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# California Breast Cancer Prevention Initiatives: Setting a research agenda for prevention

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### ABSTRACT

The environment is an underutilized pathway to breast cancer prevention. Current research approaches and funding streams related to breast cancer and the environment are unequal to the task at hand. We undertook the California Breast Cancer Prevention Initiatives, a four-year comprehensive effort to set a research agenda related to breast cancer, the environment, disparities and prevention. We identified 20 topics for Concept Proposals reflecting a life-course approach and the complex etiology of breast cancer; considering the environment as chemical, physical and socially constructed exposures that are experienced concurrently: at home, in the community and at work; and addressing how we should be modifying the world around us to promote a less carcinogenic environment. Redirecting breast cancer research toward prevention-oriented discovery could significantly reduce the incidence and associated disparities of the disease among future generations.

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## 1. Introduction

As Alice Stewart, epidemiologist and discoverer of the link between *in utero* exposure to ionizing radiation and childhood cancer observed, “the best way not to see something is not to look for it” [1]. We know too little about breast cancer and the environment because historically scientific challenges and non-scientific economic, social and political forces have put the environment out of sight and out of mind [2].

Prevailing models of scientific inquiry are ill-suited to uncovering the complex web of circumstances leading to clinically apparent breast cancer [3–5]. While breast cancer arises from a convergence of the environment and genes, [6] most research has explored one or the other factor. Environmental influences on health encompass neighborhood and social factors such as racism and the physical and chemical exposures where people live, work, and play [5]. Yet most epidemiologic studies of breast cancer have focused on a narrow range of discrete behaviors or exposures, rather than the

confluence of these interconnected factors [4,7–9]. Such a convergence may in part explain the fact that African American women are three times more likely to be diagnosed with triple negative cancer than White or Latina women [10] and at younger ages [11]; that African American women diagnosed at the same stage as Non-Latina White women have poorer survival outcomes [12]; and that in general, breast cancer in racial/ethnic minority populations appears to have a poorer prognosis [13].

Moreover, despite increasing human exposure, the role of toxic chemicals, pollutants and other similar agents has been only marginally explored. Since 1945, chemical production has increased more than 15-fold [14]. In the United States, approximately 700 new chemicals are introduced into commerce each year and more than 84,000 chemical substances are listed by the US Environmental Protection Agency for manufacturing, processing or importation [15,16]; 3000 of these chemicals are used or imported in high volumes (greater than 1 million pounds) [15]. Every day everyone is exposed to environmental chemicals in air, water, food and consumer products. Yet the overwhelming majority of chemicals, including those identified as animal mammary carcinogens or endocrine disrupting compounds, have never been examined in an epidemiologic study of breast cancer, nor been included in an animal cancer bioassay [17,18].

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Breast cancer research exploring exposure to chemical mixtures, critical windows of susceptibility, and environmental agents with the capacity to modify known risk factors are largely lacking [19]. And yet, history has provided us with experiments that document that early life exposure to environmental agents can have a profound impact on breast cancer, i.e., diethylstilbestrol (DES), ionizing radiation from the atomic bomb, and DDT [20–22].

Globally, funding to investigate prevention in general and avoidable environmental exposures specifically represents a small fraction of the resources directed to cancer research [23] (Fig. 1). This trend is mirrored in the United States, where only 6.5% of the National Cancer Institute's (NCI's) \$5.1 billion 2011 budget request was allocated to "cancer prevention and control" [24]. A federal interagency review of breast cancer and the environment found that at most, 10–11% of breast cancer research projects funded by the National Institutes of Health (NIH) and the US Department of Defense focus on environmental health and that no other federal agency supports substantial research on the environmental causes of breast cancer [6].

Thus, we have looked neither well nor hard for the role of the environment in breast cancer etiology. The gap produced by these limitations in the research has led many to believe that the environment plays little to no part in disease etiology. For example, the NCI's breast cancer prevention advice to patients downplays environmental etiology, stating "studies have not proven that being exposed to certain environmental exposures (such as chemicals, metals, dust, and pollution) increase the risk of breast cancer" [25].

Times are changing. Over the past few years, calls for shedding light on cancer and the environment have come from influential entities, including the Institute of Medicine, [3] the President's Cancer Panel [8], the federal Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC), [6] and the Agency for Toxic Substances Disease Registry with the US Centers for Disease Control and Prevention's National Center for Environmental Health [26]. A critical observation common to these diverse reports is that the environment represents a vastly underutilized pathway to prevention. As the IBCERCC stated, "By urgently pursuing research, research translation, and communication on the role of the environment in breast cancer, we have the potential to prevent a substantial number of new cases of this disease in the 21st century" [6]. The California Breast Cancer Research Program (CBCRP) is doing just that. Below we describe a four-year initiative to set a research agenda that will illuminate the links between the environment and breast cancer and uncover opportunities to prevent disease.

## 2. The California Breast Cancer Research Program

The CBCRP is the nation's largest state-funded breast cancer research effort and among the largest breast cancer research funders in the world. The CBCRP was founded in 1993 by the California legislature and through the efforts of breast cancer activists, scientists, clinicians, state legislators, and University of California officials [27]. The CBCRP is funded by a state tax on tobacco products, voluntary state personal income tax form contributions and individual contributions.

The CBCRP's program funding recommendations and strategic planning are the responsibility of the Breast Cancer Research Council (Council), a group of 15 people chosen to represent those affected by breast cancer and the institutions that can help find a solution. CBCRP supports new approaches that other agencies may be reluctant to fund. Since 1994, the CBCRP has awarded more than \$235 million in 966 grants to 107 institutions across the state.

Subsequent to a comprehensive review of CBCRP's research portfolio, in March 2004, the Council dedicated 30% of funds

between 2004 and 2009 to the coordinated, directive, collaborative Special Research Initiatives (SRI) to support research that addressed:

1. The identification and elimination of environmental causes of breast cancer; and
2. The identification and elimination of disparities/inequities in the burden of breast cancer in California.

The goal of the SRI was to fund research that not only increased knowledge about these questions, but also pointed to solutions that would reduce the suffering from breast cancer and move science closer to eliminating the disease. In total, 21 grants totaling \$23 million were awarded to address the environmental causes of breast cancer and the unequal burden of the disease [28].

In March 2010, after another thorough programmatic review, the Council built on the existing SRI by expanding the scope and devoting 50% of its research funds during 2011–2015. This new effort was titled the *California Breast Cancer Prevention Initiatives* (CBCPI). They committed an anticipated \$24 million to directed, coordinated, and collaborative research to pursue the most compelling and promising approaches to:

1. Identify and eliminate environmental causes of breast cancer.
2. Identify and eliminate disparities/inequities in the burden of breast cancer in California.
3. Population-level interventions (including policy research) on known or suspected breast cancer risk factors and protective measures.
4. Targeted interventions for high-risk individuals, including new methods for identifying or assessing risk.

Implementation of the CBCPI research agenda-setting began in 2010 and will be completed in 2015. This paper presents the CBCPI's methods and results of efforts to date to identify key research questions addressing the four topic areas, and proposes future directions in research to lead to the prevention of breast cancer.

## 3. Materials and methods

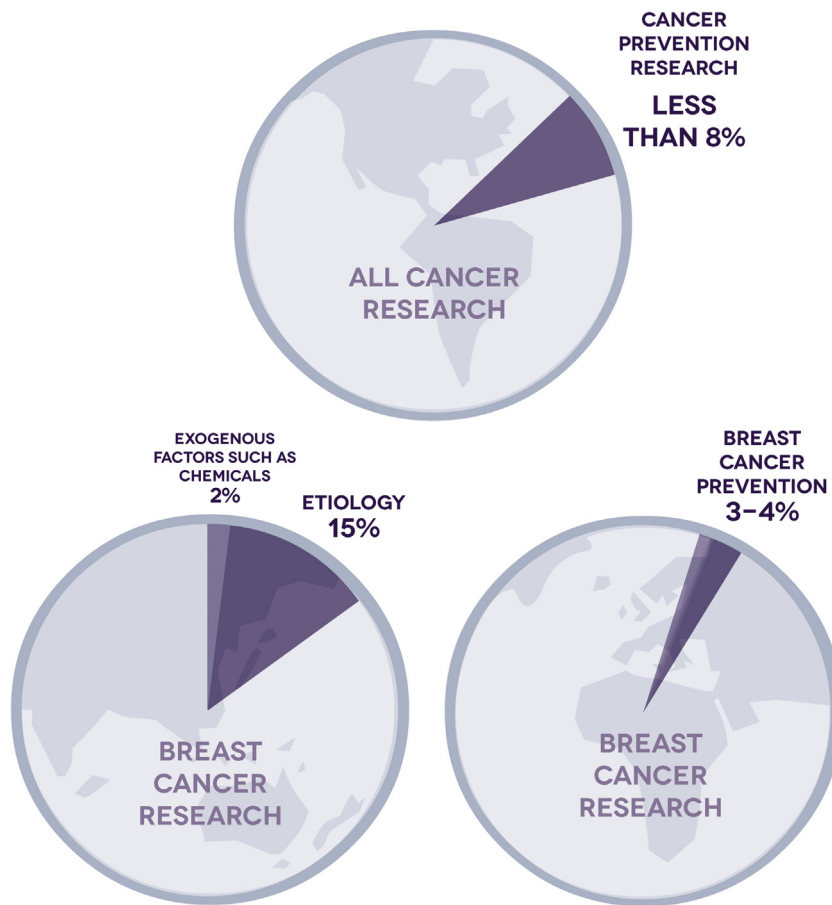
An overview of the process of developing the research agenda for the CBCPI is presented in Fig. 2. The full details of the dynamic process for determining specific research questions to fund within the four areas were articulated in a Strategy Development Plan [29].

