risk with HPV positivity [22]. Review: Authors state that several studies have found tissues positive for high-risk HPV subtypes, while other studies did not detect any HPV. "Given these conflicting data and the established complexity of the association between HPV with other cancers, a definitive relationship between human breast cancer and HPV infection has not been determined" [23]. **MMTV:** Human Tissue Analysis: Microarray-based analysis of nonmalignant and tumor samples from 23 patients revealed no evidence for MMTV or human MMTV-like virus transcripts [24]. Genetic Sequence Analysis: Authors found that retroviral sequences with homology shared with MMTV were present in 40% of sporadic breast cancers in American women. In particular, they found a 71% higher incidence of these viral sequences in inflammatory breast cancers, and conclude that the MMTV analog is associated with a particularly malignant phenotype [25]. Another study found evidence of MMTV-like sequences coding for viral envelope proteins (*env* genes) in human breast cancer tissue. Expression of Wnt-1 sequences was higher in invasive ductal carcinoma [26]. Human Case Study: MMTV-like sequences were detected in the breast tumors of a father, daughter, and mother living in the same house, all diagnosed with late onset breast cancer. Data suggest that DNA sequences were not human derived, and the possibility exists that the infection may have resulted from shared exposure to mice [27]. Human Experimental Cell Culture: Authors compared the expression profile of two breast cancer cell lines, one containing MMTV-like sequences and one without. The MMTV-like cell lines upregulated inflammatory genes. These results suggest that the cells were most likely responding to an infectious agent, and support the hypothesis that a viral infection may play a role in breast cancer pathogenesis [28].

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	Human Tissue Analysis: In 42 breast cancer specimens from an Australian breast cancer study, no MMTV *env* sequences were found via PCR. The authors caution against inferring a role for MMTV or a human analog in breast cancer without highly specific serology data to support this association [29]. Human Experimental Cell Culture: MMTV was shown to infect and rapidly spread in cultured, health mammary cells. This was the first study to show that human cells can sustain productive MMTV infection and replication [30]. **Chronic Hepatitis:** Human Case Control: Analyzed population-based insurance claims dataset in Taiwan (1,958 patients and 7,832 matched controls) for prevalence of hepatitis B and C. HCV infection, but not HBV, was associated with early onset risk of breast cancer (<50 years old) in areas endemic for HBV and HCV [31]. Human Case Control: Prospective study to evaluate the prevalence of breast tumors in patients with chronic hepatitis C infection in France (294 cases and 107 controls). Despite the trend of increased prevalence in the HCV group, the differences were not statistically significant. The authors concluded that HCV infection was not a strong promoter of breast carcinoma [32]. **HCMV:** Human Cell Culture: Specimens of normal breast tissue and carcinoma were obtained from 21 breast cancer patients. Human cytomegalovirus (HCMV) expression was detected in normal and neoplastic breast epithelial tissue in high percentage, raising the possibility that viral infection may be involved in the neoplastic process [33]. Review: Implicates HCMV as a tumor promoter via biological processes that support chronic

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	inflammation. Authors conclude that, "sufficient evidence exists to implicate a potential role of HCMV in oncogenesis via HCMV-mediated effects of cells in the tumor microenvironment and in the tumor cells themselves" [34]. Human Case Control: 123 primary breast carcinomas and matched non-tumor breast tissues were analyzed for the presence of human polyomaviruses JC and BK. Only JCV DNA was detected in breast carcinoma cases (23%). JCV was correlated with the "triple negative" phenotype, suggesting that these are viral-related tumors [35]. **HIV:** Human Epidemiologic: A cohort of 860 HIV-infected women in Brazil was followed to assess the incidence of breast cancer. Researchers found that the rate of breast cancer in this population was similar to that in the general female population of Brazil, but patients were diagnosed later and suffered worse prognosis [36]. Human Epidemiologic: In an observational cohort of sub-Saharan African HIV patients, the standardized incidence ratio for breast cancer was significantly lower than the general population of the region (SIR 0.29) after 12,746 patient-years of follow up [37]. Review: Purpose of the review was to assess the burden of non-AIDS-defining malignancies in the era of antiretroviral therapy (ART). Review cited recent studies that show a reduced risk of breast cancer with ART use, including one large cohort from the US with RR = 0.4, p=0.027 [38; 39]. Some researchers have postulated that these findings might be related the long period of HIV immunosuppression or might be due to the antiviral activity of ART, if mouse retroviruses contribute to human breast cancer (i.e. that it supports the oncoviral hypothesis) [40]. Results from a small study of 12 HIV patients diagnosed with breast cancer, suggested that the degree of immunocompromise (CD4 count) is not correlated with tumorigenicity [41]. Human Case Control: One nested case-control study (23 cases, 69 controls) in the U.S. found

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	that low breast cancer risk with HIV is specifically linked to CXCR4-using variants of HIV. These variants are thought to exclusively bind to and signal through a receptor that is commonly expressed on hyperplastic and neoplastic breast duct cells (adjusted OR = 0.10) [42]. Human Epidemiologic/Reports: Study linked 15 US population-based HIV and cancer registries to assess the burden of cancer among those living with HIV from 1991-2005. They reported an increase in the burden of breast cancer in this population over time, but it is unclear whether the incidence rate changed. Therefore, the observed trend could be due to increases in the population of women living with AIDS, as treatment prolongs life [43]. **EBV:** Meta-Analysis: 24 studies and 1535 cases were reviewed, and found that 29.32% of breast cancer patients were infected with Epstein-Barr virus, with lobular breast carcinoma showing the strongest association. There was a significant increase in breast malignancy risk in patients testing positive for the Epstein-Barr virus (OR = 6.29) [44]. Human Case Control: Serum samples from 354 BC cases and 504 matched controls were assessed for levels of EBV antigen and Interleukin-10 (IL-10) and interferon-γ (IFN-γ), which are believed to play a critical role in the host's responses to EBV infection. Results suggest that EBV may contribute to the risk of BC and that this contribution may be modified by genetic variations in IFN-γ [45]. Human Case Control: 58 cases of malignant breast disease and 63 benign controls were analyzed for the presence of EBV antigen in breast tissue. Results show that antigen expression was seen in a significant proportion of breast cancer tissue specimens from rural India and as compared to patients with benign breast diseases. These patients also have a higher immunological response against the EBV antigen [46]. Human Tissue Analysis: 55 BC patients in Chile were analyzed for HPV and EBV. HPV virus was

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	integrated into all of the tumors, but with relatively low viral load. There was a statistically significant association between EBV presence and poor survival (P=0.013). Authors conclude that it is unlikely that HPV and/or EBV play a direct role in BC etiology [47]. Human Case Control: Prospective study of 108 cases of pregnancy-associated breast cancer and 208 matched controls revealed that there was an increased risk (OR: 7.7) for individuals who had sufficient vitamin D intake and EBV antibodies. Authors suggest that EBV reactivation may be an indicator of the progression of breast cancer occurring soon after pregnancy, while the virus probably is not the aetiological agent [48]. **Exacerbating BC:** Experimental Animal: Mice latently infected with gammaherpesvirus 68 (HV-68) showed similar breast primary tumor burden, but much greater metastatic disease when compared to mock treated controls. The mechanisms responsible for this exacerbation were surmised to be indirect since no virus was detected in cancerous tissues [49]. Human Tissue Analysis: EBV-positive tumors were associated with a more aggressive phenotype, more frequent oestrogen receptor negative and with high histological grade [50]. Review: Authors posit a model for EBV in the progression of carcinomas via increased expression of factors involved in angiogenesis and cell invasion. They conclude that, "the possibility that EBV may be involved in the pathogenesis of breast carcinomas has to be taken into account, even if this type of ''association'' does not reflect ''traditional'' infection as in EBV-related tumors" [51].

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F. Ionizing Radiation

This issue was referred by the Steering Committee for a comprehensive sysrtematic review which will be conducted in 2013.

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G. Electric and Magnetic Fields

Abstract

There has only been a small amount of research on the association between EMF and breast cancer since 2007 and the majority of that research confirms the conclusions reached in the 2007 Gaps report. There have been some studies on gene regulation as a potential mechanism for EMF carcinogenicity and some additional insight into occupational exposures. However, the questions asked in the 2007 Gaps report largely remain unanswered.

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Lack of evidence for an association between magnetic field exposures and breast cancer etiology in women.	Meta-analyses [1]: Exposure to extremely low-frequency electromagnetic fields (ELF-EMF) has been suggested to increase female breast cancer risk; however, the data have been inconclusive. A total of 15 studies published over the period 2000 to 2009 including 24,338 cases and 60,628 controls were involved in this meta-analysis. The results showed no significant association between ELF-EMF exposure and female breast cancer risk in total analysis (OR = 0.988, 95% CI = 0.898-1.088) and in all the subgroup analyses by exposure modes, menopausal status, and estrogen receptor status. Review [2]: Extremely low frequency (ELF) and radio frequency (RF) magnetic fields (MFs) pervade our environment. Whether or not these magnetic fields are associated with increased risk of serious diseases, e.g., cancers and Alzheimer's disease, is thus important when developing a rational public policy. The evidence indicates that long-term significant occupational exposure to ELF MF may certainly increase the risk of both Alzheimer's disease and breast cancer. There is now evidence that two relevant biological processes (increased production of amyloid β and decreased production of melatonin) are influenced by high long-term ELF MF exposure that may lead to Alzheimer's disease. There is further evidence that one of these biological processes (decreased melatonin production) may also lead to breast cancer.
A new insight into mechanism, a new exposure assessment strategy, or the identification of a different group of highly-exposed women for study would likely be needed to change the balance of evidence.	Human epidemiologic [3]: The aim of the present study was to assess occupationally induced chromosomal damage in EMF workers exposed to low levels of radiation. The authors used conventional metaphase chromosome aberration (CA) analysis and the micronucleus (MN) assay as biological indicators of non ionizing radiation exposure. The results of this study demonstrated that a significant induction of cytogenetic damage in peripheral lymphocytes of workers occupationally exposed to EMFs in electric transformer and distribution stations. In conclusion, the findings suggest that EMFs possess genotoxic capability, as measured by CA and MN assays; CA analysis appeared more sensitive than other cytogenetic end-points. It can be concluded that chronic occupational exposure to EMFs may lead to an increased risk of

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	genetic damage among electrical workers. Animal *in vivo* [4]: When the authors compared the effects of MF exposure on cell proliferation in the mammary gland of various outbred and inbred rat strains, Fischer 344 was the only inbred strain that exhibited a marked increase in cell proliferation. Based on these data, the authors suggested that MF exposure should significantly facilitate development and growth of mammary tumors in Fischer 344 rats, which was tested in the present study. MF exposure significantly facilitated mammary tumorigenesis. The incidence of rats with grossly recorded, histologically verified adenocarcinomas was increased by 45% (P = 0.0095). The most pronounced MF effect on tumor incidence was seen in the cranial inguinal complexes (L/R5). These data indicate that Fischer 344 rats are a suitable inbred strain to study the mechanisms underlying the effects of MF exposure on mammary tumorigenesis. Animal *in vivo* [5]: Previously, the authors observed rat strain differences in the MF response of breast tissue, so that the genetic background plays a role in MF effects. The present experiment aimed to elucidate candidate genes involved in MF effects by comparison of MF-susceptible Fischer 344 (F344) rats and MF-insensitive Lewis rats.: A remarkably decreased α-amylase gene expression, decreases in carbonic anhydrase 6 and lactoperoxidase, both relevant for pH regulation, and an increased gene expression of cystatin E/M, a tumor suppressor, were observed in MF-exposed F344, but not in Lewis rats. The MF-exposed F344 breast tissue showed alterations in gene expression, which were absent in Lewis and may therefore be involved in the MF-susceptibility of F344. Notably α-amylase might serve as a promising target to study MF effects, because first experiments indicate that MF exposure alters the functionality of this enzyme in breast tissue. Human Cell Line [6]: The molecular mechanism of the impact of EMFs on cells is not yet clear, although changes in gene expression have been reported in various cellular systems. In this investigation, the interference of low-frequency EMFs with the plasminogen activator system was examined in BC cells. Expression of the urokinase plasminogen activator gene and of

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	plasminogen-activator inhibitor-1 was markedly increased. The expression of the receptor for urokinase plasminogen activator was only marginally increased in 1 of the 2 tested cell lines and expression of the tissue plasminogen activator was at least slightly down-regulated in BC cells exposed to EMFs. EMFs may be able to increase the metastatic potential of breast tumors. The use of this newly established exposure system for EMFs may allow for the study of the signaling processes involved in the induction of a metastatic phenotype of breast cancer cells.
If an interest in EMF's persists, a focus on the occupations posing the greatest potential exposures to EMF's among women may be warranted.	Human Case-Control [7]: The population-based case-control study included 2,386 incident breast cancer cases diagnosed in 2000-2003, and 2,502 controls. The authors found statistically significant excesses of breast cancer among engineers (OR=2.0; 95% CI: 1.0-3.8), economists (2.1; 1.1-3.8), sales occupations-retail (1.2; 1.0-1.5), and other sales occupations (1.2; 1.0-1.5). Industries showing significantly elevated risks included special trade contractors (2.2; 1.2-4.3), electronic and electric equipment manufacturers (1.7; 1.1-2.7); and public administration/general government n.e.c. (2.7; 1.3-5.7). Each of these findings was supported by a statistically significant positive trend for duration of employment (P<0.05).
New evidence of an underlying biological mechanism should precede future epidemiologic investigation.	

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H. Light at Night

Abstract

The role of LAN in breast cancer is being actively studied on many fronts, looking at molecular and genetic mechanisms and population studies. The measurement of the melatonin metabolite that had only been used twice when the original chapter was written has now been used to look for differences in melatonin levels in occupational and non-occupational studies of women, including BC case-control studies. Lower melatonin levels have been consistently associated with higher breast cancer risk in post-menopausal women, however the relationship has been inconsistent in pre-menopausal women. While most occupational studies continue to support the association between LAN and BC risk, this field has suffered from inconsistent definitions and measures. IARC held a workshop to address this problem. Issues of sleep timing, duration and the presence of ambient light are current areas of inquiry, with evidence of an association with BC risk. The many genetic studies have provided support for the importance of the circadian rhythm in BC. One researcher claims that "(c)ircadian deregulation of gene expression has emerged to be as important as deregulation of estrogen signaling in breast tumorigenesis." Melatonin could play a role in breast cancer treatment and prevention, with some calling for action now in healthcare settings.

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Biologic Evidence: Melatonin Actions There is mounting evidence that disruptions in the circadian rhythm play a role in breast carcinogenesis… There is substantial evidence that these effects are mediated by melatonin, although there are a number of other potential mechanisms that deserve further attention.	Many studies addressed the actions of melatonin and the mechanisms by which it may affect breast cancer initiation or promotion. The relationship between melatonin and the menstrual cycle has also been studied but is not included here. Melatonin is a Selective Estrogen Receptor Modulator (SERM) and a Selective Estrogen Enzyme Modulator (SEEM) properties. SERM actions (modulation of estrogen-regulated cell proliferation, invasiveness and expression of proteins, growth factors and proto-oncogenes are observable only in cells expressing ERα, and mediated by MT1 melatonin receptors. Melatonin acts like a SEEM, inhibiting expression and activity of P450 aromatase, estrogen sulfatase and type 1, 17β- hydroxysteroid dehydrogenase, but stimulating that of estrogen sulfotransferase [1]. The melatonin-mediated circadian regulation and integration of molecular and metabolic signaling mechanisms that may be involved in human breast cancer growth are grouped in 5 categories here. 1) The anti-proliferative effects of the circadian melatonin signal (involving the activation of MT(1) melatonin receptors expressed in human breast cancer cell lines and xenografts.) In ERα+ human breast cancer cells, melatonin suppresses both ERα mRNA expression and estrogen-induced transcriptional activity of the ERα via MT(1)-induced activation of G(αi2) signaling and reduction of cAMP levels. Melatonin inhibits cell proliferation and induces apoptosis in MDA-MB-361 breast cancer cells in vitro by suppressing the COX-2/PGE2, p300/NF-κB, and PI3K/Akt/signaling and activating the Apaf-1/caspase-dependent apoptotic pathway [2]. 2) Regulates the transcriptional activity of enzymes involved in estrogen metabolism, and the expression of core clock and clock-related genes. Significant suppression of CYP19A1 transcription and aromatase activity at pharmacological, physiological and sub-physiological concentrations [3].

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	Meltonin inhibited the individual and combined transcriptional activity of ERα by RORα1 and E(2) in MCF-7 breast cancer cells [4]. Melatonin has also been shown to downregulate the expression of antiadipogenic cytokines (TNF-α and interleukin-11 and -6), which decreases the levels of these cytokines, stimulating the differentiation of fibroblasts and decreasing both aromatase activity and expression, thereby reducing the number of estrogen-producing cells proximal to malignant cells [5]. 3) Anti-invasive/anti-metastatic actions of melatonin involve the blockade of p38 phosphorylation and matrix metalloproteinase expression. 4) Inhibits the growth of human breast cancer xenografts via MT(1)-mediated suppression of cAMP leading to a blockade of linoleic acid (LA) uptake and its metabolism to the mitogenic signaling molecule 13-hydroxyoctadecadienoic acid (13-HODE). Down-regulation of 13-HODE reduces the activation of growth factor pathways supporting cell proliferation and survival. 5)Studies in both rats and humans indicate that light-at-night (LAN) induced circadian disruption of the nocturnal melatonin signal activates human breast cancer growth, metabolism, and signaling [6]. One study's finding suggested that melatonin may modulate miRNA and gene expression as an anticancer mechanism in human breast cancer cells (found that 22 miRNAs were differentially expressed in melatonin-treated MCF-7 human breast cancer cells) [7]. Researchers found that aMT6 (metabolite of melatonin) levels were significantly positively associated with mammographic density in premenopausal women, but not in postmenopausal women [8]. Lower levels of melatonin in aging women may increase the risk of progressing ER-positive breast cancer through a decreased ability to suppress CYP19A1 expression and subsequent

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	local estrogen production in breast adipose and breast cancer-associated fibroblasts [3]. The anti-carcinogenic action of melatonin at the physiological concentrations attained at night has been demonstrated on MCF-7 cells [9]. A study of the biochemical composition and growth properties of breast cyst fluid among women with gross cystic breast disease found that melatonin and estrogen independently predicted growth inhibition and stimulation, respectively [10].
Melatonin Production & Levels Given the fairly strong evidence that melatonin is likely to play an etiologic role in breast cancer, identifying the determinants of melatonin levels should be a research priority. The recent identification of a urinary marker for melatonin levels in humans (aMT6) offers the opportunity to more directly evaluate the role of melatonin in mediating the effects of light at night. To date, only two studies have utilized this marker, offering conflicting results. Melatonin production may be especially sensitive to blue light at levels as low, or lower than, those documented in rodents. There may be a window of vulnerability to light exposures. These avenues of inquiry deserves further attention. **aMT6** = Metabolite of melatonin	Melatonin production decreases with age. Studies of postmenopausal women have identified that the melatonin metabolite aMT6 is significantly associated with a lower risk of developing breast cancer and aMT6 levels are lower among postmenopausal women with BC. Studies of aMT6 among premenopausal women with BC have been inconsistent. Among postmenopausal women breast cancer risk decreased with increasing sleep duration; those who reported 9+ h of sleep showed a relative risk of 0.67 compared with women who reported < or =6 h of sleep. This inverse association was observed primarily in lean women. Urinary aMT6 levels increased with increasing self-reported hours of sleep. Melatonin levels were 42% higher in those with 9+ versus those with < or =6 h of sleep [11]. A comparison of premenopausal night and day shift nurses found that levels of aMT6 were significantly lower and reproductive hormone (FSH and LH) levels were higher during daytime sleep and nighttime work, relative to day shift workers sleep and work times and aMT6 was also lower compared to their off-night nighttime sleep [12]. Measures of aMT6s in premenopausal women with breast cancer and matched controls showed a positive association with risk of breast cancer. However, subclinical disease may influence melatonin levels, with a possible inverse association among women diagnosed further from recruitment. The influence of lag time needs to be evaluated in further studies. [13].