### 3.1. Public and scientific engagement

We convened three expert groups to provide leadership and scientific expertise for the CBCPI, a Steering Committee and two sets of Strategy Advisors, one focused on Environment and Disparities and the other focused on Population-Level Interventions and Targeted Interventions for High-Risk Individuals. To recruit these individuals, we identified areas of expertise needed and generated a list of scientists with relevant expertise. Public engagement in the process included advocate participants in the CBCRP Research Council, community participants in the three expert groups, and community participation in Stakeholder events.

### 3.2. Identifying pivotal research questions

We used the following qualitative and quantitative methodologies to review, analyze and compile the relevant scientific findings and research recommendations to inform the development of pivotal questions for the CBCPI.



**Fig. 1.** Global research spending on breast cancer prevention and the environment (2008–2013). Data were compiled from the International Cancer Research Partnership, Cancer Research Funding from an International Perspective: Report from the International Cancer Research Partnership, 2012.

GOAL				
\$24 million dedicated to directed, coordinated, and collaborative research to pursue the most compelling and promising approaches to the environmental causes of breast cancer, disparities in breast cancer, population-level interventions, and targeted interventions.				
PUBLIC AND SCIENTIFIC ENGAGEMENT	IDENTIFIED PIVOTAL RESEARCH QUESTIONS	DEVELOPED CONCEPT PROPOSALS	CREATED FUNDING MECHANISMS	APPROACHES TO FUNDING
1 Principal Investigator and Team <sup>a</sup> 2 Twelve Steering Committee Members <sup>a</sup> 3 Sixteen Strategy Advisors <sup>b</sup> 4 Fifteen CBCRP Research Council Members	1 Targeted review of literature—23 targeted scans of topics 2 Review of 2004–2009 SRI Funded Projects 3 Interviews with SRI Principal Investigators and Strategy Team 4 Interviews with External Experts in Cancer Prevention 5 Stakeholder meetings, workshops, webinars 6 Science Assessments: Expert Assessments and Systematic Reviews	1 Identify and eliminate environmental causes of breast cancer 2 Identify and eliminate disparities/inequities in the burden of breast cancer in California 3 Population-level interventions (including policy research) on known or suspected breast cancer risk factors and protective measures 4 Targeted interventions for high-risk individuals, including new methods for identifying or assessing risk	1 Request for Qualifications 2 Request for Proposals 3 Program Directed Awards	1 Grants 2 Cooperative Agreements
DECISION-MAKING CRITERIA				
1 Increase knowledge and solutions; 2 Truly transforming; 3 Community participation; 4 Coordinated approach; 5 Synergy; 6 Compelling to stakeholders; 7 Unique; 8 Feasible				

**Fig. 2.** Overview of California Breast Cancer Prevention Initiatives 2011–2015. All four public and scientific groups engaged include a mix of scientists, advocates, clinicians and public health expertise. (a) Non-eligible for funding through initiative and (b) mixed eligible and non-eligible for funding through initiative.

### 3.2.1. Review of the literature

An initial step in the CBCPI process was to update the 2007 Gaps report “Identifying Gaps in Breast Cancer Research: Addressing disparities and the roles of the physical and social environment” [2]. This narrative review of the literature in 23 targeted environment and disparities areas was conducted by multiple experts, using a framework developed by Bigby and Holmes for studying how breast cancer differently impacts various groups of women [30]. For the update, we conducted “targeted scans” of the literature by searching PubMed for each of the 23 topics in the 2007 Gaps document to identify any substantive changes in the chapter’s findings and research recommendations. Details of the methodology can be found at [http://cbrp.org/files/other-publications/2013\\_SupplGaps\\_Final.pdf](http://cbrp.org/files/other-publications/2013_SupplGaps_Final.pdf).

We generally did not critique the included papers, but rather summarized the conclusions of the study authors. We then compiled the PubMed search findings in a list next to the “Summary and Future Directions for Research” sections at the end of each 2007 Gaps chapter to directly determine whether there was a “significant change” in the state of the science. A significant change was defined as one that could fundamentally shift the questions originally posed in the Gaps document and assist in focusing the CBCPI research agenda.

### 3.2.2. Review of 2004–2009 SRI funded projects

We compiled a summary of the results of SRI efforts in order to identify additional potential follow-on research questions and/or questions identified in the SRI but not funded [28]. This summary included: the RFP or RFQ goal, the application process results, and a description of the funded research and progress to date.

### 3.2.3. Interviews with SRI Principal Investigators and Strategy Team

We interviewed the Principal Investigators funded through the SRI and SRI advisors (advocates, clinicians, policy makers, and scientists from within and outside California) using a semi-structured interview. We solicited their suggestions for additional research topics in light of the progress or outcome of SRI efforts and/or other advances in the field that had occurred since the SRI was undertaken. We conducted data analyses using two methods: hand sorting and classification in MS Word, and auto coding according to interview question using NVivo 9 qualitative software. In order to determine the major themes from each interview question, we uploaded each unique response from NVivo into a spreadsheet and analyzed across interview questions.

### 3.2.4. Interviews with cancer prevention experts

We conducted individual semi-structured interviews and held small-group meetings at the American Association for Cancer Research’s (AACR’s) 2012 conference *Frontiers in Cancer Prevention Research* to solicit input from cancer prevention experts. We invited AACR conference speakers and co-authors to participate based on the intersection of their expertise with the CBCPI. In addition, we distributed a flyer inviting conference attendees to participate. The interviews and small group meetings began with a summary of the CBCPI, followed by an open-ended discussion of thoughts and ideas for the CBCPI research agenda. We recorded and transcribed the interviews. We used two methods for data analysis: hand sorting and classification in MS Word, and auto coding using NVivo 9 qualitative software. To identify major themes from each interview question, we uploaded each unique response from NVivo into a spreadsheet and analyzed across interview questions.

### 3.2.5. Stakeholder input

Stakeholders were engaged through representation by advocates on the CBCPI Steering Committee and both Strategy Advisor

groups. We also engaged a broad range of stakeholders through webinars, web-based surveys, CBCRP newsletters and website, and in-person meetings across the state as follows: (1) in 2011, CBCRP conducted workshops in eight different areas of the state, gathering research recommendations and priorities; (2) in 2012, 2013 and 2014, we solicited input during 1-h stakeholder webinars; and (3) in 2013, we presented CBCPI ideas to participants attending the CBCRP Symposium. During the in-person Symposium and webinars we compiled input through online ballots. We synthesized stakeholder input from all of the workshops, webinars and Symposium into research questions and major themes.

### 3.2.6. Science assessments

We commissioned science assessments on topics that the Steering Committee deemed to be of high interest but for which they needed additional information to make a decision about whether and/or how to move forward on the topic.

### 3.2.7. Concept proposals

The Steering Committee vetted the research questions identified through all of the above methodologies based on *a priori* decision-making criteria (Fig. 2). The Steering Committee prioritized specific research questions that were then developed into “Concept Proposals.” Concept Proposals outlined the rationale, objectives, methods, and estimated cost of pursuing each topic. Finally, we presented the Concept Proposals to the CBCRP Council for approval.

## 4. Results

### 4.1. Public and scientific engagement

A total of 26 individuals from across the US led or served as an official advisor to the CBCPI. The names and affiliations of these 26 individuals are provided in the Supplement in Appendices A and B. The Steering Committee members oversaw the CBCPI through video conference calls, in-person meetings and written communications with each other and with the Strategy Advisors. Approximately 300 stakeholders participated in the various stakeholder opportunities for input. All Concept Proposals were approved by the Steering Committee prior to submission to the Council.

### 4.2. Identifying pivotal research questions

#### 4.2.1. Review of the literature

The results of the targeted scans of the literature were presented in 2013 as an online document, 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” [31]. Overall, the results of the Gaps update found that the amount and relevance of research on the environment and disparities identified in 2007 varied a great deal in the subsequent five years.

Published research around the relationship between breast cancer and persistent organic pollutants (POPs) and bisphenol A (BPA) had increased. For other topics, such as pharmaceuticals, very little of the substantial research published since 2007 was related to breast cancer. A limited number of studies were found relevant to previously identified gaps in some topic areas, such as the need for specificity in definitions of neighborhood and community level variables (e.g., neighborhood socioeconomic status (SES), built environment and racial segregation). While a number of studies addressed the intersection of neighborhood racial composition and



neighborhood SES, they mainly examined how these factors affect breast cancer screening and treatment.

#### 4.2.2. Review of 2004–2009 SRI funded projects

We compiled a detailed description of the 9 topics and 18 SRI funded projects [28]. The review of this document led to the identification of several “follow-on” opportunities, specifically on the topics of immigration, an ecological model of breast cancer and chemicals testing.

#### 4.2.3. Interviews with SRI Principal Investigators and Strategy Team members

We interviewed 15 of the 20 Principal Investigators that received funding from the SRI; 1 individual declined to be interviewed; and 4 were unresponsive to 5 or more written requests. The following three research questions were found to have high (67%) agreement among Principal Investigators as topics to pursue:

1. Is there proof of concept that environmental chemical exposure during critical periods of development can induce or promote breast cancer in humans?
2. Does early life or founding generation exposures make you more susceptible to subsequent environmental exposures?
3. What are the key modifiable risk factors and conditions suggested by complex modeling systems?

Forty percent of the Principal Investigators stated that they believed that either investing in an existing cohort or supporting cross-disciplinary research teams were the best scientific approaches to addressing the research questions.

We interviewed 14 of 24 SRI Strategy Team members. The 10 individuals not interviewed included 4 who declined, 3 who were unavailable due to illness/sabbatical, and three already interviewed as SRI-funded Principal Investigators. The Strategy Team members' top priorities were:

1. Invest in an intergenerational cohort study, i.e., analyze how mother, daughter, and granddaughter respond to chemical exposures; and
2. Examine the relationship between environmental exposures and disparities across social class and race/ethnicity and incorporate a life course perspective or other time dimension into such analyses.

A cluster of responses targeted the need to improve and better utilize animal studies for indications of which environmental agents may be relevant to human health and to develop exposure assessment methods for chemicals and their metabolites suspected of adverse health impacts.

#### 4.2.4. Interviews with cancer prevention experts

We hosted six discussions at the AACR including 2 focus groups; 3 one-on-one meetings; and 1 phone interview subsequent to the AACR conference. In total, 15 scientists participated in 1 of the 6 discussions. All discussions lasted between 60 and 90 min.

The theme that recurred in most of the discussions (four of six) was the need for trans-disciplinary research teams, or “team science”, to address CBCPI research questions. Ideas for immediate funding mentioned in one or more discussions were:

1. Improve knowledge of the windows of susceptibility relative to breast cancer risk;
2. Identify pathways controlling breast density;
3. Multiple questions about breast cancer and obesity;

4. Integration of animal and human models for understanding mammary development;
5. Breast cancer risk and biological effects on the breast from a variety of environmental exposures including stress, endocrine disrupting chemicals, and ionizing radiation from medical imaging;
6. *In utero* environmental exposures with the potential to influence hormones during pregnancy; and
7. Disparities in breast cancer incidence related to race, ethnicity, ancestry, and/or immigration status.

#### 4.2.5. Stakeholder input

The statewide workshops resulted in a list of 144 research questions of interest to stakeholders. Of the 144 questions, 63 were rated “important” by two or more attendees. These questions are presented in the Supplement in Appendix C. There was statewide interest in research related to the geographic and temporal disparities in exposure to environmental chemical and social stressors, and to the range of cultural influences on breast cancer.

Of the 46 participants in our 3 webinars, 23 self-identified as staff/volunteers with breast cancer non-profit or other community-based organization; 15 as breast cancer or other researchers/scientists; 4 as interested members of the public; 3 as clinicians; and 1 as a non-breast cancer research scientist. The 25 stakeholders in the 2012 webinar provided 46 suggestions for CBCPI research directions. Major themes for research to fund that emerged included to:

1. Advance chemicals testing policy;
2. Understand the relationship between disparities in breast cancer relative to: environmental exposure to chemicals, the social determinants of health, geography, and workplace exposures; and
3. Disparities related to underserved and vulnerable populations.

The 2013 webinar involved 11 stakeholders who identified the “most compelling” topics to be: chemical exposures and prevention; hormones in the food supply; leveraging existing cohorts for opportunities to explore concurrent exposure to environmental and psychosocial risk factors for breast cancer; the impact of policy on breast cancer risk factors and incidence; and economic, housing, and education interventions. The 10 participants in the 2014 webinar reviewed themes under consideration in the population-level intervention topic area; no clear pattern of preference emerged among the participating stakeholders.

#### 4.3. Science assessments

We engaged experts to conduct assessments of three issues in order to identify the most promising research questions on these topics:

##### 1. Early Life Adversity and Breast Cancer (Disparities)

The review found preliminary evidence for an association between childhood adversity and risk for post-menopausal breast cancer, especially more severe forms of adversity, such as physical and sexual abuse. The most promising hypothesis identified was that the effects of childhood adversity are mediated by obesity, with proximal mediation by increased circulating insulin and enhanced local estrogen biosynthesis.

##### 2. Experimental Studies of Breast Cancer and Stress (Disparities)

The review confirmed that very few studies have investigated environmental stressors and toxics exposure concurrently. Research is needed that tests different windows of susceptibility, applies stressors in a manner that can translate to human scale

**ENVIRONMENT<sup>1</sup>**

- Explore windows of susceptibility to breast cancer from chemical exposures
- Quantify concentrations of hormones in beef in California
- Test (non-targeted) commercial chemicals in California's drinking water
- Assess occupational exposure to chemicals and breast cancer risk in California
- Reduce breast cancer risk through chemical safety testing\*
- Develop a new paradigm of breast cancer causation and prevention
- Assess chemical exposures of women firefighters

**DISPARITIES<sup>1</sup>**

- Explore racial/ethnic disparities in consumer product availability and use
- Assess the role of stress in race and ethnic disparities in breast cancer incidence and survival across California
- Understand the role of changes in biological, behavioral, social, psychological, and environmental factors that occur with immigration
- Conduct animal models to explore environmental and psychosocial exposures during windows of susceptibility and breast cancer
- Leverage existing cohorts for opportunities to explore concurrent exposure to environmental and psychosocial risk factors for breast cancer
- Explore psychosocial interventions on stress, depression and coping in relation to addressing breast cancer
- Identify connections between early life adversity and the risk of breast cancer (Pending)

**POPULATION-LEVEL INTERVENTIONS<sup>2</sup>**

- Develop policy interventions that can reduce or eliminate exposures to chemicals linked to breast cancer
- Identify effective population-level interventions to increase physical activity (Pending)
- Build a public health case for primary prevention of breast cancer
- Prevent exposure to ionizing radiation from medical imaging

**TARGETED INTERVENTIONS FOR HIGH-RISK INDIVIDUALS<sup>2</sup>**

- Improve risk assessment research to identify high-risk individuals
- Explore markers of individual breast cancer risk

**Fig. 3.** California Breast Cancer Prevention Initiatives topic areas for funding. (1) Except as noted, these topics have been approved by the California Breast Cancer Research Program's (CBCRP) Research Council. (2) These topics have been approved by the California Breast Cancer Prevention Initiatives Steering Committee for consideration by the CBCRP Research Council. (\*) This project would build on: Schwarzmann M. and Janssen S. 2010. Pathways to Breast Cancer: A Case Study for Innovation in Chemical Safety Evaluation. University of California, Berkeley. <http://coeh.berkeley.edu/greenchemistry/cbcrcpdocs/pathways.report.pdf>.

or is clinically relevant and investigates the effects of chronic stress exposure.

### 3. Hormones in Food (Environment)

The review summarized the current use of veterinary drugs in food animal production and the concern that this practice may expose consumers to hormonally active substances. The reviewers found that whether the use of one or more of these drugs poses a human health risk remains subject to debate, fueled in part by formidable data gaps in understanding toxicity, exposure and ultimately the potential health risk of hormones in food. The expert assessment concluded that the available data do not permit an evidence-based, quantitative characterization of breast cancer or other health risks resulting from the use of hormonal drugs in food animal production.

We also solicited systematic reviews on: environmental chemical exposure and policy interventions; and interventions to reduce exposure to ionizing radiation from medical imaging. We anticipate these results will be submitted for publication by the end of 2014 and will be used to guide the development of Concept Proposals on these two topics.

#### 4.3.1. Concept proposals

The CBCPI research agenda established to date encompasses 20 topic areas: 14 related to environment and disparities and 6 addressing population-level interventions and targeted interventions for high-risk individuals (Fig. 3). For these 20 topics, 14 Concept Proposals have been approved by the CBCRP Council.

## 5. Discussion

We undertook a four-year comprehensive effort to set a research agenda related to breast cancer, the environment, disparities and prevention. Stakeholder involvement was a key component of the

SRI and continued to be in the CBCPI, as is the case in all CBCRP projects. There was a consistent call for involving communities in CBCPI-funded research.

We identified common major themes raised by stakeholders and scientists from a variety of fields, including that the research agenda should: (1) advance complexity, i.e., "ecological" approaches that reflect the interconnectedness of peoples' lives in contrast to a reductionist "risk factor" model; and (2) pursue "team science" in order to link the necessary systems of knowledge creation required to successfully conceive, design, and implement an ecologically based research agenda. To this end, we identified many administrative and cultural barriers among scientific disciplines and institutions that must be overcome if team science in breast cancer research is to become the norm. These include time and funding levels that do not support collaboration; administrative barriers to shared funding; competitive nature of scientific discovery; lack of common language; etc.

Our findings were also consistent with recommendations for improved research on cancer, the environment and/or prevention advanced in reports released by the Institute of Medicine, [3] the President's Cancer Panel, [8] the federal Interagency Breast Cancer and Environmental Research Coordinating Committee [6] and the Agency for Toxic Substances Disease Registry with the U.S. Centers for Disease Control and Prevention's National Center for Environmental Health [26]. Together, our findings and the call to action represented in these reports document an increasing groundswell for redirecting breast cancer research toward prevention that could significantly reduce the incidence and associated disparities of the disease among future generations.

Our findings are distinct from the agendas recommended in these other reports in our emphasis on the public health approach to disease prevention. Rather than asking what individuals can do to modify risk the CBCRP agenda asks how we should be modifying the world around us to promote a less carcinogenic environment.

Notably, CBCRP defines environment as “all of the non-genetic factors that might lead to breast cancer that are also largely outside an individual’s control.” Such a definition creates a huge shift in perspective, making it transparent how societal decisions shape individual behavior and circumstances.

The CBCRP’s nascent efforts represent a concerted attempt to spark a transformation of the environment and breast cancer research agenda overall (Fig. 3). Specifically, the CBCPI research agenda reflects that breast cancer arises from a complex system and that there are windows in a lifetime when we are more susceptible to environmental exposures. The research also views the environment as inclusive of chemical, physical and socially constructed exposures that are incurred at home, in the community and at work. CBCPI will advance an ecological model of breast cancer and improved methodologies for incorporating all of the available science, such as from animal and other non-human “early warning systems” of evidence. Funded research will also explore how our food, water and consumer products contribute to risk overall and differentially among sub-populations. Finally, the environment and disparities research topics include concurrent exposure to psychosocial stress and environmental chemicals in animal and human models, and the role of discrimination, cultural and language barriers and immigration in breast cancer incidence.