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Biologic Evidence: Non-Melatonin There is substantial evidence that these effects are mediated by melatonin, although there are a number of other potential mechanisms that deserve further attention. Evaluation of the role of pineal peptides has been suggested as a course of further study.	The molecular mechanisms by which diurnal and circadian rhythms regulate cell proliferation are not well understood; a molecular interpretation of how clock-related mechanisms may link to tumor development remains elusive. LAN exposure can accelerate tumor growth *in vivo*, in part through continuous activation of IGF-1R/PDK1 signaling. In MCF-7 tumor-bearing nude rats, Proliferating cell nuclear antigen (PCNA) levels were highest in the early light phase then lowered, however the LAN exposed group continually expressed PCNA at a high level. Expression of IGF-1R correlated with fluctuations of PDK1/PCNA and circulating IGF-1 concentrations were elevated in the LAN-exposed rats [14]. No studies of pineal peptides were identified.
Epidemiologic Evidence No other occupational exposure with known or potential carcinogenicity is as common as work at night [20]. Identifying factors which may limit or reduce the harmful effects of night-shift work should be a research priority. Evaluation of whether permanent and rotating night-shift work confers the same risk may be fruitful. Future incidence studies of breast cancer among blind women would be strengthened by incorporation of measured levels of circulating melatonin, greater sample sizes, and information on age of onset of visual impairment and on other breast cancer risk factors. The results from sleep studies are intriguing and	More night and shift work studies have provide further evidence that night shift-work may increase the risk for breast cancer, however exposure continues to be defined and measured inconsistently. In addition to artificial light exposure in the working environment, several researchers call for LAN in the sleeping habitat or domestic exposure to LAN to be considered as a potential risk factor for BC. **Occupational – Night and Shift work** IARC convened a workshop in April 2009 which identified major domains to be captured in future studies: (1) shift system (start time of shift, number of hours per day, rotating or permanent, speed and direction of a rotating system, regular or irregular); (2) years on a particular non-day shift schedule (and cumulative exposure to the shift system over the subject's working life); and (3) shift intensity (time off between successive work days on the shift schedule) [15]. A few studies have used more expanded definitions/measures of shift work. While one suggests that the largest impact on risk is associated with the most disruptive shifts, another

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warrant further study.	points to the number of consecutive night shifts. Danish nurses who worked rotating shifts after midnight had a significantly increased risk of breast cancer compared to nurses with permanent day work, but not evening work. The highest OR (2.6; 1.8-3.8) was associated with long-term day-night rotating shifts [16]. Among Norwegian nurses, the only significantly increased risk was seen in nurses who worked ≥5 years with ≥6 consecutive night shifts (OR = 1.8) [17]. For Chinese women lifetime night-shift exposure indices were created using a job exposure matrix and self-reported data on frequency and duration of night-shift work. Breast cancer risk was not associated with frequency, duration, or cumulative amount of night-shift work. There were no indications of effect modification [18]. In the Nurses' Health Study cohort an increased concentration of urinary aMT6s was statistically significantly associated with a lower risk of breast cancer (OR for the highest versus lowest quartile 0.62; P(trend) = 0.004). There was no apparent modification of risk by hormone receptor status of breast tumors, age, body mass index, or smoking status. 19 **Blind Women** No relevant studies of blind women were identified. **Sleep Duration/Timing** Exposure to light-at-night (LAN) in the "sleeping habitat" was significantly associated with BC risk (OR = 1.22), controlling for education, ethnicity, fertility, and alcohol consumption [20]. In Japanese women, short sleep duration (</=6 h per day) was associated with higher risk of breast cancer, compared with women who slept 7+ h per day, (OR 1.62; P(trend)=0.03) [21]. In Connecticut, a suggestive but non-significantly increased risk of breast cancer was observed among postmenopausal women who kept lights on while sleeping (OR = 1.4), mainly slept in

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	the daytime (OR = 1.4), and did not draw the window shades while sleeping at night (OR = 1.2) [22]. **Ecologic** Researchers looking at country-level light at night found a significant positive association between population LAN level and incidence rates of breast cancer (30-50% higher risk), but not colorectal, larynx, liver, and lung cancers. The possibility that under-reporting from low-LAN countries created a spurious association was evaluated in several ways and shown not to account for the results [23].
Biologic Evidence: Genetic In evaluating the role of melatonin in breast cancer etiology, genetic susceptibility must be considered. The recent identification of a number of 'clock genes,' which regulate the circadian rhythm and appear to be important in cell cycle regulation and apoptosis throughout the body, calls for investigation of how these genes may alter an individual's susceptibility to disruptions of the circadian clock by exposures to light at night [34].	"Circadian deregulation of gene expression has emerged to be as important as deregulation of estrogen signaling in breast tumorigenesis [24]." Some have suggested that genetic variations in circadian genes could be novel biomarkers for breast cancer risk. Some researchers are exploring whether LAN exposure's effect on breast cancer risk may be modified by polymorphisms and/or epigenetic alterations in the circadian genes, and conversely whether LAN exposure can induce deleterious epigenetic changes in these genes [25]? A variety of genes have been examined: CLOCK, TIMELESS, NPAS, CRY2, Per3. Studies of genetic mechanisms do have appear to have directly addressed LAN, but some have addressed melatonin production and even sleep behavior. Significant correlations between SNPs associated with the central circadian regulator CLOCK and breast cancer risk, with apparent effect modification by ER/PR status. Hypermethylation in the CLOCK promoter reduced the risk of breast cancer, and lower levels of CLOCK expression were documented in healthy controls relative to normal or tumor tissue from patients with breast cancer. Identified a cancer-relevant network of transcripts with altered expression following CLOCK gene knockdown. Possible set of circadian gene variants as candidate breast cancer susceptibility biomarkers [26].

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	One study suggested that estrogen signaling could be affected not only in ER A-negative breast cancer, but also in ER A-positive breast cancer due to lack of circadian availability of ER A. Entrainment of the inner clock of breast epithelial cells, by taking into consideration the biological time component, provides a novel tool to test mechanistically whether defective circadian mechanisms can affect hormone signaling relevant to breast cancer [24]. Molecular epidemiologic studies suggest that the core circadian genes play a role in breast tumorigenesis, possibly by influencing hormone regulation or other pathways relevant to cancer. Researchers identified genetic and epigenetic differences of the circadian regulator TIMELESS with apparent effect modification by ER/PR status, suggesting a possible set of circadian biomarkers for breast cancer susceptibility [27]. Core circadian gene cryptochrome 2 (CRY2) CRY2- cells accumulate significantly more unrepaired DNA damage than CRY2+ cells (P = 0.040), in MCF-7 cells. While this suggested that CRY2 may be important for DNA repair, no other significant responses were noted [28]. In the Neuronal PAS domain protein 2 (NPAS2), a study of 3 non-synonymous polymorphisms found that women with the heterozygous Ala394Thr genotype had a significantly higher breast cancer risk than those with the common homozygous Ala394Ala (OR = 0.61, 0.46-0.81, P = 0.001) [29]. A novel functional SNP in NPAS2 was identified but did not find significant associations in either of two distinct case-control studies [30]. Length variant of Per3 (5-VNTR) has been associated with increased risk in young women, and this same 5-VNTR variant has also been found to predict morning diurnal type and shorter sleep duration compared to the 4-VNTR variant [25]. A study of three genes that mediate the effects of melatonin found that common genetic variation in melatonin receptors 1a and 1b may contribute to breast cancer susceptibility, and that associations may vary by menopausal status and some of variants have been associated with altered function or expression of insulin and glucose family members. (No significant

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	breast cancer associations were found for variants of AANAT) [31]. Other researchers explored five genetic and epigenetic processes and found: (1) melatonin influences transcriptional activity of nuclear receptors (ERα, GR and RAR) involved in the regulation of breast cancer cell growth; (2) melatonin down-regulates the expression of genes responsible for the local synthesis or activation of estrogens including aromatase, an effect which may be mediated by methylation of the CYP19 gene or deacetylation of CYP19 histones; (3) melatonin inhibits telomerase activity and expression induced by either natural estrogens or xenoestrogens; (4) melatonin modulates the cell cycle through the inhibition of cyclin D1 expression; (5) melatonin influences circadian rhythm disturbances dependent on alterations of the light/dark cycle (i.e., light at night) with the subsequent deregulation of PER2 which acts as a tumor suppressor gene [32].
Treatment - Melatonin Substantial and provocative findings from laboratory studies on the effectiveness of melatonin in cancer treatments highlights the need to further pursue the usefulness of melatonin/light-dark therapies in breast cancer treatment regimens. Very limited data from clinical trials in humans suggest chronotherapy, which aims to administer anticancer drugs at optimal times of the circadian clock, may be a promising avenue to pursue.	Melatonin exhibits anti-inflammatory and anticancer effects and could be a chemopreventive and chemotherapeutic agent against breast cancer. The effect of light and melatonin in breast cancer patients or survivors and well-being, fatigue, coping and stress is not included here, nor is light related therapies (e.g. cardioprotective radiotherapy.) In vitro study indicates that melatonin inhibits cell proliferation and induces apoptosis in MDA-MB-361 breast cancer cells in vitro by simultaneously suppressing the COX-2/PGE2, p300/NF-κB, and PI3K/Akt/signaling and activating the Apaf-1/caspase-dependent apoptotic pathway [2]. Melatonin in combination with all-trans retinoic acid and somatostatin potentiated the effects of melatonin alone on MCF-7 cell viability and growth inhibition; this phenomenon was associated with altered conductance through Ca^{2+} and voltage-activated K^{+} (BK) channels, and with substantial impairments of Notch-1 and epidermal growth factor (EGF)-mediated signaling. The combined treatment also caused a marked reduction in mitochondrial membrane potential and intracellular ATP production as well as induction of necrotic cell

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	death [33]. Melatonin-related compounds could be useful for treatment of the side effects associated with chemo- or radiotherapy. Because of its SERM and SEEM properties, and its virtual absence of contraindications, melatonin could be an excellent adjuvant with the drugs currently used for breast cancer prevention (antiestrogens and antiaromatases). The antioxidant actions also make melatonin a suitable treatment to reduce oxidative stress associated with chemotherapy, especially with anthracyclines, and radiotherapy [34].
Prevention While the mechanism by which disruptions in circadian rhythm affect breast cancer risk have yet to be fully elucidated, the evidence that nighttime shift work increases breast cancer risk is internally consistent and makes biological sense. No other occupational exposure with known or potential carcinogenicity is as common as work at night [20]. Identifying factors which may limit or reduce the harmful effects of night-shift work should be a research priority. Evaluation of whether permanent and rotating night-shift work confers the same risk may be fruitful.	Since the strongest suppression of nocturnal melatonin occurs with wavelength light of the blue spectral region, optical and lightening devices filtering the blue light spectrum have been proposed to avoid the risks of light-induced suppression of nocturnal melatonin [1]. Studies of the effect of shift work have identified several negative health outcomes, most notably breast cancer. Disruption of circadian rhythm by exposure to light at night has been identified as the mechanism likely responsible for this outcome. This article recommends that health care institutions work with occupational health nurses to develop and implement hazard communication and policies concerning shift work, exposure to light at night, and increased risk for negative health outcomes, particularly breast cancer [35]. Strategies now available to reduce the potential for circadian disruption include extending the daily dark period, limit light in nocturnal awakening, using dim red light for nighttime necessities, and unless recommended by a physician, not taking melatonin tablets [36]. Melatonin-related compounds could be useful for prevention, especially when the risk factors are obesity, steroid hormone treatment or chronodisruption by exposure to LAN [34].

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I. Vitamin D and Sunlight

Abstract

Research on the association of vitamin D and breast cancer conducted since 2007 largely supported the conclusions drawn in the original Gaps chapter. Since the 2007 Gaps, the evidence that vitamin D is associated with reduced risks of breast cancer has shown mixed results, with an IOM committee finding no evidence of a relationship between vitamin D and breast cancer; a large case control study finding a significant protective effect of vitamin D in postmenopausal women; and the experimental and human studies continuing to provide evidence for a protective effect of vitamin D on the breast and the benefits of vitamin D for the breast appear strongest for premenopausal women. Research since 2007 has not adequately addressed the questions posed in the Gaps chapter; in particular, there has been limited exploration of the racial or ethnic differences in sunlight exposure and vitamin D serum levels, a central issue that was also outstanding in the 2007 chapter.

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"All together, the experimental and human studies provide evidence for a protective effect of vitamin D on the breast."	Perspective/Review: Members of the IOM committee that established the Dietary Reference Intakes for vitamin D conducted a comprehensive review of the topic that revealed that research on vitamin D and cancer is inconsistent and does not establish a cause–effect relationship. The Members specifically noted that no large-scale randomized clinical trial of vitamin D has been completed with cancer as the primary pre-specified outcome [1]. Human Cell Culture: Breast cancers classified as triple negative or BRCA1 deficient are among the most aggressive and difficult to treat. Typically, BRCA1-deficient cells are growth arrested by the protein 53BP1. This study demonstrated that one of the key pathways in the development of this type of breast cancer is activation of cathepsin L (CTSL)–mediated degradation of 53BP1, allowing bypass of the characteristic growth arrest upon loss of BRCA1 function. The study found that the highest levels of CTSL were associated with low nuclear vitamin D receptor (VDR) levels, suggesting that VDR levels could be a biomarker for this type of cancer and that vitamin D supplementation could potentially be an effective therapeutic strategy [2].
"The benefits of vitamin D for the breast appear strongest for premenopausal women."	Generally, the literature supported this claim; however, there was one large case-control study that made the case for the benefits of vitamin-D in postmenopausal women. Human case-control: A population-based case-control study in Germany of incident breast cancer patients aged 50-74 found that serum 25(OH)D concentration was significantly inversely associated with post-menopausal breast cancer risk [3].
What are the racial/ethnic differences in sunlight exposure and circulating vitamin D levels among women in California?	No research
Can differences in blood serum levels of vitamin D	Human case-control: A population-based case-control study in the Southwestern U.S. found

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explain racial disparities in breast cancer progression, mortality or aggressiveness? Palmieri notes that darker skin pigmentation has been associated with larger-sized tumors and increased frequency of lymph node involvement. Are racial differences in vitamin D status – and perhaps access to sunlight--playing a role here?	similar patterns of associations between breast cancer risk and vitamin D supplementation in Hispanic and non-Hispanic white women [4]. Cohort: An investigation of vitamin D insufficiency within the Southern Community Cohort Study found statistically significant associations with three single nucleotide polymorphisms (SNPs) in five vitamin D pathway genes only in African Americans compared to Caucasians. A genotype score, representing the number of risk alleles across the three SNPs, alone accounted for 4.6% of the variation in serum vitamin D among African Americans [5]. Commentaries: Two commentaries in the Journal of the National Medical Association appear to discuss the role of vitamin D in explaining breast cancer disparities between white and black populations, but the journal was not accessible [6, 7].
How does air pollution interfere with UVB irradiance and thereby vitamin D photosynthesis among women in California?	No research
Is timing of exposure important for the anti-carcinogenic benefits of vitamin D?	No research
What aspects of the built environment – housing density, sidewalks, safety, playgrounds, community gardens, workplace policies, distance to shopping and schools – influence vitamin D levels among inhabitants and thereby the pathogenesis of breast cancer?	No research
Recommendations for beneficial sunlight exposure presume light-colored skin. Among fair-skinned	Review: A review the current literature on the health effects of vitamin D, especially the effects on inhabitants living in the northern latitudes found that fortification or

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Caucasians, for example, casual sun exposure for 10–15 minutes is said to correspond to an oral intake of 1000 IU. What are the correspondences and recommendations for black, Hispanic, and Asian women? And how do these recommendations vary by latitude within California?	supplementation of vitamin D is necessary for most of the people living in the northern latitudes during the winter season to maintain adequate levels of circulating 25(OH)D3 to maintain optimal body function and prevent diseases [8]. These findings could have implications for the northern most parts of California. No research with recommendations for sun-exposure for different racial groups.
Vitamin D is fat-soluble. How does body mass index affect bioavailable vitamin D metabolites?	Review: This study examines published data from current meta-analysis, prospective studies, and systematic reviews on cancer-specific risk attributed to high BMI and low vitamin D status found that that a low vitamin D status may explain at least 40% of the increased cancer risk attributable to increasing BMI [9].
What are the vitamin D profiles for teachers, nurses, and other occupational groups known to have high rates of breast cancer, and how do these compare to the general population?	No research

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Section II: Disparities in Breast Cancer: Domains of Individual-Level Social Inequality

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A. Race/Ethnicity

Abstract

Although a large number of studies investigating the relationships between race/ethnicity and breast cancer as well as racial/ethnic differences across the breast cancer continuum have been published since the *2007 Identifying gaps in breast cancer research: Addressing disparities and the roles of the physical and social environment report,* the majority of issues and challenges described in the 2007 chapter remain to be addressed. Since 2007 there have been:

- Increased number of studies examining racial/ethnic subgroup differences (i.e., Chinese, Filipino, etc. vs. Asian as a group) in incidence; however, the need for disaggregated racial/ethnic data remains a challenge. Furthermore, the limited number of studies and very limited data available for some racial/ethnic groups, such as American Indians/Alaska Natives (a group with potentially high rates of breast cancer incidence) remains problematic;

- A growing, although still small number, of genome-wide studies have been conducted to explore differences in racial/ethnic breast cancer susceptibility/mortality with mixed results;

- An increased number of studies examining population-based distributions of racial/ethnic specific breast cancer molecular sub-types as well as breast cancer tumor characteristics. Research to fully characterize disparities in breast cancer subtypes and/or tumor characteristics within and between racial/ethnic groups is still missing;

- An increasing number of studies examining the contribution of environmental factors to racial/ethnic differences in breast cancer incidence; fewer examine interactive effects of genetics, hormones, lifestyle/behaviors, and environment. The bulk of studies still focus on examining established risk factors such as reproductive history and behaviors. Research that elucidates the complex interplay of these factors with consideration of direction and/or magnitude of effects has yet to be conducted;

- A very large number of studies examining ethnic/racial differences in breast cancer screening with many studies focusing on elucidating individual and ecologic factors associated with racial/ethnic disparities in screening;

- A limited number of studies have explored racial/ethnic differences in diagnosis, despite robust evidence that some groups experience delays in diagnosis. Research to elucidate barriers to screening that may impact diagnosis, beyond insurance status is still missing;

- Studies examining racial/ethnic differences in treatment have begun to examine the role of psychosocial factors and socio-demographic characteristics in these disparities. This research has focused on African Americans, with little research to examine disparities among other minority groups, in addition to studies that further distill psychosocial and other relevant factors beyond race/ethnicity leading to disparities in treatment;

- Few studies have addressed issues around quality of life after diagnosis, and none compared quality of life outcomes across racial/ethnic groups. Research to understand physical and social aspects of quality of life after breast cancer, and whether and how these vary by ethnicity is still missing;

- An increasing number of studies have explored racial/ethnic differences in survival and mortality. Research in this area has explored factors related to survival for multiple racial/ethnic groups from various perspectives, including genetic, social, and psychosocial. However, research to disentangle the specific roles of these various factors, and their interplay in women of different racial/ethnic backgrounds is still missing.

- Few studies have offered insight on the on the effects of co-morbidities on different racial/ethnic groups.

- Though several studies have shown differential access to clinical trials by race/ethnicity, none have focused on breast cancer or women.

- The measurement of potential social and demographic risk factors (occupational, environmental, social, cultural beliefs and behavior, SES, migration status factors) that may contribute to disparities across the continuum of breast cancer health remain very crudely assessed. There is also growing recognition of the need to expand assessment beyond the traditional risk factors for breast cancer. This would include examining new psychosocial and behavioral risk factors.