## 6. Conclusion

In the 2013 *Ecology of Breast Cancer*, Ted Schettler proposed that the complexity of breast cancer can be understood as a “design problem” such that “we have collectively although unintentionally also designed current breast cancer patterns into the fabric of communities and society more generally” [19]. The CBCPI is an important effort to set a research agenda to help unleash the largely untapped potential of redesigning our society to prevent, rather than promote, the circumstances conducive to breast cancer. A major limitation of our efforts is that the research opportunities identified far exceed CBCRP’s funding capacity. Ultimately, it will be critical that other major funders increase support for research on breast cancer, the environment and prevention, and harness the resulting science for efforts to improve public policy if we are to succeed.

## Conflict of interest

The authors declare that there are no conflicts of interest.

## Transparency document

The [Transparency document](#) associated with this article can be found in the online version.

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expert assessment on post-menopausal breast cancer. Professor Deborah Cory-Slechta of the University of Rochester Medical Center conducted the expert assessment on experimental models of breast cancer and psychosocial stress. Dr. Tyler J.S. Smith and Dr. Keeve E. Nachman of Johns Hopkins Bloomberg School of Public Health and Johns Hopkins Center for a Livable Future, respectively, conducted the expert assessment of hormones in food. Yvonne Day was the graphic designer who crafted the figures and tables for this article. Finally, this work and all of the CBCRP’s efforts would not be possible without the on-going contribution of our vibrant community of stakeholders who ensure CBCRP’s research agenda meets the needs of the individuals, families and communities impacted by breast cancer. This work was supported by funds received by the University of California from the State of California to support the California Breast Cancer Research Program (grant number 16QB-8101).

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.reprotox.2014.09.008>.

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# Hormone Use in Food Animal Production: Assessing Potential Dietary Exposures and Breast Cancer Risk

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**Abstract** In recent years, increasing attention has been paid to the role of hormones in breast cancer etiology, following reports that heightened levels of endogenous hormones and exposure to exogenous hormones and other endocrine-disrupting chemicals through food and the environment are associated with increased breast cancer risk. Seven hormone drugs (testosterone propionate, trenbolone acetate, estradiol, zeranol, progesterone, melengestrol acetate, and bovine somatotropin) are approved by the U.S. Food and Drug Administration for use in food animals. There is concern that these drugs or their biologically active metabolites may accumulate in edible tissues, potentially increasing the risk of exposure for consumers. To date, the potential for human exposure to residues of these compounds in animal products, as well as the risks that may result from this exposure, is poorly understood. In this paper, we discuss the existing scientific evidence examining the toxicological significance of exposure to hormones used in food animal production in relation to breast cancer risk. Through a discussion of U.S. federal regulatory programs and the primary literature, we interpret the state of

surveillance for residues of hormone drugs in animal products and discuss trends in meat consumption in relation to the potential for hormone exposure. Given the lack of chronic bioassays of oral toxicity of the seven hormone compounds in the public literature and the limitations of existing residue surveillance programs, it is not currently possible to provide a quantitative characterization of risks that result from the use of hormonal drugs in food animal production, complicating our understanding of the role of dietary hormone exposure in the population burden of breast cancer.

**Keywords** FDA · Hormones · Residues · FSIS · Meat · Milk · Breast cancer

## Abbreviations

ADI	Acceptable daily intake
AGD	Anogenital distance
AR	Androgen receptor
bST	Bovine somatotropin
bPR	Bovine progesterone receptor
CFR	Code of Federal Regulations
CVM	FDA Center for Veterinary Medicine
DNFB	2,4-dinitro-1-fluorobenzene
DTH	Delayed-type hypersensitivity
E1	Estrone
E2	Estradiol
EC	European Commission
ECa	Endometrial carcinoma
EDC	Endocrine disrupting chemical
EFSA	European Food Safety Authority
EFH	EPA 2011 Exposure Factors Handbook
EPA	(United States) Environmental Protection Agency
ER	Estrogen receptor
FAO	Food and Agriculture Organization of the United Nations

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FDA	United States Food and Drug Administration
FOIA	Freedom of Information Act
FSIS	Food Safety and Inspection Service
GC	Gas chromatography
GD	Gestation day
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometer
HRT	Hormone replacement therapy
IGF-1	Insulin-like growth factor 1
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LC	Liquid chromatography
LOD	Limit of detection
MGA	Melengestrol acetate
MS	Mass spectrometry
NADA	New Animal Drug Application
NCI	National Cancer Institute
NHANES	National Health and Nutrition Examination Survey
NRC	National Research Council
NRP	National Residue Program of the USDA/FSIS
OEHHA	California Environmental Protection Agency Office of Environmental Health Hazard Assessment
PND	Postnatal day
ppb	Parts per billion
ppt	Parts per trillion
rBGH	Recombinant bovine growth hormone
rBST	Recombinant bovine somatotropin
SC	Safe concentration
TBA	Trenbolone acetate
TB	17 $\beta$ -trenbolone
TP	Testosterone propionate
USDA	United States Department of Agriculture
WWEIA	What We Eat In America

## Introduction

Breast cancer is a major cause of morbidity and mortality in the United States. The National Cancer Institute (NCI) estimated that 232,340 women would be diagnosed with breast cancer in 2013 and 39,620 women would die of it [1]. The NCI also estimated that the lifetime breast cancer risk of women born today is 1 in 8. Given the public health burden, extensive research on risk factors is currently underway. In recent years, increasing attention has been paid to the role of hormones in breast cancer etiology, following reports that heightened levels of endogenous hormones and exposure to exogenous hormones and other endocrine-disrupting chemicals through food and the environment are associated with increased breast cancer risk [2, 3, 4].

In the U.S., several active ingredients of drugs approved by the Food and Drug Administration (FDA) for use in food animal production are endogenous hormones (i.e., testosterone propionate [TP], estradiol [E2] and estradiol benzoate, and progesterone) or compounds that display a high affinity for human hormone receptors (i.e., trenbolone acetate [TBA], zeranol, and melengestrol acetate [MGA]) (Table 1) [5]. These drugs are approved for use in cattle and, in the case of zeranol, sheep to increase weight gain and improve feed efficiency (two related indications generally known as “growth promotion”). E2, progesterone, and MGA are also approved to manage estrus in beef cattle and sheep. An additional compound, bovine somatotropin (bST), is approved as a method for increasing milk production in dairy cattle. Hormones are not approved for use in poultry or swine (Table 1).

There is concern that drugs approved for use in cattle and sheep or their biologically active metabolites may accumulate in edible tissues, potentially exposing consumers [6]. There is also concern that bST used in dairy cattle increases levels of another hormone, insulin-like growth factor 1 (IFG-1), in milk and dairy products, likewise increasing consumer exposure [7]. As a result, the use of these drugs has been controversial. The U.S. and European Union (EU) governments have engaged in a decades-long trade dispute over importation of U.S. beef from cattle that have received them [8]. The question of whether these drugs pose a human health risk remains subject to debate [6, 8].

The quantitative risk assessment process developed by a National Research Council (NRC) committee in 1983 and updated in 2009 is the standard approach to estimating human health risks posed by exposure to chemicals [9, 10]. A variant of this process has been adopted by the FDA for evaluation and approval of new animal drugs for use in food animal production [11]. The NAS process consists of four steps: hazard identification, dose–response assessment, exposure

**Table 1** FDA drug approvals by species, indication, and status

Active ingredient	Beef	Dairy	Sheep	WG	FE	Estrus	Milk	Status
Estradiol benzoate	x			x	x	x		OTC
Melengestrol acetate	x			x	x	x		OTC
Progesterone	x		x	x	x	x		OTC
BST		x					x	OTC
Testosterone propionate	x			x	x			OTC
Trenbolone acetate	x			x	x			OTC
Zeranol	x		x	x	x			OTC

*WG* weight gain, *FE* feed efficiency, *Estrus* regulation/modification of estrus, *Milk* increased milk production, *OTC* over the counter, *BST* bovine somatotropin

assessment, and risk characterization [9]. This report summarizes the information available to inform each of these steps with respect to the seven drugs described above (IGF-1 is assessed as the exposure of concern linked to bST), and identifies research gaps that need to be filled in order to more adequately elucidate any risk of breast cancer or other adverse outcomes posed by their use.

## Toxicologic Evaluation

The hazard identification and dose–response steps of the risk paradigm for the seven hormone drugs are combined and summarized in this section, encompassing details from published *in vitro*, *in vivo*, and epidemiologic studies. The studies are grouped by hormone, and the hormones are grouped by their primary hormone receptor (androgen, estrogen, progesterone, and IGF-1). We have limited the scope of our review to studies in mammalian species, and given the state of the literature, a formal dose–response assessment was not pursued.

### Androgen Receptor

#### *Testosterone Propionate*

In cattle, testosterone propionate (TP) is rapidly metabolized to a form that is indistinguishable from endogenous testosterone [12]. Testosterone metabolism in cattle is not well characterized [12]. Prospective epidemiologic studies have found an association between circulating levels of testosterone and increased breast cancer risk in postmenopausal women [13–15]. Conversely, an inverse relationship between circulating levels of the testosterone precursor dehydroepiandrosterone and risk of breast cancer has been reported in premenopausal women [16]. It is believed that androgens antagonize estrogen-dependent cell growth in premenopausal women via one mechanism but stimulate cell growth in postmenopausal women via a different mechanism [16]. (For reviews of the role of androgens in breast and other cancers, see [17, 18].)

In animals, testosterone has been associated with a number of adverse reproductive and developmental effects. In female rats exposed to 1 mg TP in utero on gestation days (GDs) 16 or 19, and then to 1 µg TP on postnatal days (PNDs) 1 or 5, a high percentage of animals within groups exposed on GD 19 had modified vaginas and sexual behavior deficits compared to both vehicle-only controls and groups exposed on GD 16 [19]. This 1983 report supports the importance of "windows of toxicity," in which effects are dependent upon the developmental stage of the receptor organism. In a different study, masculinized external genitalia was more common in female rats born of dams injected with 2 mg/day TP on GDs 16–20 than in female rats born

of vehicle-only controls, although postnatal ovarian cyclicity was normal [20]. In a third study, pregnant rats were injected with 0.5, 1, 2, 5, or 10 mg/day TP on GDs 14–19. The authors reported several "androgenic effects" in rat offspring at 0.5 mg/day TP, including increased anogenital distance (AGD) at weaning and in adulthood, as well as reduced numbers of nipples and areolas [21]. In a fourth study, the same group reported that rats born of dams injected subcutaneously with 1.5 or 2 mg/day TP on GDs 14–18 had increased AGD at PND 2 (AGD remained slightly but non-significantly increased at PND 13), reduced numbers of nipples and areola, and several genital malformations [22].

#### *Trenbolone Acetate*

In cattle, trenbolone acetate (TBA) is metabolized to its most active form, 17β-trenbolone (TB), and then further metabolized to 17α-trenbolone, which is also biologically active, and trendione, which is not biologically active [23]. As the most active form of TBA, TB is the predominant focus of the toxicologic literature. In contrast to assessments of its endocrine effects, genotoxicity assays of TB have produced mostly negative results [12], although a number of these tests were conducted by the industry [24], and some positive experiments have been reported as well [25, 26]. TB has induced neoplastic transformations in Syrian hamster embryo cells *in vitro* in multiple experiments [25, 27, 28].

In general, the *in vivo* literature is sparse, and no published study of carcinogenicity was identified. Instead, studies have examined reproductive and developmental endpoints. In the castrated rat, TB increased the combined weight of androgen-sensitive reproductive tissue and decreased body and adrenal gland weights relative to controls immediately following subcutaneous injections of 50 µg/day for 10 days (days 56–65) [29]. In a 200-µg/day group, those effects were elevated further. In another study reported simultaneously, TB administration by gavage, also on days 56–65, increased androgen-sensitive tissue weight relative to controls beginning at 10 mg/kgBW/day [29]. At 50 mg/kgBW/day, these effects were heightened, and other, similar effects were also observed.

In a two-generation rat study, the same group reported that subcutaneous TB injections during pregnancy (0, 0.1, 0.5, 1, or 2 mg/day for 6 days, on gestation days 14–19) caused few effects in dams (only body weight was measured, and while a decrease was reported, statistical significance varied with the test utilized) [29]. At PND 2, however, AGD increased in a dose-dependent manner in F<sub>1</sub> female pups from 0.5 mg/day. At PND 13, the *total* number of nipples displayed was reduced in F<sub>1</sub> females at 2 mg/day, but the number of *normal* nipples displayed was reduced at 0.5 mg/day. In a continuation of the same study, AGD remained elevated at PND 23 in the 2-mg/



day group, with dose-dependent increase in AGD at 0.5 and 1 mg/day, albeit non-significantly [30]. The total number of nipples displayed at PND 23 likewise remained significantly reduced at 2 mg/day; some nipples were still missing in the 1-mg/day group, but this was also not significant. TB delayed vaginal opening (i.e., the onset of puberty) at 2 mg/day and induced a number of genital malformations at various doses, beginning at 0.5 mg/day. In F<sub>2</sub> pups, survival was reduced at PNDs 1 and 6 at 1 mg/day.

In a separate study, castrated mice were injected subcutaneously with TB each day for two weeks, and then sensitized to a T-cell antigen, 2,4-nitro-1-fluorobenzene (DNFB) [31]. At one week following sensitization, DNFB was applied to the right pinna of each mouse. The mice were monitored for delayed-type hypersensitivity (DTH) as indicated by pinna thickness, measured daily for one week. TB reduced DTH in a dose-dependent manner at both doses (50 and 200 µg/day). The responsible mechanism was unknown, although endogenous androgens are involved in immunosuppression [32, 33]. In addition, weights of androgen-sensitive reproductive tissues were decreased at both doses, in contrast to increased weights observed in castrated rats. No attempt was made to explain the contradictory result.

The FDA's website includes two Freedom of Information Act (FOIA) summaries, from 1986 and 1996 [34, 35]. In 1986, increased incidence of "hepatic neoplasia and hyperplasia" relative to controls was reported in male and female rats that received TBA in their diet at 100 parts per million (ppm) for 96 weeks (males) or 104 weeks (females). From another study, an FDA committee concluded that "increased incidence of pancreatic islet cell tumors" observed in rats born of dams that received TBA in the diet was *not* "a carcinogenic effect of trenbolone acetate," but no further detail or explanation was provided. In 1996, carcinogenicity was not reported, but "mammary gland atrophy was more frequent and/or severe" in female rats that received TBA at 16 ppm in their diet for 12 months than in controls. From the 1986 approval, the FDA determined that "hormonal activity" was the critical effect of TBA and, from a study in the female rhesus monkey, identified 40 µg/kgBW/day as the hormonal no-effect level [34]. The ADI established by the FDA is 0.4 µg/kgBW/day [36], presumably due to the division of the specified no-effect level by safety factors totaling 100, although the factors applied by the FDA are not presented in the summary.

## Estrogen Receptor

### *Estradiol*

In cattle, estrogen benzoate is converted to estradiol (E2) [37]. E2 is more potent than two other physiologic estrogens, estrone (E1) and estriol [38]. Following the administration of radiolabeled E2 to cattle, the predominant metabolite detected

in urine was 17 $\alpha$ -estradiol, as well as E1 and conjugates of E1 and E2 [37]. There is clear evidence that estrogen is a mammary carcinogen, in part based on results from large epidemiologic investigations of its safety for hormone replacement therapy in menopause [2•]. It is believed that estrogen can act as both an initiator and promoter in breast carcinogenesis. Its action as an initiator is effected by E2 metabolites that can bind and damage DNA directly and by other metabolites that can elicit DNA damage via oxidative stress. As a promoter, E2 binds estrogen receptors (ERs) and elicits both cell proliferation and inhibition of apoptosis.

Because the carcinogenicity of estrogen is better supported by current evidence, and is reviewed in detail elsewhere [2•], we have limited our review of the literature in this report.

### *Zeranol*

In cattle, zeranol is metabolized to several compounds ( $\alpha$ - and  $\beta$ -zearalenol and  $\alpha$ - and  $\beta$ -zearalanol), although the literature has focused primarily on the parent compound. Zeranol is an ER agonist with potency similar to diethylstilbestrol and estradiol-17 $\beta$  (see above) [39]. In vitro studies provide the clearest evidence that zeranol is a mammary carcinogen. Repeated zeranol treatments were shown to reduce cell doubling time, stimulate colony formation, and, most notably, induce expression of ER- $\beta$  mRNA in the MCF-10A human breast epithelial cell line [40]. Because MCF-10A is putatively ER-negative, the authors suggest that induction of ER- $\beta$  mRNA may have been redox-mediated (e.g., genotoxic; see "Estradiol" above). In ER-positive human breast carcinoma cells, low concentrations of zeranol were found to accelerate cell growth, but the same concentrations did not affect the growth of ER-negative cells [41]. At a higher concentration, zeranol induced apoptosis of both ER-positive and ER-negative cells. This report is consistent with an emerging scientific consensus on the importance of low-dose effects distinct from overt cytotoxicity at higher doses [3]. Another study found that zeranol increased the proliferation of cancerous human breast epithelial cells to a greater degree than normal cells and down-regulated expression of the tumor suppressor gene p53 [42]. Ex vivo studies of cells isolated from the tissues of rats and beef heifers implanted with zeranol have found that further exposure to zeranol in vitro increases cell proliferation, up-regulates oncogenes (e.g., cyclin D1), and/or down-regulates tumor suppressor genes (e.g., p53) relative to cells from tissues of untreated animals [43, 44].

Evidence from in vivo studies is more equivocal, and studies to date have been hampered by small sample size, short duration, and the limited attention paid to carcinogenicity. Sheffield and Welsch [45] found that ovariectomized mice (5–8 mice per group) injected

subcutaneously with zeranol from weeks 6 to 8, and then sacrificed immediately, displayed increased mammary gland growth relative to controls [45]. In contrast, two studies, one in mice (30 per group) and the other in rats (24 per group), found no significant effect on mammary gland growth or carcinogenesis following prepubertal (days 15–18) exposure to zeranol by subcutaneous injection [46, 47]. In the rat study, animals were injected with the carcinogen N-methyl-N-nitrosourea at 10 days following the last zeranol injection (day 28). Zeranol did not significantly affect mammary carcinogenesis by week 37. In contrast, zeranol exposure has been associated with precancerous changes in the liver of the Armenian hamster [48], which is especially sensitive to estrogen, and in the prostate of the Akkaraman lamb [49].

## Progesterone Receptor

### *Progesterone*

In humans, progesterone has a number of clinical applications; it is often administered in combination with estrogen during hormonal therapy [50], and has been shown to aid in the effectiveness of chemotherapy drugs (such as cisplatin) [51]. Progesterone therapy has been suggested to reduce the risk of spontaneous preterm delivery [52], and has been proposed as having neuroprotective effects when administered with estrogen [53]. Much of the epidemiologic evidence available for progesterone relates to its use in hormone replacement therapy (HRT). It has been shown that HRT increases the risk of breast cancer in postmenopausal women [54]. In a study of the specific modalities of HRT in an investigation conducted in the UK with a sample size exceeding 1 million women, it was observed that HRT with an estrogen-progesterone combination was responsible for an increase in breast cancer risk over and above that associated with estrogen treatment alone [55]. Other studies have shown that the addition of progestins to HRT can reduce the risk of endometrial cancer [56]. With regard to breast cancer, one prospective study of plasma levels of endogenous steroid hormones did not find a significant association between progesterone levels and breast cancer in postmenopausal women, despite seeing evidence of a relationship for estrogens (E1 and E2) and testosterone [15]. Other studies have examined breast cancer risk in premenopausal women; in one large study, a significant inverse association between progesterone levels and breast cancer risk was observed, whereas four smaller studies and a second large study did not find significant associations [57].