- There remains very limited consideration in recent studies of the joint contribution of race/ethnicity and SES. Race/ethnicity and SES are two related but not interchangeable indicators of social status and they can combine in complex ways to affect breast cancer risks and treatment. Existing research has given inadequate attention to the patterns of risk and resilience that may emerge when these factors are considered simultaneously.

- There remains the need for more complex models that consider the ways in which social and behavioral risk factors combine additively and/or interactively with potential exposures in the physical/chemical environment, and health access, utilization, and health care quality characteristics, as well as, tumor and clinical characteristics and biological factors to affect breast cancer risks and outcomes.

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Incidence	
"The findings that there are racial disparities in breast cancer incidence are almost exclusively based on data from studies using the social definition of race, whether it is through self-report or observer-assessment. Sequencing of the human genome has given scientists new tools to examine how closely genetic constructs correlate with social definitions of race." "A number of well-documented disparities exist across the breast cancer continuum. With the exception of incidence which is markedly higher among non-Hispanic white women minority women bear a disproportionate burden of breast cancer…" "By far the bulk of research to date on racial/ethnic disparities in breast cancer has focused on the degree to which differences in the prevalence of established risk factors between racial/ethnic groups explain the difference in breast cancer incidence rates".	A retrospective cohort study by Telli et al (2011) examined population-based distributions of breast cancer molecular subtypes among six ethnic Asian groups (Chinese, Japanese, Filipina, Korean, Vietnamese, and South Asian) in California and found significant ethnic disparities in HER2-positive breast cancer in five the six groups as compared with non-Hispanic White women (all but Japanese) [1]. Using California Cancer Registry data for Asian women diagnosed with incident, primary, invasive breast cancer between 2002 and 2007 (n=8,140), they defined immunohistochemical (IHC) surrogates for each breast cancer subtype [hormone receptor-positive (HR+)/HER2- [estrogen receptor-positive (ER+) and/or progesterone receptor-positive (PR+), human epidermal growth factor receptor 2-negative (HER2-)], triple-negative (ER-, PR-, and HER2-), and HER2-positive (ER+/-, PR+/-, and HER2+)]. After adjusting for age, stage, grade, socioeconomic status, histology, diagnosis year, nativity, and hospital ownership status, Korean [odds ratio (OR) = 1.8, 95% confidence interval (CI) = 1.5-2.2], Filipina (OR = 1.3, 95% CI = 1.2-1.5), Vietnamese (OR = 1.3, 95% CI = 1.1-1.6), and Chinese (OR = 1.1, 95% CI = 1.0-1.3) women had a significantly increased risk of being diagnosed with HER2-positive breast cancer subtypes as compared to non-Hispanic White women.
"Overall, non-Hispanic white women bear the greatest burden of breast cancer incidence. An important area for future research is to identify groups with possibly under-recognized risk. This most certainly should involve examination of racial/ethnic differences in breast cancer incidence by detailed racial/ethnic subgroup, socioeconomic status and immigration	A retrospective cohort study by Keegan et al. (2007) used data from the Greater Bay Area Cancer Registry of Northern California (1990-2002) to investigate rates of breast cancer incidence for Chinese, Japanese, Filipino, Korean, South Asian and Vietnamese women (overall, by age at diagnosis, by histologic subtype, and by stage at diagnosis). Among younger women (<50 years) significant decreases in annual incidence rates were detected for Japanese [Annual Percent Change (APC) = -4.1, p = 0.02) and Filipinas (APC = -1.9, p = 0.11) but not other groups [2]. Among older women (≥50 years) significantly increasing rates in invasive

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status."	breast cancer rates were detected for all but Filipinas (APC = -1.3, p = 0.32). Rates of breast cancer in situ increased in most subgroups over the study period. Rates lobular breast cancer increased significant among Chinese (APC = +7.46, p < 0.01) and decreased for Japanese women. Study results indicated that breast cancer rates increased among more recently immigrated Asian groups and decreased among established groups.
"Racial/ethnic disparities in the incidence of breast cancer by histologic subtype and tumor hormone responsiveness generally have not been well documented and warrant further attention."	A case-control study by Agboola et al (2012) examined the immunoprofile breast cancer tumors and patient outcomes among 308 Nigerian women using 11 biomarkers of known relevance to breast cancer. These were tumor grade-matched to women in the UK [3]. Compared with UK women, Nigerian women were more likely to be premenopausal, have large primary tumor size, high tumor grade, have advanced lymph node stage and higher rates of vascular invasion. Triple-negative and basal phenotypes and BRCA1 deficiency were "overrepresented" in the Nigerian women. No differences in HER2 expression were detected. Patient outcomes were significantly poorer among the Nigerian women. The study suggests that there possible genetic and molecular differences between an indigenous Black and UK women. Hou et al. (2012) conducted a case-control study to explore possible effects of known type 2 diabetes (T2D) risk alleles in the association between T2D and breast cancer risk [4]. Using data pooled from 7 studies, they examined 40 genetic variants known to be associated with T2D in relation to breast cancer risk among 2,651 breast cancer cases and 2,520 controls of African American and Caucasian women. Among Caucasian women, two T2D risk alleles (rs5945326-G, rs12518099-C) were positively associated with breast cancer risk (p=0.05) and two T2D risk alleles (rs1111875-C, rs10923931-T) were negatively associated with breast cancer risk. In African American women one T2D allele (rs7578597-T) was positively associated with breast cancer risk (p=0.05). Total number of risk T2D alleles was not significantly associated with breast cancer risk. Based on these findings, the authors concluded that the association between established T2D genetic susceptibility variants and breast cancer risk in women of African or European ancestry "is likely weak, if it does exist."

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"Because it appears that recent temporal trends in breast cancer incidence rates vary by racial/ethnic group, it is important to continue to monitor these patterns of incidence, both to generate hypotheses related to etiology and to target prevention and cancer control strategies."	Using data from the Black Women's Health Study (1995 to 2007), a prospective cohort study, Bosco et al. (2012) estimated incidence rate ratios (IRR) and 95 % confidence intervals (CI) for the associations of baseline and time-dependent values of cardiometabolic factors (i.e., self-reported abdominal obesity, type 2 diabetes, hypertension, and high cholesterol) and breast cancer incidence [5]. Results of the adjusted cox regression models (1,228 identified breast cancer cases) showed neither individual nor combinations of cardiometabolic factors were associated with breast cancer incidence. Multivariable IRR was 1.04 (95 % CI 0.86-1.25) for the combination of ≥3 factors relative to the absence of all factors, and 1.17 (0.85-1.60) for having all four factors. Among postmenopausal women, however, the comparable IRRs were 1.23 (0.93-1.62) and 1.63 (1.12-2.37), respectively. Results "provide some support for an association between cardiometabolic factors and breast cancer incidence among postmenopausal U.S. black women".
"The very limited data on American Indians and Alaska Natives suggesting potentially high rates of breast cancer incidence warrants further attention and underscores the need to develop better data ascertainment methods to document the cancer experience of this population in the U.S."	Roubidoux (2012) reports in a literature review that limited data available on breast cancer among American Indian and Alaska native (AI/AN) populations measures incidence among these women as a single population [6]. However, there is geographic variation among these populations; Alaska native women had a higher incidence of breast cancer than non-Hispanic white women (NHW), while the incidence among American Indian women in the Southwest was two times lower than NHW. Since 1992, the incidence of breast cancer has decreased nationally, though AI/AN populations have not experienced a similar decline. AI/AN women are more likely to be diagnosed at a later stage than NHW and have a 1.55 times higher likelihood of dying within 5 years. The mean age of diagnosis among AI/AN women is 53.5 years, compared to 63.4 years among NHW. This paper recommends that AI/AN should begin screening at age 40 (although this is inconsistent with other guidelines). This population will also benefit form annual re-screening, and community education and outreach, with mobile mammography in rural areas reducing disparities in breast cancer incidence. Eberth et al (2009) used the California Health Interview Survey (2003), a repeated cross-sectional study, to compare breast cancer screening among AI/AN women to other racial

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	groups and identify positive predictors of screening among this population [16]. Logistic regression models showed that AI/AN women had the lowest rate of mammogram screening ever and within the last two years as compared to all other racial and ethnic groups; AI/AN women had the lowest rates of clinical breast exam other than Asian women. AI/AN women were more likely to be screened for breast cancer if they were older, had a high school diploma or some college education, had visited a doctor within the past year, and had received a Pap smear within the past 3 years. AI/AN women may face greater barriers to screening than other women due to geographic isolation, language barriers, and SES-related barriers; they may also be less likely to participate in screening because of cultural beliefs. Further research should examine how these findings can be integrated into policy and practice.
"Population-based cancer registry data represent the major source for measuring and tracking racial/ethnic disparities in breast cancer incidence. Cancer registry data, however, are narrow in scope, consistent with mandates to broadly collect information for all cancers diagnosed in defined geographic areas, and the data are based on medical records. They do not include important information available from other sources on personal risk factors for breast (e.g., pregnancy history, hormone replacement therapy use) or on potential exposures to chemical contaminants in the environment or occupational settings. Supplementing CCR data--through linkages to administrative data from Medicare, Medicaid and large health maintenance organizations such as Kaiser--could greatly enhance the use of these data to evaluate cancer disparities. While	A number of studies, cited within other domains of this gap use multiple data sources in order investigate associations between breast cancer incidence and other social, demographic, geographic and contextual factors. The extent to which these data are being used to track racial/ethnic disparities in breast cancer incidence is unclear.

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tumor registries have limitations for assessing etiology, their use has been increasing in evaluating treatment patterns and quality of care."	
Etiology	
"We have yet to fully understand the etiologic factors underpinning the observed racial/ethnic disparities in breast cancer risk. Much of the research to date has been aimed at comparing the prevalence of known risk factors across racial/ethnic groups." "Several studies have concluded that known risk factors do not fully explain the differences in incidence or risk, between racial/ethnic or migrant groups. These studies generally have focused on reproductive and menstrual factors, while dietary and other behavioral risk factors, such as physical activity and smoking, have received comparatively less attention. "The currently known breast cancer risk factors, which were primarily identified by studying white women, explain only about half of all breast cancers in white women. Furthermore, it is not entirely clear that these factors impart the same risk in other racial/ethnic groups. Thus by limiting our evaluation of racial/ethnic differences to these factors, we are inherently hindering our ability to fully explain racial/ethnic	A population-based case-control study by Abdel-Maksoud et al. (2012) modeled associations between obesity, physical activity, smoking, alcohol intake, and reproductive factors and estrogen receptor (ER) status, tumor size, and histologic grade among 846 Hispanic and 1,625 NHW women diagnosed with breast cancer between 1999 and 2004 in four US states [7]. Hispanics had more estrogen receptor (ER) -negative tumors (28 vs. 20%), tumors >2 cm (39 vs. 27%), and poorly differentiated tumors (84 vs. 77%) than NHW. Among premenopausal women, obesity was associated with more ER-negative cancers among NHW [OR = 2.47 (95% CI: 1.08, 5.67)] but less ER-negative cancers among Hispanics [OR = 0.29 (0.13, 0.66)]. Obesity was associated with larger tumors among NHW [OR = 1.58 (1.09, 2.29)], but not among Hispanics. Never using mammography was associated with larger tumors in both ethnic groups. Moderate alcohol drinking and moderate and vigorous physical activity was weakly associated with smaller tumors in both ethnic groups. The authors concluded that findings suggest that the association of obesity and other behavioral risk factors with breast cancer characteristics differ by ethnicity. The authors observed a divergent pattern between Hispanic and NHW cases in the association between obesity and ER status and tumor size. These observations suggest that a complex set of metabolic and hormonal factors related to estrogen and insulin pathways influence tumor characteristics. Wang et al (2012) examined CpG island methylation, a critical factor in the development and progression of breast cancer, in a case-control study [17]. Quantitative methylation analysis and sequencing was carried out for promoter CpG islands on seven candidate genes using matched paired cancerous and non-cancerous breast tumor specimens in 32 AA and 33 EA patients. Five of the seven genes are known tumor suppressor genes (RASSF1A, RARβ2,

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disparities in breast cancer."	CDH13, HIN1 and SFRP1) and were frequently hypermethylated in breast tumor tissues, but not in adjacent non-cancerous tissues. DNA methylation was compared between AA and EA patients, with significant differences in methylation only in the CDH13 gene (p=.023). CDH13 methylation differences in AA and EA patients were more pronounced among patients in ER-negative disease (p<.005). Triple-negative cancers had increased CDH13 methylation (p=.044) and decreased SFRP1 (p<.02) and RASSF1A methylation (p<.05). Neo-adjuvant therapy may reduce methylation as tumors that received neo-adjuvant treatment had reduced RASSF1A methylation compared to chemotherapy naïve tumors (p<.005). DNA methylation of individual genes was not associated with patient outcomes; however, combined methylation at 3 loci was associated with poor outcomes among AA patients (p=.035). Differential methylation patterns in AA and EA patients may result in different outcomes among these patient populations.
"Almost completely ignored in the literature to date is an examination of the degree to which exposures to environmental contaminants play a role in racial/ethnic disparities in risk….exposures to chemical contaminants generally has not been considered in the body of literature on racial/ethnic differences in breast cancer incidence and risk. The strong regional variations observed in breast cancer incidence, with rates highest in urban and industrialized areas, suggest a potential role for these types of exposures." "While overall, non-white populations (who tend to have lower rates of breast cancer incidence), are more likely to live in highly polluted areas, there may be some specific exposures more common to white	Whitman et al (2012) examined racial disparities in breast cancer mortality among non-Hispanic Black (NHB) and non-Hispanic White (NHW) women in 24 of the 25 largest cities in the United States using the American Community Survey (2005-2007), a population-based cross sectional study, for population data and national death files to identify mortality cases due to malignant neoplasm of the breast. NHB:NHW rate ratios (RR)s were calculated for each city, with city-level ecological covariates included in the analysis. There is a significant positive correlation between NHB breast cancer mortality and the NHB:NHW disparity (r=.67, p<.0001). In 13 of 24 cities, NHB had significantly higher odds of breast cancer-related mortality than NHW. Overall, NHB had 1.40 times the odds of breast cancer-related mortality compared to NHW. Among measured covariates, only median household income (r=-0.43, p=0.037) and a segregation measure (r=0.42, r=0.039) were significantly related to the RR. The authors recommend analyzing city-level mortality rates as a useful strategy to identify disparities at the local level. The authors note that Chicago has implemented a strategy to address this disparity, which may prove successful in other cities as well. Barrett et al used 1990 and 2000 census tract data and cancer registries from Cook County, IL

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women that have yet to be identified. "…the potential role of environmental contaminants in explaining the modestly higher rates of breast cancer incidence among young African American women largely has been ignored. Future research aimed at elucidating factors responsible for racial/ethnic disparities in incidence need to move beyond considering solely the known breast cancer risk factors to identify and include occupational, environmental, and social factors." "One of the fundamental challenges in studying racial/ethnic disparities in breast cancer is disentangling the effects of genetics, socioeconomic status, immigration status, and potential exposures to environmental contaminants. There is evidence that racial/ethnic disparities persist after adjustment for socioeconomic status and vice versa. While difficult to conduct, research focused on women that are discordant for these factors may help tease out the independent effects of these highly correlated factors."	in a retrospective cohort study to analyze how upward neighborhood SES change affects likelihood of distant metastasis at diagnosis of breast cancer. A multilevel model included patient's age and race/ethnicity, baseline neighborhood SES, and degree of neighborhood SES change from 1990 to 2000. Residence in a census tract with lower baseline SES in 1990 (odds ratio [OR], 1.23; 95% confidence interval [CI], 1.12-1.36) and concentrated immigration (odds ratio [OR], 1.11; 95% confidence interval [CI], 1.02-1.21) were significantly associated with increased odds of distant metastasis at diagnosis. Women in affluent areas at baseline were significantly less likely to receive a diagnosis of distant metastasis (odds ratio [OR], 0.86; 95% confidence interval [CI], 0.79-0.93). Being African American was significantly associated with higher odds of receiving a diagnosis of distant metastasis (odds ratio [OR], 1.24; 95% confidence interval [CI], 1.03-1.48). Residence in a census tract that experienced an increase in neighborhood SES from 1990 to 2000 was also associated with increased odds of distant metastasis at diagnosis (odds ratio [OR], 1.09; 95% confidence interval [CI], 1.01-1.18). The authors recommend that areas experiencing socio-economic change are targeted for screening and follow-up programs in addition to other targeted areas and populations.
Screening	
"Controversy remains as to whether further efforts to increase screening will significantly improve racial/ethnic disparities in survival…."	Grabler et al (2012) examined black:white differences in breast cancer stage and biology among "regularly screened" (mammogram $\leq$ 2 years of breast cancer diagnosis) and "irregularly screened" women (no mammogram within 2 years of diagnosis) through a retrospective cohort study. No significant black:white differences in early breast cancers were

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"Debate persists over the ideal interval between screening mammograms, especially among women age 40–49.""	found in either group (regularly screened: black = 74 %; white = 69 %, p = NS; irregularly screened: black = 60 %; white = 68 %, p = NS) [8]. Black women in the regularly screened population were less likely than irregularly screened black women to have estrogen negative breast cancers (26 vs. 36 %, p <0.05), progesterone negative breast cancers (35 vs. 46 %, p <.05), and poorly differentiated breast cancers (39 vs. 53 %, p < .05.) White women in the irregularly screened population also had worse prognostic factors than white women in the regularly screened population, though these were not statistically significant. Regular mammographic screening can contribute to the narrowing of black:white differences in presentation of breast cancer.
"…the efficacy of mammography screening in women under age 50 years remains a source of debate. Breast tissue in younger women is more sensitive to radiation and is denser, making mammograms less effective."	A retrospective cohort study by Tian et al (2012) examined possible associations between demographic, poverty and spatial accessibility factors associated with racial disparities in breast cancer mortality among African-American (AA) and Hispanic women residing in Texas from 1995 to 2005 [9]. Data were derived from the Texas Cancer Registry data and the 2000 Census and Geographic Information System techniques were used to construct accessibility variables. Logistic regression models were employed to predict census tracts with "significant racial disparities in breast cancer mortality based on racial disparities in late-stage diagnosis and structured factors from the principal component analysis". Significant predictors census track-level significant racial disparities in breast cancer mortality included late-stage diagnosis, poverty factors, and demographic factors. Significant racial disparities in breast cancer mortality were significantly associated with higher poverty census tracks for both AA and (odds ratio [OR], 2.43; 95% confidence interval [CI], 1.95-3.04) and Hispanics (OR, 5.30; 95% CI, 4.26-6.59). No significant prediction in disparities in breast cancer mortality were found for spatial accessibility to mammography facilities suggesting that other factors, such as ability to pay, might be more salient determinants of racial disparities in breast cancer mortality.
"…while the relatively small differences in screening rates seem to suggest that racial/ethnic differences in stage and survival are not due to disparities in screening, others would argue such a conclusion is premature (i.e., observations have been largely based on surveys of mammography use that are self-reported, only consider recent use, and do not take into account reasons for mammography and frequency of use)."	
"(limited research suggest that) compared to white women, African American, Hispanic, Asian, and Native American women (to be) more likely to receive inadequate mammography screening….(there is a) need to firmly identify the optimal level and components of screening necessary to minimize late-stage diagnoses and ultimately maximize reductions in breast cancer mortality."	Wilson et al (2011) conducted a medical record review at six Indian Health Service (IHS) units in Montana and Wyoming to identify factors associated with primary and secondary breast

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	and cervical cancer screening among American Indian (AI) women [20]. Rates of primary and secondary screening during a three-year period (2004-2006) were determined in an age- and clinic-stratified random sample of 1,094 AI women. Three-year mammography prevalence rates among AI women over 45 years were 37.7% (95% CI, 34.1- 41.3) for primary screening and 58.7% (95% CI, 43.9-73.5) for secondary screening. Primary mammography screening was significantly and positively associated with both number of clinic visits (p<.001) and receiving care at an IHS hospital (p<.001). Secondary mammography screening was inversely associated with driving distance to an IHS facility (p=0.035); screening was highest among women living in a town with a mammography facility (p=.019). The authors conclude that improvements in breast and cervical cancer screening among AI women attending IHS facilities are necessary to meet Healthy People 2020 goals of mammography screening of 81% of women over age 40.
Correlates of Screening Behavior	
"…sociodemographic characteristics beyond race/ethnicity may be more important predictors of mammography utilization…lack of health insurance may be one of the largest contributors to underutilization of screening mammography among all racial/ethnic groups…uninsured Asians (report) the lowest screening rate. Having a usual source of care also appears to be an important predictor of mammography…regardless of race/ethnicity." "Major research efforts have sought to explain the factors underlying the well-documented underutilization among some Asian and Pacific Islander women. Asian/Pacific Islander women often share many of the structural barriers with other minority	A lower proportion of African American (AA) women elect to undergo genetic counseling related to breast cancer compared to other racial and ethnic groups, which may be due to cultural preferences rather than disparities. Halbert et al (2012) conducted a prospective cohort study of 135 AA with an increased risk of BRCA1/2 mutation to determine how satisfied AA women were with participation in genetic counseling [21]. Women reported their satisfaction one month after participating in genetic counseling. 96% of women were satisfied with their decision to participate. 88% felt that genetic counseling was consistent with their family values, and 84% reported that genetic counseling was beneficial to their family. Women who declined pre-test counseling reported significantly lower satisfaction (p=.01). No socio-demographic or clinical covariates were significantly associated with satisfaction. The authors conclude that it is important to ensure racial differences due to values and preferences are not misclassified as disparities in order to focus resources appropriately.