A study in postmenopausal mice has shown that hormonal therapy with estrogen and progesterone stimulates epithelial cell proliferation, which is believed to be a factor in the development of breast cancer [58].

Aside from its potential role in breast carcinogenesis, progesterone has been shown to have other cellular effects. Studies in rats have demonstrated that progesterone treatment can increase cellular susceptibility to the effects of cadmium [59, 60]. A different study in the ovaries of Chinese hamsters and four different human cell lines (HeLa, Chang liver, Hep G2, and Caco-2) found that progesterone treatment inhibited cholesterol synthesis, resulting in the accumulation of cholesterol precursors, ultimately resulting in cholesterol auxotrophy [61].

### *Melengestrol Acetate*

MGA metabolism in cattle remains unclear: according to one study reported by employees of an MGA sponsor, the percentage of total residue accounted for by MGA was 29 % in the liver and kidney, 48 % in muscle, and 84 % in fat [62]. A number of metabolites were detected but not identified. MGA and other progestins have been investigated in animals as chemoprophylactic agents against hormone-sensitive cancers, including breast cancer. In the rat, 5 µg MGA/g feed for 30 days was associated with increased mammary lobulo-alveolar development relative to controls in intact animals but not ovariectomized animals [63]. In SHN virgin mice ( $n=25$ ), 10 mg MGA implanted subcutaneously increased mammary tumorigenesis but slightly inhibited the formation of preneoplastic hyperplastic alveolar nodules relative to controls ( $n=44$ ) implanted with cholesterol [64]. The authors suggested that heterogeneity in the hormonal response of clones accounted for these seemingly contradictory responses. In the BDII/Han rat, in which incidence of endometrial carcinoma (ECa) approaches 90 % in later life, MGA *suppressed* ECa in all rats receiving 250, 500, or 1,000 ppm MGA in their diet from days 24 to 28 ( $n/group=17-20$ ), while the incidence in untreated controls ( $n=20$ ) was 85 % [65].

In addition to controlled experiments in rodents, mammary carcinogenicity has been reported in small observational studies of captive wild felids in which MGA was used as a contraceptive [66] (others are cited in [67]). There is also evidence that prepubertal exposure to MGA accelerates the onset of puberty in the beef heifer [68]. Reproductive toxicity per se was not assessed in the published literature; in the rabbit, however, oral administration of MGA to two dams on gestation day (GD) 14 increased MGA residues in fetal tissues at GD 27, indicating in utero exposure [69].

## Insulin-Like Growth Factor 1 Receptor

Insulin-like growth factor 1 (IGF-1) is an endogenous protein hormone produced by the liver in response to somatotropin [70]. Bovine somatotropin (bST or, in some cases, bovine growth hormone [bGH], recombinant bovine

somatotropin [rbST], and recombinant bovine growth hormone [rbGH]) is approved by the FDA for use in dairy cattle to increase milk production [5]. It is injected subcutaneously. As acknowledged by the FDA and the industry, the use of bST increases IGF-1 levels in milk, although the magnitude of this increase has been disputed [71–73] (see the following section). The key questions for a toxicological evaluation in support of risk assessment include what fraction of IGF-1 in milk is absorbed intact in the human gut, how this affects endogenous IGF-1 in circulation, and the biological significance of an increase in circulating IGF-1 levels.

Bovine IGF-1 in milk is identical to human IGF-1 [71]. Nevertheless, the FDA and industry maintain that milk-borne IGF-1, as a protein hormone, is digested in the gut and not absorbed intact [71, 73]. For that reason, IGF-1 was approved with limited toxicity studies (two 2-week experiments in the rat). Both assays included groups dosed subcutaneously and groups dosed by gavage [71, 72]. Treatment-related effects were observed only in the subcutaneous groups, and it was argued that this supports the contention that IGF-1 is not orally active. It could not be determined from published reports whether a change in circulating IGF-1 levels was assessed in either study. The effect of lifetime oral exposure, which is more relevant when the vehicle is milk, was not assessed. The latency periods of clinical endpoints associated with increased circulating IGF-1 levels in the epidemiologic literature (e.g., breast, colorectal, and prostate cancers) is almost certainly longer than two weeks in the rat.

The relationship between plasma and serum IGF-1 levels and breast cancer risk has been assessed in numerous epidemiologic studies. A 2004 meta-analysis of six case-control studies reported significant associations in premenopausal women (OR [95 % CI]=1.65 [1.26–2.08]) but not in postmenopausal women (0.95 [0.65–1.58]) [74•]. However, a more recent meta-analysis of individual data from 17 prospective studies reported associations in both premenopausal and postmenopausal women (ORs [95 % CIs]=1.21 [1–1.45] and 1.33 [1.14–1.55], respectively) [75•]. Heightened IGF-1 levels have also been associated with increased risk of colorectal and prostate cancers [74•]. The reported associations between circulating IGF-1 levels and cancer risks are supported by biologically plausible mechanisms [76].

Dairy consumption has been associated with higher circulating IGF-1 levels [77, 78]. Despite this fact, a weak association between dairy consumption and breast cancer risk was found in one meta-analysis [79], and no significant association was found in another [80]. Dairy consumption may not be an appropriate surrogate for IGF-1 exposure attributable to bST use, however, as IGF-1 and other hormones are present in the milk of untreated cows, and by 2008, the use of bST had fallen to 17.2 % of the U.S. dairy herd [81, 82].

## Residues of Hormones and Hormone Metabolites in Food Animal Products

Understanding the burden posed by dietary hormone exposure requires data on residue levels in food animal products. For hormones administered to food animals, in order to obtain FDA approval, drug companies (known as “sponsors”) are required to conduct feeding studies that show the rates of depletion of these compounds in the edible tissues of dosed food animals. These studies are used to inform recommended dosages and to set withdrawal periods (i.e., the number of days before slaughter that use of the drug must end) that are intended to ensure that remaining residue concentrations have fallen to levels the FDA considers “safe” for human consumption. In addition, some residue data are available from federal food safety monitoring programs and independent research studies. Available data are described below.

### Residue Determination Via Food Animal Feeding Studies and Retail Market Samples

As part of the NADA process, the sponsor of a new animal drug is required to conduct and submit studies to the FDA that characterize residues that may persist in animal products when the drug is used in accordance with the conditions of use proposed in the NADA. The extent of study data and summaries that are publicly accessible is limited. Even for drugs where residue depletion summaries are accessible, confidence in any of the conclusions drawn is limited by problems with data design and results reporting. An example can be found in the case of NADA 141–043, for a combination implant drug containing TBA and estradiol benzoate [83]. In the FOIA summary associated with this approval, serious issues are apparent regarding study design (i.e., data from half [heifers] of the 24 animals tested were dropped, leaving only 12 animals [steers], with unspecified exposure group assignment) and reporting clarity (i.e., number of animals per group is not reported, no control data are reported, urinary and fecal residue measurements are not reported) that would challenge the value of this study for determining anticipated residues. In this particular case, the study was used to support the decisions not to require marker residue tolerance or withdrawal periods for the drug.

Feeding studies conducted outside the NADA process were uncommon. Daxenberger and colleagues examined residues of MGA that persisted in edible tissues and plasma under FDA-approved conditions of use and following overdosage (i.e., 3–10 times the approved dose) in heifers post-56-day treatment [84]. Detectable residues of MGA were observed in tissues in the following order: fat >> liver > kidney > muscle > plasma, with increasing residue concentrations tracking with increases of administered dose. The authors found that tripling the recommended dose resulted in fat residue

concentrations that exceeded FDA residue tolerance levels. A compilation of studies of experimental animals implanted with hormones (written in French and summarized by the European Food Safety Authority [EFSA]) examined tissues for residues of endogenous and exogenous hormones in treated and control animals [85]. For the examined exogenous hormones (zeranol and trenbolone), measurable concentrations (from sub-parts-per-billion [ppb] to single-digit ppb concentrations) were present in all tissues examined (liver>kidney>muscle~fat). Marked increases were seen in endogenous hormone (E2, testosterone, and progesterone) residues of implanted animal tissues, with greater differences seen in non-liver tissues (with the exception of E2).

While the literature describing various techniques for determining hormone residues in animal products is expansive, few studies were identified of residues in retail animal products, and mid- or large-scale evaluations of residues in retail animal products were not identified. The focus of the majority of studies identified was on free/unconjugated hormone residues, as these are believed to be the most biologically active forms [86]. Concerns have been raised, however, that conjugated estrogens can be deconjugated in the gastrointestinal tract, resulting in the release of free forms of these compounds, which then may become available for absorption and subsequent binding to hormone receptors [87].

To date, the largest body of literature available is for hormone residues in dairy products; studies of E1 and E2 levels in various milk products were most common. Studies typically analyzed small numbers of retail samples; single samples per product type were not uncommon, and studies rarely exceeded ten samples per product. Estrogens, particularly forms of E2, were the most frequently examined [86, 88–92]. Looking across studies, some patterns emerge, though it is necessary to acknowledge that the limited number of studies and small sample sizes within those studies do not allow for statements of great certainty.