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women, including lack of insurance, lack of health care access, low socioeconomic status, lack of a usual source of care and lack of encouragement by physicians. Sociocultural factors, including low level of education, limited knowledge of breast cancer, and low English proficiency have been found to be associated with low mammography utilization among Asian/Pacific Islander women." " Furthermore, level of cultural assimilation, often measured by length of U.S. residency and English proficiency, has also been a critical determinant of mammography….some qualitative studies …have explored cultural beliefs that underlie health- seeking behaviors…(and) identified other perceived barriers to utilization, including having a male physician, fear of being exposed unnecessarily to radiation, and the lack of sensitivity from hospital staff regarding their embarrassment of having to undress for a mammogram, which often discouraged them from returning for subsequent visits." "… other studies have shown a potential interaction between immigration status, cultural beliefs, and income (or other socioeconomic status-related variables) for perceived barriers to breast cancer screening. Unfortunately, many of these variables overlap with one another and are hard to measure	

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quantitatively. Regardless, these studies illustrate the complexity with which the structural and sociocultural barriers operate in this heterogeneous population."	
Diagnosis	
"Disparities exist in staging and tumor size across racial/ethnic groups in all socioeconomic groups in California. These differences remain despite relatively small differences in rates of screening mammography, as previously noted. " "Determining the underlying reasons for these disparities will require the consideration of factors in addition to mammography. Several other possible reasons for delayed detection could include less frequent clinical breast exams, lag-time in follow-up on abnormal results, rapid tumor growth, or other biological factors." "In addition, there may be more complex reasons for these disparities that relate to acculturation and other social and physical aspects of the environment."	Hoffman et al (2011) investigated the impact of race/ethnicity and health insurance on diagnostic time (i.e., number of days from suspicious finding to diagnostic resolution) in a retrospective cohort study of 1538 women examined for breast abnormalities between 1998-2010 at six District of Columbia clinics and hospitals [10]. They examined measured mean diagnostic times between non-Hispanic whites (NHWs), non-Hispanic blacks (NHBs), and Hispanics with private, government, or no health insurance in respective average geometric mean (95% CI) diagnostic times (in days). The following racial/ethnic differences were found: "government insured NHWs had significantly shorter diagnostic times than government insured NHBs ($P = .0003$) and Hispanics ($P < .0001$); privately insured NHWs had significantly shorter diagnostic times than privately insured NHBs ($P = .03$) and Hispanics ($P < .0001$); and privately insured NHBs had significantly shorter diagnostic times than uninsured NHBs ($P = .03$)." The authors conclude that "diagnostic delays in minorities are more likely caused by other barriers associated with race/ethnicity than by insurance status".
Treatment	
"Apparent racial/ethnic disparities in treatment, particularly for early stage disease, are not necessarily explained by differences in tumor characteristics or	A retrospective cohort study by Balasubramanian et al (2012) investigated racial differences in treatment delays for early breast cancer of "237 Black and 485 White women aged 20-64 years diagnosed with early breast cancer between 1997 and 2001" using linked New Jersey

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clinical attributes of the patient. It is also not clear to what extent women of different racial/ethnic groups are being offered comparable treatment options." "Cultural and economic factors appear to play large roles in differing treatment patterns. Black/white differences appear to be better explained by socioeconomic status than by race. Disparities observed for several Asian/Pacific Islander and Latina groups, particularly among recent immigrants, appear to be largely influenced by cultural beliefs, language barriers, and economic resources." "Future work in this area will require attentiveness not only to the heterogeneity of breast tumors, but also to the heterogeneity of the patient population, as well as associated inequalities in socioeconomic resources and access to care."	Cancer Registry and Medicaid Research data. Results from logistic regression models indicated black:white differences in treatment initiation [11]. Compared with whites, blacks experienced more frequent adjuvant chemotherapy delays and had two-fold odds (95% confidence interval, 1.04, 4.38) of > or = 3 months delay in adjuvant chemotherapy. Blacks were also more likely to experience radiation treatment delays (NS). No differences were observed for delays in surgical and hormonal treatment. The similar socioeconomic status and insurance access of the population suggests that delays may be due to cultural and/or psychosocial factors. A retrospective cohort study by Christiansen et al (2012) examined the impact of race (African American (AA) vs. non-AA groups) on disease recurrence and survival in patients with non-metastatic triple-negative breast cancer (TNBC) treated with adjuvant chemotherapy, using a primary outcome of disease-free survival (DFS) [12]. The 2003-2008 Georgia Cancer Specialist Database was used to identify patients with stage I-III confirmed TNBC who had received adjuvant chemotherapy. The 209 identified patients (42.6% AA) were followed-up from initial diagnosis to death, cancer recurrence, or loss to follow-up. Kaplan-Meier curves were constructed to compare DFS and recurrence and adjusted multivariate Cox models (age, comorbidity, body mass index (BMI), smoking status, initial TNBC stage, surgery, and radiation therapy) were used to model impact of AA race on outcomes. No AA vs. non-AA differences were found in mean age at diagnosis (53.2 vs. 54.4 years; P =.487) and with surgery and radiation rates (98.9% vs. 100%; P = .244; 68.5% vs. 62.5%; P = .365, respectively). AA patients had significantly higher BMI (30.4 vs. 28.6 kg/m(2); P = .0477). AA patients were significantly less likely to be diagnosed at stage I (31.5%vs. 51.7%; P = .0107) than non-AA patients and had a lower 5-year DFS rate (45.2% vs. 79.7%; P = .0005) and a higher 5-year recurrence rate (42.5% vs. 7.0%; P = .0005). AA race was associated with a worse outcome irrespective of later stage at presentation or higher BMI.

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Quality of Life after Diagnosis	
"… little research has been dedicated to exploring quality of life among specific racial/ethnic groups of breast cancer survivors. The few studies conducted in this area offer some insights into understanding the impact of the illness on these women, but more refined efforts are needed, especially in a population with such cultural diversity." "To date, the studies seem to indicate some common themes of negative body image and other forms of emotional burden. Research attention should be given to examining some of the specific sociocultural burdens of psychosocial stress on breast cancer survivors and ways to reduce such stress in each of these groups." "In order to evaluate ethnic variations across studies, reliable and valid measurement tools to measure the quality of life construct need to be developed and used."	A case-control study by Von Ah et al. (2012) compared health-related quality of life (QOL) of African American (AA) breast cancer survivors (BCSs) (n=62) with AA women with no history of breast cancer (n=78 "controls") [13]. Participants were at least 18 years old and 2 to 10 years post diagnosis. Adjusted results (age, education, income, and body mass index) indicate that AA BCSs experienced more fatigue (P = .001), worse hot flashes (P < .001), and worse sleep quality (P < .001) than controls. AA BCSs, however, had more partner social support (P = .028) and more positive change (P = .001) than controls.
Survival/ Mortality	
"The greatest burden of breast cancer mortality is borne by African American women. Compared to non-Hispanic whites, all racial/ethnic groups, other than Japanese American women, have worse relative survival. These differences persist after adjusting for	A retrospective cohort study by Keegan et al (2010) examined the impact of nativity (US- versus foreign-born), neighborhood socioeconomic status (SES) and Hispanic enclave (neighborhoods with high proportions of Hispanics or Hispanic immigrants) on breast cancer stage at diagnosis and survival among among 37,695 Hispanic women diagnosed from 1988 to 2005 with invasive breast cancer from the California Cancer Registry [14]. Nativity was based

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stage at diagnosis."	on registry data or, if missing, imputed from case Social Security number. Neighborhood variables were developed from Census data. Stage at diagnosis was analyzed with logistic regression and survival (based on vital status determined through 2007) was analyzed with Cox proportional hazards regression. Compared to US-born Hispanics, foreign-born Hispanics were more likely to be diagnosed at an advanced stage of breast cancer (adjusted odds ratio (OR) = 1.14, 95% confidence interval (CI): 1.09-1.20), but they had a somewhat lower risk of breast cancer specific death (adjusted hazard ratio (HR) = 0.94, 95% CI: 0.90-0.99). Living in low SES and high enclave neighborhoods was associated with advanced stage of diagnosis, while living in a lower SES neighborhood, but not Hispanic enclave, was associated with worse survival.
"…Yet unidentified biological factors may play a role in survival disparities." "Identifying the factors that impart better survival among Japanese Americans may provide important clues to improving survival among other groups."	Shu et al (2012) conducted a two-stage genome-wide association study (GWAS) to identify potential markers for total mortality after diagnosis of breast cancer among 6,110 Chinese women with tumor-node-metastasis (TNM) stage I to IV breast cancer [15]. The first stage included 1,950 patients and evaluated 613,031 common single nucleotide polymorphisms (SNPs). The top 49 associations were evaluated in an independent replication stage of 4,160 patients with breast cancer. Cox regression models showed a significant and consistent association with total mortality for SNPs rs3784099 (P_{trend}=1.17×10(-7)) and rs9934948 (P_{trend}=5.75×10(-6)). SNP rs3784099, located in the RAD51L1 gene, was associated with total mortality in both the discovery stage (P_{trend}=1.44×10(-8)) and replication stage (P-combined=1.17×10(-7)). Adjusted hazard ratios for total mortality were 1.41 [95% confidence interval (CI), 1.18-1.68] for the AG genotype and 2.64 (95% CI, 1.74-4.03) for the AA genotype, when compared with the GG genotype. The variant C allele of rs9934948 on chromosome 16 was associated with an increased risk of total mortality (P-combined=5.75×10(-6)). These results were compared with 1145 Caucasian patients from the Nurses' Health Study, and a significant association of SNP rs9934948 with total mortality was found in a combined analysis with the Chinese data (P = 1.39 × 10(-7)). The authors suggest these results provide strong evidence that the RAD51L1 gene and a chromosome 16 locus are associated with breast cancer prognosis.

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	Giraldo-Jimenez et al (2012) conducted a population-based retrospective cohort study among Puerto Rican women with triple-negative breast cancer (TNBC) to assess survival and clinicopathological characteristics of TNBC among a population of Hispanic women [22]. Fifty-four women in Puerto Rico with TNBC were identified and followed for a median period of 24 months (range, 2-78). The median age at diagnosis was 55 years. Among 54 cases, 51 women had stage I-III presentation. T1/T2 tumors were found in 88.9%; 68.5% had an absence of nodal involvement. Lymph node involvement (p=.002), tumor size greater than 2 cm (p=.037) and stage IV (p<.001) were significantly associated with progression free survival. Kaplan-Meier estimates were used to calculate 5-year survival, found to be 81%, and 5-year progression free survival was 80%. These data do not reflect biological or genetic difference from other studies of women in North America and Europe; therefore, the authors conclude that disparities in clinical outcomes among Hispanic women with TNBC are likely due to differences in SES and access to care among this population. Further research is necessary to better understand differences in TNBC among Hispanic women. Burke et al (2011) conducted a qualitative study of Filipina women with breast cancer in the San Francisco Bay Area to explore social and cultural factors related to their experiences with the disease [23]. Participant observation of a Filipina support group, individual, and small group in-depth qualitative interviews were used to elucidate cultural meanings and understand of cancer, supporting cancer patients, and survivorship. Women normalized cancer as one of many challenges in the context of immigration, and viewed it as a chance for change. Survivorship was described as a goal for their children, and many women were concerned for family living abroad. Filipina women were mainly motivated to participate in a support group in order to help others by sharing their stories, rather than to receive support themselves. The authors recommend that support and outreach programs include a translational perspective.

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	Review: Maskarinec et al (2011) conducted a literature review to compare breast cancer survival rates of all major racial and ethnic groups in the United States, including African Americans, Latinos, Native Americans, Asian Americans and Native Hawaiians [24]. Compared to Caucasian women, African American women have the poorest breast cancer survival of all groups in the United States. A range of studies found an elevated risk of mortality among African Americans compared to Caucasians, with hazard ratios ranging from 1.2 to 2.6. Latinos, Native Americans and Native Hawaiians experience better outcomes than African Americans, though worse than Caucasian women. Outcomes among Asian Americans varied by sub-groups and immigrant status: Japanese and Chinese Americans have better outcomes than Caucasian women, whereas Korean, Filipino, Vietnamese, and South Asian Americans had worse outcomes compared with Caucasians. Although overall breast cancer mortality has decreased over the last two decades, significant disparities remain between racial and ethnic groups in the US. The authors note that SES and lifestyle behaviors are likely responsible for much of the presented disparities, though further research is required to disentangle the roles of social and genetic factors in breast cancer disparities. **Systematic Review:** *Although not specific to breast cancer*, a 2013 systematic review reported on the possibility of a Hispanic mortality advantage from *any cause*. The authors conducted a systematic review and meta-analysis of the published longitudinal literature reporting Hispanic individuals' mortality from any cause compared with any other race/ethnicity. The authors found across 58 studies (4 615 747 participants), Hispanic populations had a 17.5% lower risk of mortality compared with other racial groups (odds ratio = 0.825; P < .001; 95% confidence interval = 0.75, 0.91). The results differed by racial group: Hispanics had lower overall risk of mortality than did non-Hispanic Whites and non-Hispanic Blacks, but overall higher risk of mortality than did Asian Americans.

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B. Sexual Minority Women

Abstract

The section on cancer in the recent Institute of Medicine's (2011) report, The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding, states "…when the IOM report Lesbian Health was published, insufficient research had been conducted to determine whether lesbians were at greater risk for breast cancer than heterosexual women. Unfortunately, 12 years later the same is true." They summarize limited literature on breast cancer risk factors and conclude that lesbians and bisexual women and women who have sex with women are "likely to be at greater risk for some cancers than heterosexual women". Like the IOM report this scan found few studies since the 2007 Chapter that contribute substantial knowledge or understanding. Additionally, like the IOM report that states, "Research on cancer among the transgender population has been extremely limited", the results of the scan show a need for research with this important SMW subgroup (no studies for transgender persons were mentioned in the 2007 Chapter). The current scan uncovered a small (n=5 studies) but emerging breast cancer literature including both Male-to-Female and Female-to-Male transgender people. Although the majority of these studies are clinical cases involving one or two persons, one study, by Weyers et al. (2010) examined mammography and sonography experiences of 50 Dutch speaking transsexual women.

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"The overall effect of sexuality is not well understood because few studies have explored its role in breast cancer. The studies that have been conducted have generally focused on risk factors, screening behaviors, and quality of life."	Brown and Tracy (2008) conducted a review of the literature from 1981 – 2007 using the domains of the cancer continuum focusing on lesbians. Of the 51 articles reviewed the majority "were related to breast and cervical cancer screening" and, of the whole, there was "a lack of research…for specific aspects of the cancer continuum and almost no attention to incidence, etiology, diagnosis, treatment, survival, morbidity, or mortality [1]."
Biologic Evidence	
"Sexual orientation is a proxy for many individual and social risk factors that potentially influence breast cancer risk and outcomes."	No updated information.
Primary Prevention	
Not mentioned.	No updated information.
Incidence	
"The incidence of breast cancer among SMW is not known." "While existing data strongly suggest that SMW are at increased risk of breast cancer, both the reality of increased risk and the magnitude of the presumed increase remain uncertain."	No updated information.

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Etiology	
"Risk factors associated with SMW include nulliparity, older age at first birth, alcohol consumption, smoking and obesity." "Most research suggests that lesbians differ from heterosexual women in that they are more likely to be nulliparous and more likely to consume alcohol, smoke and be overweight."	Zaritsky and Dibble (2010) studied breast cancer risk factors among older lesbian-heterosexual sister pairs (n = 42 pairs with at least one sister >50 years or 84 women). They found significant differences between lesbian and heterosexual sisters in several breast cancer risk factors. Lesbians had significantly more education, fewer pregnancies, less total months pregnant, fewer children, and fewer total months breastfeeding, higher body mass indices (BMI) and exercised fewer times per week. Lesbians also performed breast self-examinations significantly less. No significant differences in smoking or alcohol were found [2]. A cross-sectional analysis by Brandenburg et al. (2007) used data from the Multi-site Women's Health Study (1994-1996) to examine differences in estimated 5-year and lifetime breast cancer risk between lesbians (n=550) and heterosexual women (n=279) from Chicago, New York City, and Minneapolis-St. Paul. Findings indicated a "small but significant difference in calculated breast cancer risk estimates of lesbians and heterosexual women [3]".
Screening	
"SMW receive mammograms less frequently than heterosexual women, potentially increasing their risk for later-stage diagnosis and worse prognosis." One study "found lesbians, but not bisexual women, to be less likely to have a clinical breast exam within the previous two years." "Research suggests that SMW have lower screening	Buchmueller and Carpenter (2010), using data from the Behavioral Risk Factor Surveillance System (BRFSS), found that women in same-sex relationships were significantly less likely to have had a have a medical check-up within the past year or to have had a recent mammogram than women in different sex relationships [4].

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rates than do heterosexual women."	
Correlates of Screening Behavior	
"Several researchers have also explored the reasons why SMW may receive less screening…include cost, scheduling, discomfort, competing life demands, fear, and embarrassment. Conversely reasons for seeking mammograms included good health practices, responding the perception of being at high risk of cancer, and desire to ensure early detection."	Health insurance: Although they did not investigate associations between insurance coverage and screening, the study by Buchmueller and Carpenter (2010) found women in same sex relationships to be significantly less like to have health insurance coverage than women in different sex relationships [4]. Homophobia/Heterosexism: A study by Dehart (2008) conducted a cross-sectional survey of 173 exclusively homosexual women and found that women who perceived heterosexism/homophobia from their providers were significantly less likely conduct breast self-exams, visit health care providers, and use complementary/alternative services [5].
Interventions to Increase Screening	
"Few interventions have been developed to improve breast cancer screening rates among SMW compared to most racial and ethnic minority groups, SMV have little research dedicated to improving their screening rates." An RCT of a breast cancer risk counseling intervention had reductions in anxiety and fear about breast cancer and increased screening among lesbian and bisexual women for up to two years post-intervention.	No updated information.

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Access to Clinical Trials	
"Nothing is known about participation of SMW in clinical trials."	No updated information.
Diagnosis	
Little is known about breast cancer diagnosis in SMW. One of the "few studies investigating breast cancer diagnosis in SMW…found no significant differences in diagnostic … procedures…between lesbians and heterosexual women."	No updated information.
Treatment	
Little is known about breast cancer treatment in SMW. The same study as mentioned above "investigated breast cancer treatment found no significant differences in surgical procedures or chemotherapy or radiotherapy regimens between lesbians and heterosexual women." The same study found that lesbians reported more side effects from chemotherapy than heterosexual women.	No updated information.
Morbidity	
"Little is known about morbidity associated with breast cancer treatment and survivorship."	Weight (obesity is associated with an increased risk of recurrence and reduced survival). Boehmer et al. (2011) studied self-reported weight in heterosexual (n=257) and lesbian/bisexual (n=69) female breast cancer survivors and found no differences in obesity due to sexual orientation [6].

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Quality of Life after Diagnosis	
"Overall, current research findings conclude that SMW experience quality of life similar to that of heterosexual women after breast cancer diagnosis, though their qualitative experiences may differ."	Breast reconstruction: A small qualitative study by Boehmer et al. (2007) examined issues related to decision-making for and satisfaction with reconstructive surgery after mastectomy among SMW who had received a mastectomy (n=15 women who partner with women, lesbians and bisexual women) and support persons (n=12). SMW identity and body image perceptions were important in the decision to have or not to have reconstructive surgery and women who elected for reconstruction expressed regret while those who did not believe that they adjusted [7] .
Interventions to Improve Quality of Life after Diagnosis	
One study "found that a 12-week support program for lesbians was helpful in reducing emotional distress and improving coping."	Boehmer et al. (2012) conducted a qualitative study with 22 SMW diagnosed with non-metastatic breast cancer to examine their perceptions of how their sexual minority status impacts their survivorship. Many participants deemphasized the importance of their sexual minority status which conflicts with the "research community that emphasizes the importance of this status [8]".
Survival	
"Nothing is known regarding survival…differences among SMW and heterosexual women."	No updated information.
Mortality	
"Nothing is known regarding...mortality differences among SMW and heterosexual women."	Cochran et al. investigated sexual orientation-related differences in risk for fatal breast cancer in a nationally-representative sample of married/living as married women who participated in the National Health Interview Survey (NHIS) between 1997 -2003; 693 women

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	reported being in a same sex partnership and 136,174 reported being in a opposite sex partnership. Women in same-sex couples, compared with those in different-sex couples, had greater age-adjusted risk for fatal breast cancer [9].
Policy interventions	
Not mentioned.	Not mentioned.

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C. Disability Status

Abstract

Key gaps include the need for a more specific definition of disability within breast cancer research, much like other domains in the individual-level social inequalities literature reviews. Much of the literature focused on access to mammography e.g. physical limitations or access to other screening and education e.g. how intellectual disabilities limit screening. There was little to no research on how breast cancer screening and treatment might further affect existing disabilities. In addition, there was no specific research on breast cancer and hearing impaired women. Although there was a focus on blindness or vision impairment in past scans of the literature, there was only one article that mentioned the relationship between blindness, breast cancer and melatonin. There is also a lack of literature on what constitutes a mental disability and the relevance of mental disability to breast cancer prevention and treatment. For example serious mental health issues could include depression or schizophrenia. Since the literature does not address mental disability, there is a large gap in understanding whether it is necessary to approach prevention and treatment differently for women with mental disability.

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"Conspicuous by its absence is any information about whether their specific disability-related needs are met or even addressed in the processes associated with breast cancer diagnosis, treatment, and recovery."	Retrospective Cohort Study: Cohort of 4610 community-dwelling Medicare beneficiaries ≥ 65 years included in the 2004-2005 Medicare Current Beneficiary Survey. Women with disability were more likely than women with no disability to report lower mammography use (unadjusted, moderate disability OR = 0.76; 95% CI = 0.64, 0.91; severe disability OR = 0.46; 95% CI = 0.40, 0.54). Lower use was significant for women with severe disability (adjusted, OR = 0.67; 95% CI = 0.54, 0.83) and women with fair-poor self-rated health, no HMO enrollment and ≥ 3 comorbidities. Mammography use decreases with increasing level of disability. Common reasons for underutilization are no physician recommendation, no need, dislike/pain during the test and forgot it [1]. Retrospective Cohort Study: Unmarried women with disabilities (WWD) may be a particularly vulnerable group for underutilization of repeat mammography screening. This study compared the breast cancer screening experiences of unmarried WWD (n=93) versus women with no disabilities (WND) (n=93). WWD were less likely to be on-schedule than WND in univariable (54.8% vs. 71.0%; relative risk, 0.77; 95% confidence limits, 0.61, 0.97), but not multivariable, analyses. In multivariable analyses, there was a significant interaction between disability status and positive experiences as the reasons for returning to the same mammography facility. Among WWD, screening rates were only 37% among those who did not report any positive experiences and increased to a maximum of 60% regardless of whether women endorsed one to four or all five positive experiences. Severity and type of disability were not associated with repeat screening [2]. Cross-Sectional Study: Data from the 2008 BRFSS were used to estimate disability prevalence and state-level differences in breast and cervical cancer screening among women by disability status. Women with a disability were less likely than those without to report receiving a mammogram during the past 2 years (72.2% vs. 77.8%; $p < .001$). However, disparities in breast cancer screening were more pronounced at the state level [3]. Cross-Sectional Study: Korean women over 40 (n=503) were asked about intentions to obtain

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	a mammogram. Predictor variables included health status and other factors known to influence the use of cancer screening, such as age, education, income, marital status and the presence of co-morbid illnesses. Health status was assessed by using the EuroQol (EQ-5D). Women who had problems with mobility or anxiety/depression showed lower intention to undergo future screening mammography. Health status is significantly associated with intention regarding screening mammography use. Physicians or other health professionals should be aware that health status is an important component for health promotion, and should pay more attention to clients' possible vulnerability in screening mammography use due to their poor health status [4].
"Comprehensive studies are needed to understand the breast cancer-related experiences of women with a broad spectrum of disabilities, from risk factors to screening to treatment to recovery to long-term survival and quality of life."	Cross-sectional study: Adult cancer survivors with preexisting disabling conditions who had completed active treatment were recruited from throughout the United States. 145 survey respondents were breast cancer survivors with preexisting neuromuscular conditions such as polio and multiple sclerosis. The average time since cancer diagnosis was nine years. Disabled women reported poorer physical well-being than other cancer survivors without preexisting disabling conditions. Health-promoting behaviors and psychosocial factors, such as depressive symptoms and self-efficacy, added significantly to the prediction of physical, social, emotional, and functional components of health-related quality of life after contextual factors entered the equations [5]. Qualitative Study: This study explored the perceptions of patients with breast cancer with mobility impairments of the physical accessibility of healthcare facilities and equipment. 20 women with chronic mobility impairments who developed early-stage breast cancer prior to age 60. Three were recruited from oncologist panels and 17 from informal social networks of disabled women nationwide. The 20 participants identified issues with inaccessible equipment, including mammography machines, examining tables, and weight scales. The patients sometimes needed to insist on being transferred to an examining table when physicians preferred to examine them seated in their wheelchairs. Women with major mobility issues who developed breast cancer confronted numerous physical barriers during

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	the course of their breast cancer diagnosis and treatment [6]. Cross-Sectional Study: This study explored specific accommodations described as necessary by WWD who have accessed screening services, and the presence of such accommodations in community-based screening programs. WWD (n=1348) in the Carolina Mammography Registry were surveyed to determine what accommodations were needed when accessing breast-screening services, and whether or not these needs were met. The most frequently needed accommodations were an accessible changing area with a bench (60.0%), oral description of the procedure by the technologist (60.5%), and handicapped/accessible parking (27.6%). Handicapped parking was the need most likely to go unmet (3.1%) [7]. Cross-Sectional Study: This study examines the determining factors related to the low usage of mammography among women with disabilities. Data from 2006 & 2008 Taiwanese national surveillance data was used to identify women between age 50 and 69. Only 8.49% of the disabled women used mammographies. When women with disabilities were in higher income level, they were more likely to use mammography for breast cancer screening. Similar findings were found for education levels. Moreover, subjects with a more severe form of disability were less likely to use mammography with ORs of 0.84, 0.63, and 0.52. Disabled women with major organ malfunction, chronic mental illness, or mental retardation had a higher likelihood to use mammography services, whereas women with multiple disabilities had the lowest likelihood of usage [8]. Qualitative Study: The aim of this study was to investigate intangible or non-physical barriers to participation of 75 women with disability in mammography screening. Three key intangible barriers were identified related to the women's expectations to be informed, to be involved and to be treated with respect. Details of the content, type, timing of appropriately presented information as well as who should provide it were emphasized. Barriers to active involvement to manage their disability and take control over their experience were identified. The women also indicated the specific treatment they received from screening staff which negatively

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	impacted on their experience [9]. Population-Based Cross-Sectional Study: Secondary data analysis of the Massachusetts Department of Developmental Services database, compared women who had a mammogram within 2 years with women who had not on variables related to the ecological model. The study sample's (n = 2907) mean age was 54.7 years; 58% lived in 24-hour residential settings, 52% received nursing health coordination, and more than 25% had clinical examination needs (eg, sedation). Residential setting, health coordination, and recent influenza vaccination were all associated with mammography. Having a guardian, higher level of activities of daily living needs, and examination needs (requiring sedation or limited wait time for examinations) were associated with lower rates. Several system-level variables were significantly associated with mammography and, in some cases, seemed to ameliorate intrapersonal/behavioral barriers to mammography. Community agencies caring for intellectually disabled women have potential to impact mammography rates by using health coordination [10].
"For example, to what extent do information and communication barriers prevent Deaf women or women with cognitive disabilities from seeking and obtaining preventive screenings, or from obtaining optimal treatments?"	Cross-Sectional Study: Women in the Carolina Mammography Registry aged 40 to 79 years (n = 2970) were surveyed. These women had been screened from 2001 through 2003 and did not return for at least 3 years, to determine reasons for noncompliance. In addition to women without disabilities, women with visual, hearing, physical, and multiple (any combination of visual, hearing, and physical) limitations were included in the analyses. The most common reasons cited by women both with and without disabilities for not returning for screening were lack of a breast problem, pain and expense associated with a mammogram, and lack of a physician recommendation. Women with disabilities were less likely to receive a physician recommendation. Women with disabilities are less likely than those without disabilities to receive a physician recommendation for screening mammography, and this is particularly the case among older women and those with multiple disabilities. There is a need for equitable preventive health care in this population [11].

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"To what extent do inaccessible facilities and equipment prevent women with physical disabilities from gaining access to preventive services, breast cancer screenings, and treatment?"	Focus Group Study: The Gateways to Cancer Screening project documented the challenges for women with disabilities in their access and experiences of screening for breast, cervical and colorectal cancer. 5 peer-led focus groups were held with 24 women with mobility disabilities. Study participants identified multiple and interacting institutional barriers to cancer screening including scheduling & attending appointments, normative judgments on their disabled bodies & securing reliable health care and information. This data was used to redesign cancer screening services & education of health providers [12]. Retrospective Descriptive Study: This study examined contraceptive methods and the extent of screening for breast and cervical cancer in women with neuromuscular disease, compare these results with data and guidelines for the general population and determine the environmental and attitudinal barriers encountered. Complete datasets were available for 49 patients. 70% of women used contraception (hormonal contraception in most cases). Architectural accessibility and practical problems were the most common barriers to care and were more frequently encountered by wheelchair-bound, ventilated patients [13]. Cross-Sectional Study: This study examined the relationship between disability status and routine breast and cervical cancer screening among middle-aged and older unmarried women and the differences in reported quality of the screening experience. 630 unmarried women in Rhode Island, 40-75 years of age, stratified by marital status (previously vs. never married) and partner gender (women who partner with men exclusively [WPM] vs. women who partner with women exclusively or with both women and men [WPW]). WWD were more likely than those without a disability to be older, have a high school education or less, have household incomes <$30,000, be unemployed, and identify as nonwhite. After adjustment for important demographic characteristics, the authors found no differences in cancer screening behaviors by disability status. However, the quality of the cancer screening experience was consistently and significantly associated with likelihood of routine cancer screening [14]. Qualitative Study: Telephone interviews with 14 mammographers in north central Florida

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	were conducted to examine their knowledge and experiences with patients with physical disabilities. There is currently no minimum required competency for mammographers regarding imaging patients with physical disabilities. The extent, content, and delivery of disability training varied among participants. Analysis revealed respondents' personal desires for training focused on positioning to "get the best breast image," while mammographers' advice to colleagues focused on the need to afford patience and respect to the patient. Mammographers value the disability training they receive as a foundation for continued learning on the job. Training should comprise both technical and social aspects of performing mammography on women with disabilities, including positioning, disability etiquette, and disability advocacy [15].
"How do women with mental health disabilities, or mental health issues secondary to some other primary disability, cope differently with issues related to screening, treatment, recovery, and survival?"	Retrospective Cohort Study: Surveillance, Epidemiology, and End Results program data, linked with Medicare files and Social Security Administration disability group. 90,243 women under age 65 were stratified into 4 disability groups and one nondisabled group. Compared with nondisabled women, those with mental disorders and neurological conditions had significantly lower adjusted rates of breast conserving surgery and radiation therapy. Survival outcomes also varied by disability type. Compared with nondisabled women, certain subgroups of women with disabilities are especially likely to experience disparities in care for breast cancer [16]. Cross-Sectional Study: This study used the Modified Toronto Breast Self-Examination Inventory (MTBSEI) to examine proficiency, motivation and knowledge regarding breast cancer screening and awareness of nurses working within an Intellectual Disability setting. Results reflected that the majority of nurses in this study (n = 105) do not promote breast awareness for women with intellectual disabilities. This study identifies the need to support nurses within Intellectual Disability settings with on-going education in relation to breast awareness, in order that breast awareness be promoted in clinical practice [17]. Cross-Sectional Studies: Women with developmental disabilities are significantly less likely

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	than women without disabilities to receive cervical and breast cancer screening according to clinical guidelines. This study examined the extent of women's knowledge about cervical and breast cancer screening, with the intention of informing the development and testing of interventions to increase cervical and breast cancer screening rates for these women. 202 community-dwelling women with developmental disabilities, most women had little knowledge of cervical and breast cancer screening. Women who were living at home with family caregivers had the most limited understanding of cervical and breast cancer screening [18]. Focus Group Study: Women with intellectual disability (ID) are surviving to the age group at greatest risk of developing breast cancer (50-69 years). However, as a result of cognitive deficits and communication difficulties these women are dependent upon staff to support them to attend the breast screening clinics. 6 focus groups were held with community nurses and residential staff who work in the field of ID in one region of the UK. Although many of the participants recognized the risk factors and signs/symptoms of breast cancer, there was still a deficit of knowledge. The participants identified 'a lack of health educational material' and also negative 'emotions, attitudes and physical barriers' as inhibiting factors for attendance. Development of user-friendly health educational literature using 'pictures, symbols, signs' and simplified words should be accessible to all ID staff, healthcare staff, and also women with ID [19]. Focus Group Study: This paper is a report of a descriptive study of understanding of breast cancer and experiences of breast mammography among women with an intellectual disability.4 focus groups were undertaken with 19 women identified as having a borderline to moderate intellectual disability all of whom had received a breast mammography. The women's knowledge of breast cancer including associated risks, preventative factors and signs and symptoms were extremely limited with their sources of knowledge primarily coming from caretakers or nursing staff on receipt of an invitation for mammography. Although these women expressed a positive attitude towards their experiences of breast mammography,

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	they also described negative feelings of fear and anxiety, attributed to a lack of understanding about the screening process. A lack of information and embarrassment were identified as the main barriers to screening for this group [20]. Qualitative Study: This study explored perceptions and understanding of mammography for women with intellectual disabilities (ID) and some of the potential reasons they would or would not have the test. 27 ID women were recruited through a variety of community groups and interviewed using a semistructured interview guide. Participants in this study described being poorly prepared for mammography: they did not understand its purpose and were not prepared for the logistics of the experience. The latter was more upsetting to participants and contributed to their negative perceptions of mammography. Participants reported feeling unprepared and singled out for being unprepared, despite their desire to have at least 1 mammogram, as do other women their age [21].
"Given that women with disabilities constitute one of the most economically disadvantaged populations living in this country (an estimated 26 percent of California women with severe disabilities live in poverty), large disparities in breast cancer are likely to exist."	Retrospective Cohort Study: A study of female Medicare beneficiaries over age 69 diagnosed with breast cancer (n=413) using Surveillance Epidemiological End Results (SEER)-Medicare linked database. The total number of women was 413 with SSDI and 8,989 without. Bivariate analysis showed that significantly fewer women with SSDI used screening mammography (45% vs. 38%, P = 0.0006) during the two years prior to diagnosis. Mean tumor size at diagnosis was 2.91 mm (95%, CI = 1.10, 4.73) larger in the group with SSDI. This study found that older women whose original reason for Medicare benefits was disability present with larger tumors at breast cancer diagnosis compared to those who were not. Screening mammography may partially mediate the disparity [22]. Retrospective Cross-Sectional Study: This study compared breast cancer stage at diagnosis and treatment among women with disabilities enrolled in Medicare managed care versus fee-for-service (FFS) Medicare. Women enrolled in FFS Medicare were classified into levels of healthcare utilization during the 6 to 18 months before breast cancer diagnosis. Disabled patients enrolled in FFS Medicare without contact with the healthcare system and those with

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	fewer than 12 physician visits during the 6 to 18 months before breast cancer diagnosis were more likely than disabled patients enrolled in Medicare managed care to be diagnosed as having breast cancer at a late stage. Managed care enrollment or increased contact with healthcare providers could result in earlier stage at breast cancer diagnosis [23]. Retrospective Cohort Study: Surveillance, Epidemiology, and End Results-Medicare linked dataset was used to identify beneficiaries older and younger than 65 years entitled to Medicare benefits because of disability (SSDI) who subsequently were diagnosed as having breast cancer (n = 6839) or non-small cell lung cancer (n = 10,229) from 1988 through 1999. Women with continuous HMO insurance had earlier-stage breast cancer diagnosis (adjusted relative risk, 0.77; 95% confidence interval, 0.65-0.91) and were more likely to receive radiation therapy following breast-conserving surgery (adjusted relative risk, 1.11; 95% confidence interval, 1.03-1.19). Women having continuous HMO insurance had better breast cancer survival, primarily resulting from earlier-stage diagnosis. When diagnosed as having breast cancer or non-small cell lung cancer, some Medicare beneficiaries with disabilities fare better with managed care compared with FFS insurance plans [24].
"What is the interaction between a preexisting disability, along with secondary conditions often associated with that disability, and additional functional limitations caused by the cancer and/or its treatment?"	Descriptive cohort study: With older age, the risk of comorbid conditions and functional impairment increases. A useful tool in the management and follow-up of these elderly patients could be a comprehensive geriatric assessment (CGA). Eligibility: Women aged> or =70 at diagnosis; early breast cancer treated surgically. 91 patients were seen. Mean age at surgery: 76 (70-92). Mean age at CGA: 80 (71-95). Older patients with early breast cancer on follow-up have a high prevalence of comorbidity. In the series, function and independence were maintained. A selection bias cannot be excluded, as the fitter patients are those who usually continue with the follow-up, while those frail patients who do not continue because of their functional impairment are usually lost [25]. Qualitative Study: This study analyzed transcripts from in-depth in-person or telephone interviews with 20 English-speaking women who had early-stage breast cancer, were <60

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	years of age, and had chronic difficulty walking or used wheeled mobility aids at the time of their breast cancer diagnoses. Most women reported difficulty obtaining mammograms, primarily because of inaccessible equipment, positioning problems, and difficulties with uncontrollable movements. Many women made decisions about surgical approach and chemotherapy by explicitly considering how various therapies would affect their arms, which are essential to their mobility (they use ambulation aids, self-propel manual wheelchairs, or otherwise rely on their arms for mobility or safety). Managing at home after surgery posed major mobility challenges, especially for women who lived alone. Several women reported feeling they suffered more chemotherapy side effects than do women without mobility problems. Weight gains with endocrine therapy compromised the mobility of several women [26].
"Future incidence studies of breast cancer among blind women would be strengthened by incorporation of measured levels of circulating melatonin, greater sample sizes, and information on age at onset of visual impairment and on other breast cancer risk factors."	Cross-Sectional Study: This survey study evaluated whether blind women with no perception of light (NPL) have a lower prevalence of breast cancer compared to blind women with light perception (LP). The authors surveyed a cohort of 1,392 blind women living in North America (66 breast cancer cases). Women with NPL had a significantly lower prevalence of breast cancer than women with LP (odds ratio, 0.43; 95% confidence interval, 0.21-0.85). The authors observed little difference in these associations when restricting to postmenopausal women, non-shift workers or when excluding women diagnosed with breast cancer within 2 or 4 years of onset of blindness. Blind women with NPL appear to have a lower risk of breast cancer, compared to blind women with LP. More research is needed to elucidate the impact of LP on circadian coordination and melatonin production in the blind and how these factors may relate to breast cancer risk [27].