Free E2 (non-specific to  $\alpha$ -E2 and  $\beta$ -E2 forms) concentrations in milk samples have been reported in ranging from less than the limit of detection (LOD) to 5.84 pg/mL [86, 90, 92]. Studies of free  $\alpha$ -E2 and  $\beta$ -E2 in milk found concentration levels ranging from below the LOD to 3.7 pg/mL and 0.5–10.7 pg/mL, respectively. Generally, as the fat content of milk increased, free E2 concentrations were higher (this was observed especially in  $\beta$ -E2, less so in  $\alpha$ -E2) [92]. No differences in E2 concentrations were observed when comparing USDA certified organic milk to conventionally produced milk [90], though comparisons of unprocessed (raw) milk and processed milk showed that the processing step can significantly reduce free E2 concentrations [91]. Reported ranges of total (free and deconjugated) E2 spanned 20.4 to 61.52 pg/mL, with the highest concentrations found in samples with the most fat content [86, 90]. Total levels of  $\alpha$ -E2 and  $\beta$ -E2 did not appear to track well with fat content [88, 91]. A single

study examined raw milk across the three trimesters of pregnancy, and found a clear trend in E2 levels increasing with trimester [91]. One study reported total E2 concentrations in butter, cream, and half-and-half of 15.8 and 6 pg/g, and 1.9 pg/mL, respectively [92].

A limited number of studies examined E1 levels in dairy products. Among processed milk samples, free E1 concentrations ranged from 1.1 to 14.45 pg/mL [86–88, 90, 92]. A single study reported a free E1 concentration of 28.3 pg/g in milk fat. Some variability was observed across studies in free E1 concentrations within the same types of dairy products (a single study reported considerably lower concentrations than all others). In the aforementioned study looking at raw milk across trimester or pregnancy, E1 concentrations were highest in late pregnancy, and the impact of milk processing was significant on residual free E1 [91]. Studies of total E1 reported levels ranging from 8.2 to 397.0 pg/mL in processed milk, and a peak value of 1,266 pg/mL in raw milk from a cow in its third trimester of pregnancy [87–91]. One study examined butter, cream, and half-and-half, reporting total E1 concentrations of 118.9 pg/g, 54.1 pg/g, and 20.4 pg/mL, respectively [92].

Two French studies by the same group examined levels of testosterone in dairy products [88, 89]. The first, which measured  $\alpha$ -testosterone, reported a concentration range of 27.46 to 94.86 ng/L [89]. Concentrations increased as a function of fat content of the milk. The other study reported a range for total testosterone of 2.9–20.4 ng/L [88] (more than 50 % of which was in conjugated form), which was considerably lower than the group's earlier study. No obvious patterns were observed for total testosterone with regard to fat content. The same two French studies examined residues of total  $\alpha$ -E2 and  $\beta$ -E2, E1, and  $\alpha$ -testosterone and  $\beta$ -testosterone in eggs [88], finding measurable levels of all compounds. Concentration ranges of 0.03–0.85 and 0.15–1.45  $\mu$ g/kg were reported for  $\alpha$ -E2 and  $\beta$ -E2, whereas E1 was measured at 0.15–2.47  $\mu$ g/kg. The earlier of the two studies measured levels of 1.54–2.62 and 1.06–1.56  $\mu$ g/kg for  $\alpha$ -testosterone and  $\beta$ -testosterone, respectively, and the later study found a range of 0.16–1.88  $\mu$ g/kg for total testosterone.

Concerns related to the use of rBST have focused on resulting levels of IGF-1 in milk products. While IGF-1 is present in untreated cow's milk, the use of rBST has been examined for its propensity to increase concentrations of the drug in commercial milk [93]. The European Commission (EC) published a report in 1999 that examined available literature regarding impacts of rBST treatment on IGF-1 levels [94]. The report found evidence that rBST treatment resulted in milk IGF-1 concentrations two to five times greater than those in milk from untreated animals. Earlier research cited in the EC report had identified a range of IGF-1 concentrations in cow's milk of 1–34 ng/mL, whereas later research found that milk from treated animals had an average concentration of



5.9 ng/mL as compared to an average of 3.7 ng/mL in untreated animals (the difference was statistically significant) [95]. JECFA reported concentrations of IGF-1 in milk from treated and untreated cows in a range of 1–13 and 1–9 ng/mL, respectively, and noted that the levels of IGF-1 were influenced by stage of lactation, nutritional status, and animal age. Attempts to find additional studies of IGF-1 levels in commercial milk were unsuccessful, though references in the literature of declining frequency of rBST use were found [81].

A smaller number of studies have attempted to characterize residues of synthetic hormones in beef products [88, 96–98]. One study successfully measured hormone residues in these products, finding fractions of ppb residues in the liver, kidney, and muscle tissue of cattle implanted with E2 and TBA [88]. Most other studies examined beef tissue for residues of zeranol, and never found concentrations above quantitation limits [96, 97]. One older study that lacked a clear description of its analytical methods looked at beef liver, kidney, and muscle tissue for a suite of hormones (E2, MGA, progesterone, TBA, testosterone, and zeranol) and found no measurable residues [98]. A Turkish study of meat and sausage products from markets in Istanbul [99] reported detection of zeranol and TBA residues in 100 % and 80 % of samples tested, respectively; reported concentrations were considerably higher, approaching ppm concentrations in some instances. Given the limited clarity provided regarding the methods and meat sourcing, confidence in the findings was low.

#### FDA Hormone Residue Tolerance Levels

The FDA is responsible for setting levels of tolerance for residues of hormones that may remain in animal products as a result of their administration to food animals. These levels are set as residue limits in the specific tissues of a particular species (Table 2). No residue tolerance regulations are in place for TBA or zeranol; the rationale for their absence is likely the

FDA's position that residues of human health concern are unlikely under permitted drug use specifications. Interestingly, in the aforementioned example (NADA 141–043, for a combination implant drug containing TBA and estradiol benzoate), the agency notes that a marker residue is not needed because the tested edible tissues of steers are below codified "safe concentrations." Despite this logic, however, an examination of 30-day liver concentration of TBA is reported as "mean: 85.23 ppb SD: 45.15 ppb," which is less than a single standard deviation away from the codified safe concentration of 100 ppb.

#### Hormone Residue Testing under the USDA/FSIS/National Residue Program

Within the U.S., the National Residue Program (NRP, which is administered by the Food Safety and Inspection Service of the USDA) is the only federal effort that routinely examines animal products for drug residues. Challenges exist in the utilization of NRP data for the purpose of understanding dietary hormone exposure. In its entire history, the NRP has only examined TBA, MGA, and zeranol. There are year-to-year variations in which of these hormones is subjected to examination, and in some years, none are assessed (Fig. 1). Testing is performed in tissues not commonly consumed by people (e.g., kidney and liver), requiring extrapolations to estimate concentrations in muscle tissue and milk. Further, residue data reporting is extremely crude, and does not allow for the construction of residue concentration distributions or descriptive statistics. Many of these shortcomings are likely a result of the core conflict between the purpose of the NRP and the need for exposure assessment, as the primary purpose of the NRP—the removal of animal products with violative residue levels from the food supply—may require data that is different from that needed to understand residue exposure in people.

**Table 2** FDA hormone tolerance limits

Hormone	Muscle mg/kg	Liver	Kidney	Fat	ADI mg/kgBW-day
Estradiol <sup>a</sup>	0.00012	0.00048	0.00036	0.00024	N/A
Melengestrol acetate	N/A	N/A	N/A	0.0025	N/A
Progesterone	0.005	0.015	0.03	0.03	N/A
Testosterone propionate <sup>a</sup>	0.00064	0.0026	0.0019	0.0013	N/A
Trenbolone	Tolerance not needed <sup>b</sup>				0.004
Zeranol	Tolerance not needed <sup>b</sup>				0.00125

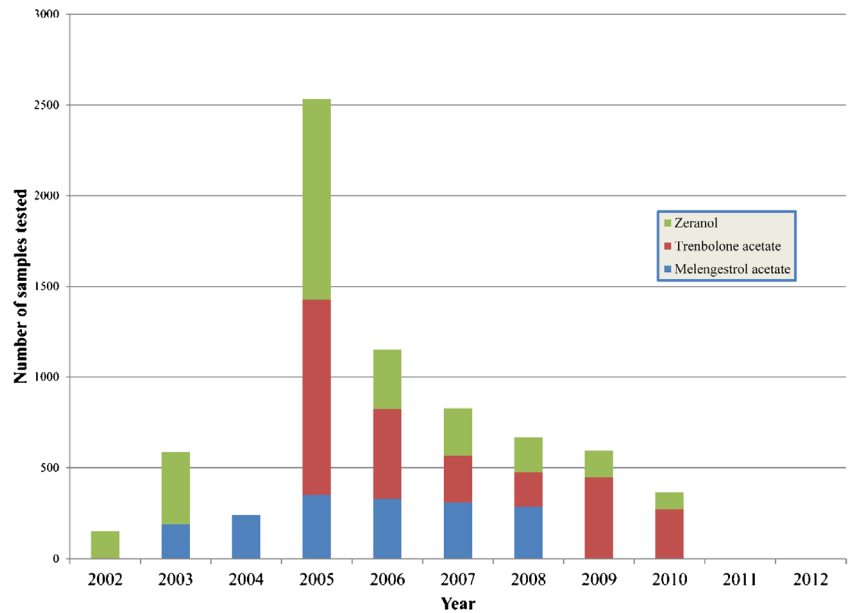
<sup>a</sup> Residues of these compounds are not permitted in excess of these increments above the concentrations of these compounds naturally present in untreated animals

<sup>b</sup> As specified in the CFR

ADI acceptable daily intake, N/A not applicable

Code of Federal Regulations Title 21 Subchapter E – Animal Drugs, Feeds, and Related Products, Part 556: Tolerances for Residues of New Animal Drugs in Food

**Fig. 1** Hormone monitoring in the USDA/FSIS National Residue Program, by year. \*Data represent the number of samples examined under the monitoring program, which is the routine surveillance program. A small number of additional samples are analyzed in selected years under inspector-generated mechanisms or in imported animal products



**Characterizing Intake of Animal Products**

Estimation of the intake of hormones through consumption of animal products requires an understanding of patterns of consumption for meat, milk, and egg products. Nationwide dietary intake data (including entries for animal products) are collected in the What We Eat in America (WWEIA) dietary survey of the National Health and Nutrition Examination Survey (NHANES) [100, 101]. These data were analyzed by the EPA and reported by product as per capita or

consumer-only intake rates in the 2011 Exposure Factors Handbook (EFH) [102]. In some cases, animal product intake rates are reported by life stage (or age grouping) or by race/ethnicity. Table 3 summarizes intake rates from the EFH for animal products.