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D. Culture

Abstract

One key gap is the need for a more specific definition of culture within breast cancer research. Most studies use acculturation as a predictor for breast cancer screening rates, access to treatment, success of treatment or mortality rates. This literature is difficult to summarize because acculturation is measured in a number of varying ways including: acquisition of the English language; number of years in the United States; immigration status; and neighborhood demographics characteristics e.g. ethnic enclaves. Another gap is exploring breast cancer concerns of non-Latina or non-Asian (Chinese, Korean) women, since most studies focus on Latinas and Asians. Only one or two studies focus on South Asian, Middle Eastern or other populations and no studies targeted Native American or indigenous populations specifically in terms of culture and breast cancer. Part of this gap may also include the lack of specific race and ethnicity information on population-based culture studies.

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"Limited breast cancer studies of African American, Hispanic/Latina, American Indian/Alaska Native, Asian American, and Native Hawaiian and other Pacific Islander women as they move through the breast cancer care continuum suggest that all are at risk for poorer outcomes. The breast cancer risk for newer immigrant groups also increases with increasing levels of acculturation. First is the constraint of accuracy on collection of data on subpopulations within the larger ethnic categories. Even in California, the error rate in ethnic classification is quite high for some groups, for example, American Indians."	Review/Commentary: Examined health-related quality of life (HRQOL) in Latina breast cancer survivors. Reviewed 37 studies. Echo the 2007 Gap scan in determining a lack of research examining community-, institutional-, and policy-level factors, such as health care access, legal and immigration factors, physical and built environments, and health care affordability. This is especially true within longitudinal and intervention studies [2]. Cross-Sectional study: Convenience multi-ethnic sample of 99 women examining perceived health status & demographic characteristics. Demographic Information for Immigrants from the Former Soviet Union Survey (DIFSU) and Language, Identity, and Behavior Acculturation Survey (LIB) were used to collect data. Women with better English language skills were more likely to conduct breast self-exam but considered their health status as poor or fair; the longer women were in the United States, the more likely they were to receive a mammogram. The model indicated that age and language acculturation significantly predicted health status [18]. Prospective cohort study: This study assessed differences in acculturation, knowledge, beliefs, and stages of readiness for mammograms from pre- to post-intervention among Korean American women aged 40 years or older (n=300). Women attended a 45-minute interactive breast cancer early screening education session (GO EARLY) organized according to stages of readiness for mammography use, with a 6 week post-intervention follow up. At pre-intervention stages of readiness, women thinking about having a mammogram (contemplators) had significantly lower knowledge scores and higher cons to mammography use than women who had mammograms in the past (relapsers). Women not thinking about having a mammogram (pre-contemplators) had significantly lower self-efficacy for having a mammogram and higher cons than relapsers. The GO EARLY session was most effective in increasing knowledge, decreasing perceived cons, and increasing perceived self-efficacy. No statistically significant intervention effect was noted on upward shift in stage of readiness for mammography use post-intervention. The GO EARLY intervention, the first study to assess

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	stages of readiness for mammography use among Korean American women, was feasible and culturally sensitive and can be replicated in various Korean American communities [24]. Other intervention studies with Korean women have support culturally sensitive intervention to increase rates of mammography, clinical breast examination and breast self-examination [48]. Qualitative content analysis: Descriptive content analysis of interviews of 107 Jordanian and Palestinian immigrant women provided data on breast cancer screening barriers. Data revealed 4 barriers that affect Jordanian and Palestinian immigrant women's participation in BCS: (1) culture-specific barriers such as embarrassment, family relationships, fatalism, and traditional healers consultation; (2) immigration-related barriers (citizenship issues and language); (3) general barriers (including nonparticipation in health screening, stigmatization of cancer, fear, and ignorance about BCS); and (4) irrelevant barriers [35]. Other studies have investigated similar populations using convenience cross-sectional sampling [44]. Qualitative focus group study: There is minimal empirical data that describe the cancer practices, beliefs, and needs of African-born women & breast cancer outcomes. 2 focus groups with 20 African women explored their knowledge and attitudes about breast cancer practices and identified potential intervention targets. Women were primarily from the western region of Africa (e.g., Nigeria, Ivory Coast), but there were representatives from the southern (e.g., Zimbabwe) and eastern (e.g., Ethiopia) regions as well. Findings indicated that women's knowledge and exposure to breast cancer prevention and screening were limited, and common explanations for breast cancer were that it is a boil or is a punishment from God. Barriers included limited knowledge, lack of insurance, spiritual beliefs, and secrecy. Suggestions for promoting breast health in this community included using culturally relevant materials and involving African men. Findings from this descriptive study provide useful insight to begin to understand the breast health experiences of African immigrant women[40]. Cross-sectional study: Stage at breast cancer diagnosis and receipt of primary therapy were

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	examined by ethnicity and birthplace among US-born Hispanic, foreign-born Hispanic, and white women. The study included 31,012 Hispanic women and 372,313 white women with a first diagnosis of invasive breast cancer during 1988 and 2005. Foreign-born Hispanics had lower adjusted rates of stage I breast cancer at diagnosis (35.4%) than US-born Hispanics (40.6%), birthplace-unknown Hispanics (42.3%), and whites (47.4%). Foreign-born Hispanics and birthplace-unknown Hispanics had lower rates of BCS with radiation (34.9%, 30.7%) than US-born Hispanics (41.5%) and whites (38.8%). Identifying factors mediating these disparities may help in developing culturally and linguistically appropriate interventions and improving outcomes [42. Cohort intervention study: CPBR study testing culturally based breast cancer screening program among low-income Hmong women in central and southern California. Compared with women in the comparison community, women in the intervention community significantly improved their attitudes toward, and increased their knowledge and receipt of, breast cancer screenings. Culturally informed education materials and intervention design were effective methods in conveying the importance of maintaining and monitoring proper breast health. The strength of community collaboration in survey development and intervention design highlighted the challenges of early detection and screening programs among newer immigrants, who face significant language and cultural barriers to care, and identified promising practices to overcome these health literacy challenges [46].
"A corollary to this second factor is the lack of clarity and precision in the definitions and use of the terms race, culture, ethnicity, and acculturation. These concepts must be scientifically applied to produce results that are trustworthy and comparable."	Prospective Cohort Study: This study proposed a model to elucidate pathways through which acculturation (indicated by language use) and reports of communication effectiveness specific to medical decision making contribute to decisional outcomes (i.e., congruency between preferred and actual involvement in decision making, treatment satisfaction) and quality of life among Latinas and non-Latina White women with breast cancer. Latinas (N = 326) and non-Latina Whites (N = 168) completed measures 6 months after breast cancer diagnosis, and quality of life was assessed 18 months after diagnosis. In Latinas, greater use of English was related to better-reported communication effectiveness. Differences in quality of life and

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	effectiveness in communication were observed between racial/ethnic groups. Findings underscore the importance of developing targeted interventions for physicians and Latinas with breast cancer [11]. Cross-sectional study: Using the Health Belief Model, this study explored knowledge and beliefs (perceived risk factors, susceptibility, benefits, common barriers, and cultural barriers) in relation to mammography screening practices among Chinese American women 40 years or older (n=100). The strongest factor associated with having a mammogram within the past year was having an immediate family member diagnosed with breast cancer, followed by having insurance that covered a mammogram and lower perceived barriers to obtaining a mammogram [30]. Cross-sectional survey: Focuses on English proficiency & its influence on effective functioning in the health care environment. Breast cancer is the most prevalent cancer in Asian-American women but little is known about its adverse consequences in this population. The study examined the extent to which English proficiency was associated with symptoms and QOL in Chinese- (n = 72) and Vietnamese-American (n = 25) breast cancer survivors in Houston, Texas. English proficiency has a significant impact on symptom distress and QOL. These findings may help the development of services to meet the unique needs of Vietnamese- and Chinese-American breast cancer survivors [39].
For example, what is it about lower acculturation levels that are associated with possibly worse breast cancer survival? Is it due to lack of access to quality care, language barriers, cultural beliefs about disease process, a foreign paradigm of health and well-being, or something else?	Mixed Methods Study: To explore how and to what extent acculturation and immigration affect Chinese-American immigrant women's breast cancer experience. Chinese-American women (n=107) with breast cancer completed the structured questionnaire survey, and 16 women completed face-to-face in-depth interviews. In the quantitative findings, acculturation was related to health beliefs, social support and life stress. Cultural interpretations of the qualitative information are offered to show that breast cancer experience was intertwined with cultural adaptation in a given immigrant environment. Chinese cultural beliefs persistently, even after years of immigration, guide Chinese-American immigrant women to

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	respond to breast cancer across the meaning of health and illness, family ties and involvement and social interaction. The findings show that acculturation is related to health beliefs, social support and life stress in the trajectory of breast cancer adaptation. Life stresses derived from immigration bring additional difficulties for immigrant women living with cancer. This study pinpoints that traditional cultural beliefs and immigration stress may influence Chinese-American women to cope with breast cancer [5]. Scale validation: Women with nonmetastatic breast cancer diagnosed from June 2005 to February 2007 (n= 2290) with oversampling of Latinas and African Americans. A worry scale was constructed as the mean score of 3 items: worry about cancer returning to the same breast, occurring in the other breast, or spreading to other parts of the body. Race/ethnicity categories were white, African American, and Latina (categorized into low vs. high acculturation). Low acculturated Latinas reported more worry and African Americans less worry than whites ($P < .001$). With all factors in the model, less worry was associated (all $Ps < .05$) with greater ease of understanding information, better symptom management, and more coordinated care. Race/ethnicity remained significant controlling for all factors ($P < .001$). Less acculturated Latina breast cancer patients are vulnerable to high levels of worry. Interventions that improve information exchange, symptom management, and coordinating care hold promise in reducing worry [16]. Cross-sectional study: This paper is a report of a study of the correlates of mammogram use among Korean American women (n=100). They measured screening-related health beliefs, modesty and use of Eastern medicine. Only 51% reported past mammogram use. Korean American women who had previously had mammograms were statistically significantly older and had higher perceived benefit scores than those who had not. Perceived benefits and breast cancer susceptibility were statistically significant correlates of mammography experience, whereas cultural factors did not correlate. Post hoc analysis showed that for women with some or good English skills, cultural factors statistically significantly correlated

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	with health beliefs and breast cancer knowledge (P < 0.05) [20]. Cross-sectional interview study: To describe breast cancer risk perceptions, determine risk comprehension, and evaluate mammography adherence among Latinas over age 35 (n=450). Risk comprehension was calculated as the difference between numeric perceived risk and Gail risk score. Adherence was associated with older age, having insurance, greater acculturation (OR = 1.18, 95% CI = 1.02-1.36), and higher breast cancer knowledge. Among Latinas, screening interventions should emphasize knowledge and target education efforts at younger, uninsured, and less acculturated mammography-eligible women [28].
"Future research should also explore the impact of legal status (e.g. naturalized citizen, legal resident, undocumented immigrant, refugee) on acculturation and health. The complex immigration history and anti-immigrant sentiments in the U.S., often directed at specific groups, may inhibit the acculturation process."	Case-control study: Mexican-origin women in Harris County, Texas (n=714), where the rates of breast cancer mortality for Latina women have doubled since 1990. Half of breast cancer cases (n=119) were diagnosed in women aged <50 years. In a multivariate model, women who had a family history of breast cancer (odds ratio [OR], 4.3), who were born in Mexico and had high levels of language acculturation (OR, 2.5), and who did not have health insurance (OR, 1.6) had the highest risk for breast cancer. Because the current results indicated that Mexican-origin women are at high-risk for early onset, premenopausal breast cancer, the authors recommended policies that target screening, education, and treatment to prevent increased disparities in mortality. The authors concluded that the inclusion of community members and policymakers as partners in these endeavors would further safeguard against an increase in cancer health disparities and aid in formulating a policy agenda congruent with scientifically based, community-driven policy efforts that address breast cancer screening, education, and treatment in this vulnerable population [17]. Cross-sectional study: The purposes of this study are 1) examine the relationships among breast cancer risk knowledge, general cancer beliefs, and breast examination practices and 2) determine the predictors of breast examination practices among Chinese women in New York (N = 135). Age, acculturation, private insurance status, legal status, and length of stay in New York were related to screening. Evidently, providing information regarding cancer prevention

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	targeted for female Chinese immigrants can help increase use of cancer screening tests [25]. Review/commentary: This paper examines the literature on migration and female breast cancer. A comprehensive review aimed at identifying risk and protective factors that cut across races and ethnicities was performed. A total of 79 studies (1971-2005) from 16 countries were reviewed. While the acculturation-based risk transition model is strong, it is not always supported. As a new direction for migrant studies, the authors extrapolate the review findings to the experience of Eastern European (EE) immigrants. Health data on this population, typically characterized by low health motivation and passive receipt of preventive efforts, are largely unavailable. Based on relevant theory, empirical and qualitative studies, two breast cancer prevention models for the EE immigrant population are proposed and the need for future research using ethnically disaggregated data is discussed [31]. Descriptive Study: This study highlights the culturally competent implementation and reports the outcomes of a breast cancer screening patient navigation program for refuge/immigrant women from Bosnia. Refugees/immigrant women from Bosnia age 40-79 were contacted by a Serbo-Croatian speaking patient navigator who addressed patient-reported barriers to breast cancer screening and, using individually tailored interventions, helped women obtain screening. The proportion of women up-to-date for mammography was compared at baseline and after 1-year using McNemar's Chi-Square test. 91 Serbo-Croatian speaking women were eligible for mammography screening. At baseline, 44.0% of women had a mammogram within the previous year, with the proportion increasing to 67.0% after 1-year (P = 0.001). A culturally-tailored, language-concordant navigator program designed to overcome specific barriers to breast cancer screening can significantly improve mammography rates in refugees/immigrants [37]. Cross-sectional study: This study investigated heterogeneity in ethnic composition and immigrant status among US Asians as an explanation for disparities in breast cancer survival. Immigrant status, neighborhood socioeconomic status, and ethnic enclave as well as mortality

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	among Chinese, Japanese, Filipino, Korean, South Asian, and Vietnamese women diagnosed with breast cancer from 1988 to 2005 were examined. US-born women had similar mortality rates in all Asian ethnic groups except the Vietnamese, who had lower mortality risk. Except for Japanese women, all foreign-born women had higher mortality than did US-born Japanese, the reference group. Survival after breast cancer is poorer among foreign- than US-born Asians. Research on underlying factors is needed, along with increased awareness and targeted cancer control [41].
"Measures should be developed to appropriately assess, address, and incorporate these cultures into cancer research. Future studies should also measure the impact of public policy decisions on health behavior and on breast cancer outcomes."	Mixed-Methods Study: To explore the relationships between cultural health beliefs, acculturation, treatment-related decisions, the doctor-patient relationship, and health behaviors among Asian American breast cancer survivors (AABCS; n=206), and Korean American breast cancer survivors (KABCS; n=11) for the qualitative part. Standardized (i.e., cultural health beliefs, doctor-patient relationship, and acculturation) and newly developed instruments (i.e., health behaviors and treatment-related decisions) were used in the quantitative phase. Inter-intrapersonal health beliefs, doctor-patient relationship, and shared decision making were positively associated with adopting healthy lifestyle practices. Results highlight the need for greater attention to the cultural contexts of AABCS to promote healthy behaviors and recognition of the significant relationship between health professionals and breast cancer survivors [3]. Scale Validation Study: This study focused on mammography behaviors among Asian American (Thai) women. Champion's belief scale was translated into Thai and cultural items were added. The Thai breast cancer belief scale (TBCBS), the Suinn-Lew self-identification acculturation, and the Asian values scale-revised were administered to 250 Thai immigrants. The TBCBS was tested for face validity, construct validity, and internal consistency. Factor analysis reflected the 4 constructs of the health belief model and accounted for 45.8% of the variance. Cronbach's α ranged from .77 to .90. Modest correlations were observed between TBCBS subscales and acculturation scales. Results indicate that the TBCBS measures breast

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	cancer beliefs among Thai immigrant population [9].
"Rigorous inductive qualitative research is a critical step for uncovering the salient cultural factors impacting breast cancer diagnosis, treatment, and outcomes."	Pilot Cohort Study: A focus group study U.S. born African-American women (N = 60) to determine the factors associated with decreased utilization of mammography. Findings from the study suggest that African-American acculturation and Health Temporal Orientation were significantly associated with mammography utilization (p = 0.01). There was no significant relationship between other cultural beliefs, health-care avoidance, or sociodemographic status indicators [15]. Focus group study: Through focus groups and individual interviews, data were gathered on the emotional, informational, and instrumental support needs of 22 immigrant Latina women. A thematic analysis revealed that participants who perceived to receive social support reported less psychological distress and better adjustment to breast cancer than those who did not perceive this support. Types and sources of support varied across survivorship stages. Many needs were related to financial, linguistic, and cultural barriers participants encountered in the course of the disease. Based on the findings, the authors conclude with several clinical recommendations to improve the quality of life in this medically underserved population [23]. Qualitative interview study: This study describes the concept of prevention and identifies the knowledge, perceived benefits and barriers, as well as the practices of early detection of breast cancer among women from different cultural backgrounds and socioeconomic levels. The study population consisted of women in Barcelona who were either native (Spanish) or immigrants from low-income countries, aged 40 to 69 years. Narrations of the 68 informants were subjected to sociological discourse analysis. Place and culture of origin, social class and the migratory process can either facilitate or constitute barriers to breast cancer prevention [32] Qualitative mixed methods study: Focus groups and one-on-one interview data was collected

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	from 71 women (37 Chinese immigrant, 7 US-born Chinese, 27 Non-Hispanic White - NHW) who were breast cancer survivors (BCS). All BCS were diagnosed with breast cancer at stage 0-IIA between 2006 and 2009, and had survived for 1-4 years without recurrence. Interviews were conducted in Cantonese, Mandarin, or English. Chinese immigrant BCS were less likely to have their issues resolved compared to NHW and US-born Chinese who were more likely to question physicians, ask for referrals, and make repeat attempts if their problems were not resolved. Some Chinese immigrant BCS turned to Traditional Chinese Medicine for relief or accepted the idea that physical distress was part of survivorship. Furthermore, they may express symptoms in culturally unique ways (e.g., hot-cold imbalances). Further research is needed to determine how to best improve survivorship care experiences in this understudied population, with the goal of decreasing BCS' physical distress and improving quality of life [36]. Qualitative study: Grounded theory is used to examine rates of cancer screening among Korean immigrant women. 20 Korean immigrant women, aged between 20 and 81 years, participated in a set of 2 consecutive qualitative interviews conducted in the Korean language. "Balancing relationships within a discordant world" is the core concept of the process of breast cancer screening among Korean immigrant women. There are sociocultural discord in perceptions of breast cancer and screening procedures between Asian ways of thinking and Western biomedical premises. The elicited situation-specific theory sheds light on what Western healthcare professionals have missed and what they should consider in caring for culturally diverse populations [47]. Qualitative interview study: This study examined experiences related to self-discovered breast cancer symptoms from the perspective of Punjabi immigrant women residing in Canada. Interviews were conducted with 25 women, 19 of whom had received a diagnosis of breast cancer. Using narrative analysis, 4 types of stories were identified. In the stories that were based on constructions of breast symptoms as "nothing serious," women emphasized that they had not even considered the possibility of breast cancer and were encouraged to dismiss

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	concerns about their health. Stories focusing on suspicions about the presence of a health problem included descriptions of mounting concern and tension as the women began to realize that the breast symptoms they experienced might not be of the regular or normal variety. In stories dominated by worry, vivid descriptions of fears of breast cancer were juxtaposed with explanations about how women protected family members by downplaying their symptoms. Finally, in stories that focused on gaining strength in readiness to deal with whatever may lie ahead, women drew on the support of their extended families, their religious beliefs, and their need to care for their families. These findings provide a basis for guiding the development of culturally appropriate health education for Punjabi women [49].
"However, methodologically rigorous deductive quantitative studies are needed as well for assessing the relative impacts of cultural factors on health among diverse African American, American Indian/Alaska Native, Asian American, Pacific Islander and Hispanic/Latino subgroups."	Cross-Sectional study: This study examined differences in cervical & breast cancer screening among a heterogeneous group of Hispanic women (n=257). The women were from Mexico, the Dominican Republic, Puerto Rico, and countries throughout Central and South America. Differences in Clinical Breast Exam (CBE) and Breast Self Exam (BSE) screening behaviors were found based on country of origin ($P < .01$). However, after adjusting for the independent variables, only acculturation and knowledge remained significant correlates to BSE and CBE ($P < .01$). Dominican women had higher BC knowledge scores ($P < .01$) adhered most to BC screening guidelines. Heterogeneity in BC screening was found among Hispanic sub-groups and suggests that health promotion programs should be tailored appropriately, particularly among recent immigrants [8]. Cross-sectional study: The authors compared breast cancer risk factors among three groups of postmenopausal Canadian women at substantially different risk of developing breast cancer - Caucasians (N = 413), Chinese women born in the West or who migrated to the West before age 21 (N = 216), and recent Chinese migrants (N = 421). Information on risk factors and dietary acculturation were collected by telephone interviews using questionnaires, and anthropometric measurements were taken at a home visit. Compared to Caucasians, recent Chinese migrants less often had a family history of breast cancer or a benign breast biopsy. The authors estimated five-year absolute risks for breast cancer using the Gail Model and

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	found that risk estimates in Caucasians would be reduced by only 11% if they had the risk factor profile of recent Chinese migrants for the risk factors in the Gail Model [19]. Review/commentary: Asian women worldwide have increasing rates of breast cancer due to acculturation which may be altering, gene-to-gene and/or, genetic and environmental interactions at the cellular level. This review focuses on Korean women specifically, reviewing English and Korean literature since 1983. Korean women need knowledge about the effect of acculturation on breast cancer risk and patterns of familial inheritance of breast cancer. Screening is especially important among younger women (younger than age 35), those with a strong family history, and women in community settings where acculturation has its greatest impact. In the United States and Korea, Korean nurses are needed to specialize in breast cancer screening as well as cancer genetic risk assessment and genetic counseling [29].
Cancer registry and other population-based data sources used to assess patterns of cancer incidence and mortality should aim to include more complete information on birthplace. Emphasis should be placed on developing methods to obtain additional information, such as imputing years in the U.S. through other information and acculturation characteristics of the neighborhood through census track data.	Retrospective cohort study: This study investigated differences in breast and stomach cancer risk and survival in migrants to the Netherlands. Invasive breast and stomach cancer cases diagnosed between 1996 and 2006 were selected from the Netherlands Cancer Registry. Standardized incidence ratios (SIR) were computed as the ratio of observed and expected cancers. All migrant women exhibited a significantly lower risk for breast cancer compared with Dutch natives. However, 5-year RSR was lower in all migrants (range 68-73%) compared with Dutch natives (85%). Death rates were increased in Moroccan [HR = 1.2 (1.0-1.5)] and reduced in Indonesian [HR = 0.8 (0.8-0.9)] patients with breast cancer. Both lower breast cancer rates and higher stomach cancer rates point to a strong link between environmental exposures, behavioral patterns and cancer risk during the life course [6]. Retrospective Cohort Study: Asian Americans (AA) have the lowest rates of cancer screening of all ethnic groups. This study compared the relative impact of access vs. acculturation on breast and cervical cancer screening for AA subgroups (Chinese, Filipino, Japanese, Korean, South Asian, and Vietnamese origins). Access explained more variation that acculturation alone in cancer screening for most AA women. The exceptions were in mammograms for

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	Japanese, Koreans and South Asians. No insurance reduced the likelihood of clinical breast examination for immigrant Chinese and Filipinos. Access indicators represent the ability to navigate the US health care system but have a differential impact on AA groups. These differences should be integrated into interventions designed to improve cancer-screening rates [7].
"Emphasis, however, should be placed on including more questions addressing the concept of acculturation, and on disaggregating the larger ethnic subgroups in analyses."	Descriptive study. Comparing Caucasian (n=182) & Latina (n=98) Latina breast cancer survivors. Caucasians reported significantly higher levels of total perceived social support and QOL than Latinas. Psychiatric illness comorbidity and lower level of education in Latinas were factors in the disparity of QOL. Factors such as cultural values, comorbidities, and education level likely influence perceived social support, uncertainty, and QOL [1]. Cross-Sectional Study: Investigated family flexibility, social support, and family communication on health-related quality of life (HRQOL) for Chinese- and Korean-American breast cancer survivors (BCS). A total of 157 Chinese (n = 86)- and Korean-American (n = 71) BCS were recruited from the California Cancer Surveillance Program and area hospitals in Los Angeles County. Family communication was directly associated with HRQOL for both groups; (2) family flexibility was indirectly associated with HRQOL through family communication for Korean-Americans only; (3) social support mediated the relationship between family flexibility and family communication for Chinese-Americans only; and (4) acculturation was directly related to social support for both groups. The results show that while there are commonalities in family characteristics among Asian-Americans, specific ethnic variations also exist. Therefore, specific cultural and familial contexts should be assessed to better inform interventions to enhance family communication strategies and improve HRQOL [10]. Cross-sectional study: This study focused on health disparities & the use of genetic services (including genetic counseling and testing) for breast cancer risk, with women of African descent less likely to use genetic services compared with Whites. Baseline data from 146 women of African descent (56% US born and 44% foreign born) meeting genetic breast cancer

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	risk criteria and participating in a larger longitudinal study. In multivariate analyses, being foreign born was a significant predictor of anticipated negative emotional reactions about genetic testing. Results suggest an influence of acculturation and breast cancer-specific distress on perceived barriers to genetic testing among women of African descent [26].
"Secondly, the research should not strictly be performed on culturally distinct populations, but in cooperation and partnership with them. Several CBPR studies that relied on multidirectional communication and circular feedback between researchers and the communities studied have been extremely effective in changing the landscape of cancer perception, and in transforming (without acculturating) subgroups to play a more active role in prevention and seeking treatments."	Cross-sectional study: A study was designed to recruit a large and representative sample of these subgroups. Incident cases were selected by rapid case ascertainment (RCA) in the Los Angeles Surveillance, Epidemiology, and End Results Registry with oversampling of Latinas and African-Americans (n=1223). The RCA definition of Hispanic origin was validated by self-reports. The Short Acculturation Scale for Hispanics index for Latina respondents was used. The RCA definition of Hispanic identity was highly sensitive (94.6%) and specific (90.0%). Lower acculturation was associated with lower education and literacy among Latinas. High response rates among all subgroups were achieved due to the use of RCA, an incentive, extensive telephone follow-up, a native Spanish-speaking interviewer, and a focused questionnaire. The low acculturation index category identified a highly vulnerable subgroup. This large sample representing subgroups with greater problems will provide a basis for developing better interventions to assist these women [22] Cross-sectional study: When compared to other racial/ethnic minorities and immigrants in Miami, Florida, Haitian women are more likely to be diagnosed with late-stage breast cancer when the prognosis for survival is poor. Previous research has not examined the frequency of mammography use among Haitian women in Miami. This study addresses this gap. In 2007, Community Health Workers (CHWs) recruited nearly 1,000 Haitian women from community venues across Little Haiti, the predominantly Haitian area in Miami, to participate in Rapid Assessment Surveys (RAS). Data indicate Haitian women are less likely than other women in Florida to report regular mammography. Such findings, though not surprising, suggest that grouping all black persons, regardless of ancestry, into one research category may mask variation in disease risk. (27) Other studies have also focused on the Haitian population in the

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	United States [43]. Qualitative focus group study: Evidence indicates that South Asian (SA) immigrant women are vulnerable to low rates of breast cancer screening and few studies on this population. Semi-structured focus groups (FG) to elicit perspectives of health and social service professionals on possible solutions to barriers. 35 health and social services staff members participated in 5 FG. Three dominant themes were identified: (i) 'Target and Tailor' focused on awareness raising through multiple direct and indirect modes or approaches with underlying shared processes of involving men and the whole family, use of first language and learning from peers; (ii) 'Enhancing Access to Services' included a focus on 'adding ancillary services' and 'reinforcement of existing services' including expansion to a one-stop model; and (iii) 'Meta-Characteristics' centered on providing 'multi-pronged' approaches to reach the community, and 'sustainability' of initiatives by addressing structural barriers of adequate funding, healthcare provider mix, inter-sectoral collaboration and community voice [34]. Qualitative mixed methods study: In 2004, a community- university partnership resulted in the first Filipina breast cancer support group in the San Francisco Bay Area. Building on this partnership, the study explored the social and cultural contexts of Filipinas' experiences with breast cancer to inform development of culturally appropriate and sustainable support services and outreach. Interviews and observations revealed the influences of social context and immigration experiences on women's understandings of cancer, what "surviving" cancer means, and what it means to take care of someone with breast cancer (or be taken care of). Findings highlight the importance of a transnational perspective for the study of immigrant women's experiences of cancer and survivorship [38].
"Many cultures do not distinguish spiritual, religious, and traditional customs from medicine. Engaging these communities through partnerships with leaders within their populations, retaining cultural distinctions, and	Qualitative/Focus group study: This focus group study examined participation status in breast and cervical cancer screening of a group of American immigrant Arab Muslim women (AMW). Perceived knowledge of and barriers to screening participation, relationships among demographic variables, health practice and beliefs, and self-reports of traditionalism and

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applying culturally-appropriate perspectives to screening, navigation, and treatments will greatly benefit the cause of neutralizing breast cancer disparities."	acculturation also are studied. Factors including religious and cultural beliefs, economic concerns, and modesty and embarrassment were considered. To reach the goals of Healthy People 2010 (HP 2010), an effective and meaningful educational initiative to raise awareness about breast and cervical cancer of AMW will require specific interventions consistent with their cultural and religious traditions [4]. Prospective Cohort Study: This study explores the relationship between types of religiosity to breast and cervical cancer screening efficacy and behavior among Vietnamese women (n=111) recruited from a Catholic Vietnamese church and a Buddhist temple in the Richmond, Virginia. The potential moderating effect of acculturation was of interest. Acculturation moderated the relationships between religiosity and self-efficacy for breast cancer screening. Acculturation also moderated the relationship between religiosity and breast cancer screening. Specifically, for less acculturated women, increasing levels of intrinsic religiosity and personal extrinsic religiosity were associated with lower likelihood probability of Pap testing. The authors' findings demonstrate the need for further investigation of the dynamic interplay of multi-level factors that influence cancer screening [12]. Cross-Sectional Study: This study examined the association between belief in divine control and coping and how the association was moderated by ethnicity/acculturation in a multi-ethnic sample of Latina, African American, and non-Hispanic White older women with newly diagnosed breast cancer (N=257) from a population-based survey. Belief in divine control was positively related to approach coping (i.e., positive reframing, active coping, and planning) in all ethnic groups. Belief in divine control was positively related to acceptance and negatively related to avoidance coping (i.e., denial and behavioral disengagement) among low-acculturated Latinas [13]. Qualitative interview study: Little is known about spirituality and religious involvement of Filipina Americans who have been diagnosed with breast cancer. Ten (n = 10) in-depth qualitative interviews with Filipina immigrant breast cancer survivors identified prayer to be

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	the most common religious practice, followed by prayers by others and spiritual support from the Catholic Church. These findings can help clinicians and researchers understand the role of spirituality and religion in providing comfort and support for Filipina immigrant breast cancer patient as they face the stress of diagnosis and treatment [33].

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Section III: Neighborhood Context and Breast Cancer

Abstract

Key gaps identified include the need for a continued specificity in definitions of neighborhood (e.g. census tract or zip code or something else) and community level variables such as neighborhood SES, built environment and racial segregation. Much of the literature on neighborhoods overlaps heavily with other sections of the gap scan including issues of environmental exposure, race/ethnicity, physical activity and class (as discussed in race/ethnicity). Since 2007 a few studies have examined the gap in literature surrounding rural, suburban and urban differences in breast cancer outcomes. A number of studies filled the 2007 identified gap of studies examining the intersection of neighborhood racial composition and neighborhood SES. These studies mainly examined how these factors affect breast cancer screening and treatment. Only one study filled the stated gap of neighborhood characteristics on histological subtypes of breast cancer. The main issue is accuracy of measurement of neighborhood effects and the concerns about individual versus neighborhood aggregate measures like socioeconomic status. Another big concern and ongoing gap in the literature is the lack of longitudinal information about neighborhood. Many women move frequently, so cross-sectional neighborhood data collection does not take time or migration into account in terms of SES, environmental exposures and other breast cancer risk factors.

Key existing gaps in Neighborhood & Breast Cancer research:

- Measurement & accuracy concerns for neighborhood-level measures of SES, segregation and other risk factors for disparities in BC screening, treatment and mortality;
- Lack of longitudinal data that takes movement and migration into account of how neighborhood might impact breast cancer risk;
- Inability to change inherent built environment or rural/urban characteristics e.g. lack of medical facilities in rural areas and thus difficulty in modifying BC risk factors.

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Future research on the impact of neighborhoods on cancer and other health outcomes needs to examine specific direct, indirect, and interactive pathways through which neighborhoods impact health. Attention also needs to be paid to the level of neighborhood or place that is most relevant to the pathway being studied.	Mixed methods study: Cancer screening uptake is generally lower in UK cities but quantifying city-level effects from causes due to population composition that comprise cities is hampered by data limitations. A unique data linkage project combining a 2001 Census-based longitudinal study in Northern Ireland with the NHS Breast Screening Program. Validated uptake in the three years following the Census for Belfast Metropolitan Urban Area was compared against the rest of the country with adjustment for cohort attributes defined at Census. Belfast Metropolitan Urban Area contained 34.8% of invited women but a greater proportion who rented their accommodation (40.3%) or who did not have a car (47.1%). After full adjustment for demographic and socio-economic factors, Belfast Metropolitan Urban Area uptake was lower for first and subsequent screen (Odds ratio (OR) 0.72; 95% CIs 0.66, 0.78 and OR 0.58; 95% CIs 0.55, 0.62 respectively). There were no significant interactions between patient characteristics and area of residence indicating that all residents in Belfast Metropolitan Urban Area are equally affected. The reduced uptake of screening in cities is a major public health issue; the effects are large and a large proportion of the population are affected, organizational factors appear to be the primary cause. Strategies to correct this imbalance might help reduce inequalities in health [1]. Retrospective cohort study: Clinical guidelines recommend breast-conserving surgery (BCS) with radiation as a viable alternative to mastectomy for treatment of early-stage breast cancer. Asian Americans are more likely than other groups to have mastectomy or omit radiation after BCS. Data from 20,987 California Asian Americans diagnosed with stage 0 to II breast cancer from 1990 to 2007 were analyzed. The percentage receiving mastectomy ranged from 40% among U.S.-born Chinese to 58% among foreign-born Vietnamese. Factors associated with mastectomy included tumor characteristics, patient characteristics (older age and foreign birthplace), and additional factors including hospital [smaller hospital size, not NCI cancer center, low socioeconomic status (SES) patient composition, and high hospital Asian Americans patient composition] and neighborhood characteristics (ethnic enclaves of low SES). These hospital and neighborhood characteristics were also associated with BCS without radiation. By focusing on interactions among patient, hospital, and neighborhood factors in

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	the differential receipt of breast cancer treatment, this study identifies subgroups of interest for further study and translation into public health and patient-focused initiatives to ensure that all women are fully informed about treatment options [18]
Studies of neighborhoods also need to address rural, as well as urban and suburban, environments.	Cross-sectional & follow up study: The objectives of this study were to examine the outcomes of late stage breast cancer diagnosis, receiving first course treatment, and breast cancer-related death by race, age, and rural/urban residence in Georgia. The authors used cross-sectional and follow-up data (1992-2007) for Atlanta and Rural Georgia cancer registries that are part of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (N = 23,500 incident breast cancer cases in non-Hispanic whites or non-Hispanic African Americans). Women residing in rural areas had significantly decreased odds of receiving radiation and surgery with radiation (OR = 0.59, p = 0.0001), and for receiving breast-conserving surgery compared to mastectomy (OR = 0.73, p = 0.005). Factors affecting each level of the breast cancer continuum are distinct and should be examined separately. Efforts are needed to alleviate disparities in breast cancer outcomes in hard-to-reach populations [2].
Future research might examine residential history to help focus analyses on the critical exposures or timing of exposures that lead to greater breast cancer incidence in urban areas.	Prospective Cohort Study: While this study does not have life history analysis, it does include more than one data point for residential history for women. There have been reports of greater breast cancer incidence and mortality at northern compared with southern latitudes postulated to be related to vitamin D exposure. Among 71,662 participants in the Women's Health Initiative Observational Study (WHIOS) free of cancer at baseline (1993-1998), associations were explored between incident invasive postmenopausal breast cancer (n = 2,535), and the following: (a) region of residence at birth, age 15 years, age 35 years; (b) region of residence at WHIOS baseline; and (c) clinic center solar irradiance. Hazard ratios and 95% confidence intervals (CI) for breast cancer were estimated after adjustment for individual level confounders. There was no difference in breast cancer risk by region of earlier life, baseline residence, or solar irradiance measured in Langelys (gm-cal) per cm(2). In conclusion, region of residence and geographic solar irradiance are not consistently related to risk of breast cancer and may not be sufficient proxy measures for sunlight/vitamin D exposure. The

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	observed association between time spent outside and breast cancer risk support the hypothesis that vitamin D may protect against breast cancer [3].
However, for research to move forward, we need to have not only better multilevel data, but also clearer analytic strategies for examining specific pathways that may link rural/urban residence to breast cancer	Cross-sectional study: Neighborhood characteristics on breast, prostate and lung cancer incidence in Denmark were examined from registry data for women aged 30-83 years were followed for breast cancer between 2004 and 2008. Individual level characteristics, population density and neighborhood socioeconomic status (the proportion of unemployed) on the parish level were analyzed. A significantly lower HR of breast cancer was found in areas with low population density (HR=0.93; CI 0.88 to 0.99), while neighborhood unemployment had no effect [4]. Population-based Cross-Sectional Study: The aim of this study was to investigate the utilization of breast, colon and prostate cancer screening in the adult Croatian population in a period without national cancer screening programs, with a special interest in respondents' rural versus urban origin. Self-reported screening utilization was investigated in the Croatian Adult Health Survey, which collected health-related information from a representative sample of the adult Croatian population. One in five women reported breast cancer screening uptake in the year preceding the survey (22.5%), while only 4.5% reported a colon screening. Respondents with rural origin reported all sites screening utilization less frequently than those of urban origin (breast: 14.5%). Multivariable models indicated that people with higher SES more commonly reported breast cancer screening uptake. Rural origin was associated only with lower odds of breast screening (adjusted odds ratio 0.60 [95% confidence interval 0.48-0.74]). Opportunistic cancer screening uptake is low in the Croatian adult population, with existing SES differences in breast screening. Rural origin was significantly associated with breast screening, even after adjustment to socioeconomic status and problems in access to health care. Overall, access to health care is the strongest cancer screening predictor, and this should have a prominent role in the development of a systematic cancer screening program on a national level [5].
Rural/urban variations in breast cancer incidence and mortality need to be examined with respect to race and	Population-Based Cohort Study: This UK study compared mammographic breast densities of women living in London with those of women living in rural and suburban areas. Using the

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ethnicity. Some of the work on screening and treatment that looks at distance traveled for medical care could examine the interactive effects of SES and race/ethnicity. Having to travel a greater distance for screening and medical care may be more problematic for rural residents with low income than for rural residents with higher income.	standard four American College of Radiology Breast Imaging Reporting and Data System (BIRADS) categories of mammographic density, 318 mammograms of women from London and 654 mammograms of women from outside the capital aged 27-87 years who had received mammography at the Princess Grace Hospital, London, were assessed for density. Adjusting for age, London residents had significantly higher levels of density (OR = 1.32, 95% CI 1.04-1.70, p = 0.02). The major difference occurred in the age group 45-54 years and was most strongly manifested as a higher rate in London for density of 25% or more (BIRADS categories 2-4) as compared to almost entirely fatty (BIRADS 1) (OR = 2.22, 95% CI 1.05-4.68, p = 0.035). The higher density is likely to be due to a different prevalence of risk factors in the London population. This study cannot ascertain the reason for the higher density in this urban population, but the result is a cause for concern given that screening uptake is lower in London. Increased attention to screening in urban areas and attention to screening quality for dense breast tissue might be prudent. However, race was not addressed [6]. Population-Based Cohort Study: This study sought to identify mediators of the effect of neighborhood poverty on physical functioning using longitudinal data from a Missouri cancer registry-based sample of 909 female breast cancer survivors. Survivors were recruited 1 year after diagnosis (Y1) and completed two telephone interviews, at Y1 and 1 year later (Y2). The association between census-tract-level poverty and physical functioning (RAND SF-36) was tested using a multilevel a priori path model with 19 hypothesized mediators, demographic and socioeconomic confounders, and covariates. Hypothesized mediators included clinical and treatment variables, psychosocial factors (depression, stress, social support), perceived neighborhood characteristics, behavioral risk factors (physical activity, smoking, body mass index, alcohol use), and comorbidity. In unadjusted analysis, women living in neighborhoods with higher poverty were more likely to report lower physical functioning at Y2 (β = -.19, p < .001). Breast cancer survivors living in neighborhoods with greater poverty reported lower physical functioning, but this effect was fully explained by physical activity and body mass index. Community-based lifestyle interventions sensitive to the unique challenges faced by cancer survivors and the challenges of living in a high-poverty neighborhood are needed to

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	ameliorate neighborhood socioeconomic disparities in physical functioning [7].
Future investigations should also consider different histological subtypes of breast cancer, especially lobular cases, which appear to be particularly elevated in the highly urbanized areas of California.	Population-based case control study: This study examined spatial associations between place of birth and breast cancer by subtype, using hormone receptor status and molecular profiles of breast tumors. Data were drawn from the Western New York Exposures and Breast Cancer study of pathologically confirmed breast cancer (1996-2001) in Erie and Niagara Counties. Included were women born in the study area (579 cases and 931 controls). Clustering of breast cancer subgroups relative to controls was examined by the k-function method in groups stratified by estrogen receptor (ER), progesterone receptor (PR), and HER2 status, and by DNA methylation status and p53 mutation status, and the k-function difference was used to compare relative spatial aggregation and spatial range of the difference between case subgroups and controls. They found a tendency to cluster among ER positive, PR positive, and HER2 negative cases (i.e., luminal A subtype), especially among premenopausal women, but not among the other groups defined by hormonal receptor status, or by either methylation or p53 mutation status. While the findings cannot rule out clustering of cases by birthplace because of shared behaviors related to residence location, they also suggest that early life environmental exposures may affect subsequent breast cancer risk, and that premenopausal breast tumors of the luminal A subtype may be more affected by these early life exposures than other subtypes [8].
Regarding breast cancer incidence, future research could examine whether there are factors associated with living in high-SES areas that contribute to increased breast cancer risk, over and above individual SES. In terms of the neighborhood service environment, do women living in higher- SES neighborhoods use medical care systems that are more likely to emphasize hormone use? In terms of the neighborhood social environment, are there particular social norms in higher-SES areas that produce behaviors putting	Population-Based Cohort Study: Study of higher SES & higher BC incidence. Data were extracted from the Canadian Cancer Registry for the 229,955 cases of adult female invasive breast cancer diagnosed from 1992 through 2004. Postal code at diagnosis was used to determine neighborhood income quintile. Breast cancer incidence was examined by year, region, age and neighborhood income quintile. Census data for 1991 on children ever born and British Columbia data for 2006 on first-time attendance at mammography screening were analyzed by neighborhood income quintile. Residence in the lowest as opposed to the highest neighborhood income quintile was associated with a 15% lower risk of being diagnosed with breast cancer. Higher income levels were associated with lower parity in 1991 and a higher prevalence of first-time screening mammography in British Columbia in 2006. Canadian data

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women at greater risk of breast cancer?	support an association between the diagnosis of invasive breast cancer and neighborhood income quintile. Parity and mammography screening may account for some differences in incidence [9].
It will also be important to examine multilevel interactions between individual and neighborhood SES.	Prospective cohort study: Data from the Black Women's Health Study (1995-2009) was used to examine the relationship between individual & neighborhood SES and breast cancer incidence (n=1343). Individual SES was defined as the participant's self-reported level of education, and neighborhood SES was measured by a score based on census block group data for 6 indicators of income and education. In age-adjusted analyses, SES for both individuals and neighborhoods was associated with an increased incidence of estrogen receptor-positive breast cancer. However, the associations of breast cancer with SES may be largely mediated by reproductive factors that are associated with both estrogen receptor-positive breast cancer and SES [10]. Population-based cohort study: This population-based study investigated the relationship between individual and neighborhood SES and mortality rates for major cancers in Taiwan. A population-based follow-up study was conducted with 20,488 cancer patients diagnosed in 2002. Each patient was traced to death or for 5 years. The individual income-related insurance payment amount was used as a proxy measure of individual SES for patients. Neighborhood SES was defined by income, and neighborhoods were grouped as living in advantaged or disadvantaged areas. A cross-level interaction effect was found in lung cancer and breast cancer. Lung cancer and breast cancer patients less than 65 years old with low SES in advantaged neighborhoods carried the highest risk of mortality. Findings indicate that cancer patients with low individual SES have the highest risk of mortality even under a universal health-care system [11]. Prospective Cohort Study: This study examined whether area and individual measures of (SES) affected cancer screening participation in Singapore and prospectively evaluated an access-enhancing community-based intervention. The study population involved all residents aged >40 years in two housing estates comprising of owner-occupied (high-SES area) and rental

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	(low-SES area) flats. From 2009 to 2011, non-adherents to regular cancer screening were offered free convenient screening over six months. In the low-SES area, 7.7% (33/427), 20.4% (44/216), and 14.3% (46/321) had regular colorectal, cervical and breast cancer screening respectively. Post-intervention, screening rates in the low-SES area rose significantly to 19.0% (81/427), 25.4% (55/216), and 34.3% (74/216) respectively ($p<0.001$). Area SES was more consistently associated with screening than individual SES at baseline. Access-enhancing community-based interventions improve participation among disadvantaged strata of Asian societies [12]. Population-Based Cross-Sectional Study: The aim of this study was to investigate the effect of level of neighborhood deprivation on mortality after a wide range of cancer diagnoses. This 1990-2004 follow-up study included all individuals in Sweden aged 25-74 years and used multilevel logistic regression with individual-level variables at the first level and the level of neighborhood deprivation at the second level. For individuals with cancer, the overall risk of mortality was 24% higher for men and 20% higher for women living in the most deprived neighborhoods than in those living in the least deprived neighborhoods. Mortality differences were also found in women with cancer of the breast, cervix, endometrium, and small intestine, and leukemia. In conclusion, neighborhood deprivation predicts the risk of mortality among adults with certain cancers [25].
Little is known about how multilevel SES and age interact over the life course to affect breast cancer incidence and outcomes. Most studies only look at SES at time of diagnosis. Early life SES may also have an important impact on breast cancer risk and only a few studies have looked at this issue.	There were no studies that examined SES over time or by age with regards to BC diagnosis, treatment or screening.
Few studies have directly examined how the different neighborhood contexts of racial and ethnic groups may affect breast cancer incidence and outcomes. This is an important gap in the literature, conceptually and	Population-based surveillance study: This study evaluates the role of black residential segregation and spatial access to health care in explaining the variation in late-stage diagnosis of breast cancer in metropolitan Detroit. Data pertaining to female breast cancer from 1998 to 2002 were obtained from the Michigan Cancer Surveillance Program. An isolation index is

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empirically.	used to assess black segregation. While SES factors at ZIP code level are controlled, ordinary least squares and spatial lag models are used to explore the association between the rates of late-stage diagnosis and segregation and health care access. Results suggest that living in areas with greater black segregation and poorer mammography access significantly increases the risk of late diagnosis of breast cancer. Disadvantaged populations including those with low socioeconomic status or sociocultural barriers tend to experience high rates of late diagnosis. Findings emphasize the need for heightened screening, surveillance, and intervention programs in these areas [13]. Population-based surveillance study: This study tested associations between three measures of neighborhood SES (poverty, median income, and a composite neighborhood score) on breast cancer staging in two urban counties of the state of New Jersey. Data for these counties were obtained from the New Jersey Surveillance, Epidemiology, and End Results tumor registry and were selected because of their large racial/ethnic and socioeconomic diversity and pilot prevention efforts taking place in these areas. Study population included Black, Latina, and White women (N = 4,589) diagnosed with breast cancer from 1999 to 2004. Each cancer case was geocoded and linked to socioeconomic data obtained from the 2000 U.S. census. Census tracts served as proxies for neighborhoods. Women living in neighborhoods with lower versus higher neighborhood scores were significantly more likely to have advanced-stage disease (odds ratio, 1.6; confidence intervals, 1.1-2.3), after adjusting for age at diagnosis and race/ethnicity. In analyses stratified by race/ethnicity, results remained significant for all neighborhood measures for White and Black women, but not for Latinas. Moreover, neighborhood poverty showed a weaker socioeconomic gradient in breast cancer staging among White women. Study findings support the use of a multidimensional neighborhood index to better capture differences in cancer staging risk across racial/ethnic groups and provides evidence that population-based cancer data could be used to identify local needs specific to local populations [14]. Population-Based Cohort Study: This study explored the association between neighborhood

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	residential racial composition and breast cancer mortality among Black and White breast cancer patients in Georgia and whether spatial access to cancer care mediates this association. Participants included 15,256 women living in 15 metropolitan statistical areas in Georgia who were diagnosed with breast cancer between 1999 and 2003. Residential racial composition was operationalized as the percent of Black residents in the census tract. Black women were 1.5 times more likely to die from breast cancer than White women. Residential racial composition had a small but significant association with breast cancer mortality (hazard ratios [HRs] = 1.04-1.08 per 10% increase in the percent of Black tract residents). Individual race did not moderate this relationship, and spatial access to care did not mediate it. Residential racial composition may be part of the socioenvironmental milieu that produces increased breast cancer mortality among Black women. However, there is a lack of evidence that spatial access to oncology care mediates these processes [15]. Population-Based Multilevel Study: There are significant relationships between racial residential segregation (RRS) and a range of health outcomes, including cancer-related outcomes. This study explores the contribution of metropolitan area RRS, census tract racial composition and breast cancer and all-cause mortality among black and white breast cancer patients. This study has three units of analysis: women diagnosed with breast cancer (n = 22,088), census tracts where they lived at diagnosis (n = 1,373), and the metropolitan statistical area (MSA)/micropolitan statistical area (MiSA) where they lived at diagnosis (n = 37). Neighborhood racial composition was measured as the % of black residents in the census tract. Metropolitan area RRS was measured using the Information Theory Index. Breast cancer mortality disparities were largest in racially mixed tracts located in high MSA/MiSA segregation areas (RR = 2.06, 95 % CI 1.70, 2.50). For black but not white women, as MSA/MiSA RRS increased, there was an increased risk for breast cancer mortality (HR = 2.20, 95 % CI 1.09, 4.45). For all-cause mortality, MSA/MiSA segregation was not a significant predictor, but increasing tract percent black was associated with increased risk for white but not black women (HR 1.29, 95 % CI 1.05, 1.58) Racial residential segregation may influence health for blacks and whites differently. Pathways through which RRS patterns

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	impact health should be further explored [16]. Prospective cohort study: This analysis sought to determine the relationship between neighborhood-level SES and regular mammography screening behavior. 1229 women [484 African-American (39%) and 745 White (61%)] ages 40 to 79 years who obtained an "index" screening mammogram at one of five urban hospitals in Connecticut between October 1996 and January 1998 were enrolled in this prospective study with complete data. Neighborhood-level SES was determined using 1990-census tract information. Neighborhood-level SES variables (quartiles) were associated with nonadherence for African-American women [neighborhood-level education and composite socioeconomic position index (SEP Index)] and White women (neighborhood-level crowding and neighborhood-level assets). Using race-specific categorizations reflective of individual-level SES distributions, the SEP Index and neighborhood-level education were associated with nonadherence to mammography screening guidelines for African-American women (marginally significant for White women). The results of this analysis underscore the importance of examining neighborhood social context as well as individual factors in the study of mammography screening behavior [17].
Research on racial segregation and breast cancer incidence, screening, diagnosis, treatment, and mortality would further our understanding of the complex barriers that women face, and the contexts in which they face them.	Retrospective Cohort Study: To better inform cancer control efforts, this study examined incidence trends by nativity and incidence patterns by neighborhood socioeconomic status (SES) and Hispanic enclave (neighborhoods with high proportions of Hispanics or Hispanic immigrants). Information about all Hispanic women diagnosed with invasive breast cancer between 1988 and 2004 was obtained from the California Cancer Registry. Nativity was imputed from Social Security number for the 27% of cases with missing birthplace information. Neighborhood variables were developed from Census data. Rates were 38% higher for U.S.- than foreign-born Hispanics, with elevations more pronounced for localized than regional/distant disease, and for women>50 years of age. Residence in higher SES and lower Hispanic enclave neighborhoods were independently associated with higher incidence, with Hispanic enclave having a stronger association than SES. Compared with foreign-born, U.S.-born Hispanic women in California had higher prevalence of breast cancer risk factors, suggesting that incidence patterns largely reflect these differences in risk factors. Further

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	research is needed to separate the effects of individual- and neighborhood-level factors that affect incidence in this large and growing population. (19) Another study using data from the same registry found that living in low SES and high enclave neighborhoods was associated with advanced stage of diagnosis, while living in a lower SES neighborhood, but not Hispanic enclave, was associated with worse survival. Identifying the modifiable factors that facilitate this survival advantage in Hispanic immigrants could help to inform specific interventions to improve survival in this growing population [20]. Population-Based Cross-Sectional Study: This study team has previously reported that cancer incidence for lung, female breast, and colon and rectum for Hispanics decreases with increasing percentage of Hispanics at the census tract. This study investigates the hypothesis that Hispanics living in census tracts with high percentages of Hispanics are diagnosed with more advanced cancer, with respect to tumor size and stage of diagnosis. Data from the Surveillance, Epidemiology, and End Results registry and the U.S. Census Bureau were used to estimate the odds of diagnosis at a "late" stage (II, III, IV) versus "early" stage (I) and breast cancer tumor size among Hispanics as a function of census tract percent Hispanic. Hispanic ethnicity in the Surveillance, Epidemiology, and End Results registry was identified by medical record review and Hispanic surname lists. The study also used income of Hispanics living in the census tract and controlled for age at diagnosis and gender. The authors found that Hispanics living in neighborhoods with higher density of Hispanic populations were more likely to be diagnosed with late-stage breast, cervical, or colorectal cancer, and to have a larger tumor size of breast cancer. Findings suggest that the benefits of lower cancer incidence in high tract percent Hispanics are partially offset by poorer access and reduced use of screening in conjunction with lower income, poorer health insurance coverage, and language barriers typical of these communities [21]. Population-Based Cohort Study: Socioeconomic and ethnic factors leading to this survival difference between inflammatory BC & other types of BC are not fully understood. The association between county-level percent of persons below the poverty level and BC-specific

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	(BCS) survival for cases diagnosed from 1990 to 2008 in the Surveillance, Epidemiology, and End Results (SEER) database linked to census derived county attributes was examined. A sub-analysis of cases from 2000 to 2008 also examined BCS survival by an index combining percent below poverty and less than high school graduates as well as metropolitan versus non-metropolitan county of residence. Residing in a lower SEP, non-metro county significantly worsens BCS survival for non-IBC in multivariate proportional hazards models. African American cases appear to have worse survival than non-Hispanic Whites regardless of inflammatory status, stage, county-level SEP, tumor, or treatment characteristics. This is the first study to examine IBC survival by SEP in a nation-wide population-based tumor registry. As this analysis found generally poorer survival for IBC, regardless of SEP or race/ethnicity, it is important that interventions that help educate women on IBC symptoms target women in various SEP and race/ethnicity groups [22]. Retrospective Cohort Study: This study examined the impact of metropolitan racial residential segregation on stage at diagnosis and all-cause and breast cancer-specific survival between and within black and white women diagnosed with breast cancer in California between 1996 and 2004. Data from the California Cancer Registry was merged with Census indices of five dimensions of racial residential segregation, quantifying segregation among Blacks relative to Whites; block group ("neighborhood") measures of the percentage of Blacks and a composite measure of socioeconomic status. The authors also examined simultaneous segregation on at least two measures ("hypersegregation"). For all-cause and breast-cancer specific mortality, living in neighborhoods with more Blacks was associated with lower mortality among black women, but higher mortality among Whites. However, neighborhood racial composition and metropolitan segregation did not explain differences in stage or survival between Black and White women. Future research should identify mechanisms by which these measures impact breast cancer diagnosis and outcomes among Black women [23].
Future work should explore how the neighborhood social environment impacts breast cancer, including attention to the neighborhood experiences of: social	Interview/Cross-Sectional Study: Although social integration is a well-established influence on health, less is known about how the specific types of social connection (social roles, social networks, and social support) influence knowledge, attitudes, and practices for specific

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trust and social capital, social stress, social support and interaction, and social norms and behaviors.	prevention goals, and how to utilize these influences in interventions with priority populations. This research examined the prevalence of social roles, networks and support among 576 urban African-American women age 45-93 in East Baltimore, Maryland, and the association of these social factors with breast cancer related knowledge, attitudes, and practices. Using data from 1997-1998 in-home interviews, the authors developed indices of six possible social roles, social networks of family, neighborhood and church, and instrumental and emotional social support. They found substantial variation in social integration among these women, with social integration positively associated with overall health and well-being. Social roles and networks were positively associated with screening knowledge, and emotional support and church networks were positively associated with attitudes conducive to early detection and treatment. In regard to screening behaviors, family networks were associated with both screening recency and intention. Women with greater church networks and emotional support held more conservative attitudes towards lumpectomy, reconstruction, and clinical trials [24]
Research into the effects of the built environment may open a new avenue for breast cancer risk reduction by examining how neighborhood attributes may be changed to reduce the burden of breast cancer and other diseases.	Retrospective Cohort Study: This exploratory study was to investigate whether stage of breast cancer at diagnosis among Chicago residents is associated with characteristics of the neighborhoods in which proximate mammography facilities are located. Those characteristics may influence likelihood of utilizing the service routinely and partly explain differences in stage at diagnosis. 3 years of data from the Illinois State Cancer Registry (ISCR) and information on locations of mammography facilities, public transportation service, crime, and area demographic and economic characteristics. Using a Geographic Information System (GIS), the authors identified the five facilities located nearest to each case's residence. They found that the number of homicides in areas in which the nearest mammography facilities were located was associated with increased odds of later stage diagnosis. This effect was independent of age, race, and residential area education and income. The authors found no effect on stage of distance, public transportation service, or measures of neighborhood social similarity. The "spatial dynamics" of health may involve geographies beyond the immediate neighborhood. The results of the study suggest that areas in which the nearest mammography facilities are located may be one such geography [26].

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