Per capita intake rates for dairy products were the highest of all animal products among the general population, more than eight times that of beef or poultry, and nearly 17 times that of pork products. Based on survey data, the EPA reported that 88 %, 80 %, and 75 % of persons consume beef, pork, and

**Table 3** Per capita body weight-adjusted intake rates for animal products

	Total meat g/kg-day	Beef	Pork	Poultry	Dairy products	Eggs
Whole population	2.00	0.77	0.39	0.77	6.60	0.4
Age group						
Birth to 1 year	2.70	0.34	0.17	0.69	11.70	0.3
1 to 2 years	4.10	1.38	0.75	1.87	43.20	1.3
3 to 5 years	3.90	1.42	0.79	1.65	24.00	0.91
6 to 12 years	2.80	1.11	0.52	1.18	12.90	0.51
13 to 19 years	2.00	0.83	0.36	0.80	5.50	0.33
20 to 49 years	1.80	0.73	0.36	0.71	3.50	0.31
Females 13 to 49 years	1.60	0.60	0.28	0.66	3.80	ND
50 years and older	1.40	0.58	0.33	0.50	3.30	0.33
Race/ethnicity						
Mexican American	2.30	0.94	0.43	0.82	8.60	ND
Non-Hispanic black	2.20	0.79	0.40	1.01	5.00	0.48
Non-Hispanic white	1.90	0.74	0.38	0.70	6.60	0.36
Other Hispanic	2.30	0.89	0.36	0.97	8.10	ND
Other race - including multiple	2.30	0.84	0.41	1.00	6.70	ND

poultry, respectively (an estimate of the percentage of persons consuming dairy products was not available). Consumption of meat and dairy products, on a body-weight-adjusted basis, is highest early in life.

The EFH includes some animal product intake data specific to premenopausal women. Women between the ages of 13 and 49 years consume approximately 20 % less meat and half the amount of dairy products compared to the general population, after adjusting for body weight. While data specific to women 50 years of age and older were not available, estimates for persons 50+ (for males and females combined) suggest that both total meat intake and beef, poultry, and dairy product intake were further reduced from women aged 13–49; pork intake was slightly higher. Data for animal product-specific intake rates for postmenopausal women are

needed in order to estimate dietary hormone exposure levels in this subpopulation.

## Discussion and Conclusions

We have assembled literature relevant to the hazard identification, dose–response assessment, and exposure assessment steps of the NRC risk paradigm. Our review of the published literature has identified gaps in current knowledge germane to each step. A description of the most important of these gaps follows.

There appears to be a lack of chronic (especially lifetime) bioassays of oral toxicity of the seven hormone compounds in the published literature. While evaluations of these compounds are submitted to the FDA as part of the drug approval process,

**Table 4**

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- GAP 1:** Important gaps remain in the published literature concerning the dose–response relationships between oral exposures to hormones and various health outcomes. Currently, there are few high-quality chronic/lifetime, oral studies; without these, uncertainty clouds the understanding of the biological significance (if any) of long-term, low-dose hormone exposures through diet. Furthermore, available mechanistic and epidemiologic studies suggest that traditional toxicologic endpoints may not be appropriate for evaluation of hormone-mediated carcinogenicity.
- OPPORTUNITY 1:** Independent toxicologic studies that examine chronic or lifetime oral exposure to low doses of FDA-approved hormonal animal drugs and/or their active metabolites in relation to both frank effects (e.g., breast carcinomas) and upstream precursors (e.g., perturbations in endogenous hormone levels) would allow for determination of exposures that pose an acceptable (or no) risk, and thus support evidence-based regulatory decision-making by the FDA.
- GAP 2:** Better information is needed regarding the toxicological consequences of hormone exposure during specific life stages or critical “windows of toxicity.” In the case of breast cancer, it is possible that perturbations of circulating hormone levels at certain life stages may have greater biological significance than perturbations at other times. Identification of these windows is important, and would be complemented by an understanding of dietary patterns during these key time periods.
- OPPORTUNITY 2:** In addition to chronic or lifetime studies, developmental toxicity studies that incorporate in utero or pre-pubertal exposures, and build upon existing developmental studies of the compounds covered by this report, may reveal specific effects not detected in studies that are not reflective of the growing knowledge of the importance of these windows of toxicity.
- GAP 3:** Too little information is available regarding the human food safety evaluations that form the scientific basis for FDA animal drug approvals, especially for hormones. Specifically, toxicological and residue assessment of hormones is supported primarily by industry studies that are not made available to independent scientists for review; as a result, it is impossible to assess potential impacts of study age and conflict of interest on the quality of the studies and how they are interpreted.
- OPPORTUNITY 3:** Independent review of industry submissions could be possible if study reports and the associated data submitted to the FDA in the drug approval process were made available to independent researchers. Legal measures should be pursued to gain access to these documents. FOIA requests may be an opportunity to secure access to these studies.
- GAP 4:** Dietary intake rate data are limited and provide little information about the distributions of consumption rates (across life stage, gender, race/ethnicity, etc.) for specific animal products. This is especially important for development of hormone-specific intake rates. With regard to breast cancer, intake rates for specific animal products are not available for post-menopausal women, limiting the ability to understand how diet may contribute to hormone exposure at important life stages.
- OPPORTUNITY 4:** Raw data from WWEIA (which are publicly accessible), especially across multiple examination cycles/years, allow for in-depth analyses that could yield more precise estimations of intake rate distributions for subgroups of particular concern in breast cancer prevention efforts. These rates would better support dietary exposure estimation for hormones in vulnerable populations.
- GAP 5:** Federal approaches to hormone residue testing are inadequate. A small, changing number of compounds are not consistently tested from year to year. The tests rely on potentially outdated methods and do not permit longitudinal evaluation of residue levels in animal products. A search of the open literature did not identify representative studies of residues in retail animal products.
- OPPORTUNITY 5:** A review of novel analytical methods for hormone residue analysis would yield recommendations for modernizing regulatory methods for federal residue monitoring systems, and may facilitate a uniform approach for testing retail animal products. Given the limitations of the NRP, independently conducted market-basket studies of retail meats that incorporate highly sensitive analytic methods would yield data to support defensible estimations of dietary hormone exposures at biologically-relevant concentrations.
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\*Our review has revealed that numerous deficiencies exist in publicly available literature. Here, we identify key gaps in current knowledge and suggest opportunities for further research that would likely generate the foundation for interventions, if needed

this information is not made available to the public for independent evaluation, and thus these evaluations cannot be used to estimate risks and related burdens for persons consuming animal products. The existing literature primarily utilizes subcutaneous dose delivery in which the bioavailability of the administered dose approaches 100 %. This route does not account for variation in toxicological parameters that may result from differences in bioavailability or metabolism of compounds that can occur following oral exposure. Furthermore, the endpoints assessed in the published literature may not reflect an emerging understanding of the importance of upstream markers (e.g., circulating hormone levels) on subsequent clinical disease. Published animal studies have studied adverse effects resulting from exposure during key periods of pregnancy or pre-puberty, suggesting that the timing of exposure, in addition to the level of exposure, plays a key role in the biological significance of exposure to exogenous hormones.

Products containing the hormones reviewed in this paper were originally approved by the FDA several decades ago, using studies submitted by the industry; the most recent approval, for rBGH, came in 1993. The agency based subsequent approvals of products that contained these compounds on the studies submitted in support of original approvals. The FDA also does not routinely review and update approvals. As a consequence, the approvals of many hormone products are based on studies conducted decades ago by companies seeking approval, and predate current scientific understanding of relevant human health risks, such as endocrine disruption [103]. The studies are not easily obtained by scientists outside the FDA—typically, only summaries of the studies are posted online, and access to older summaries not available online or studies that are referenced requires FOIA submission. In our experience, including requests for hormone studies, the time from submission to receipt of records has spanned several years.

The ability to estimate dietary hormone exposure is severely hampered by the state of the existing literature. Residue depletion studies, which are submitted to the FDA as part of drug approvals, are difficult to access, and when access is possible, careful examination of study summaries suggests that conclusions drawn from these studies are not well founded. Literature describing the residue content of retail animal products is limited; the best available studies primarily focus on estrogens in dairy products. Studies of retail animal tissue products are rare. Regulatory methods specified for analysis of TBA, MGA, and zeranol frequently rely on older GC-MS-based methods, and may not be on par with a wide array of newer available methods, which are supported by a rich literature.

Body-weight-adjusted per capita animal product intake estimates are available from the EPA EFH. These are the best-suited estimates for assessing levels of hormone exposure through food products, as they are derived from the most

recent synthesis of NHANES dietary data. The EPA estimates suggest that dairy products are consumed at considerably higher rates than other animal products, and that body-weight-adjusted animal product intake peaks early in life (between 1 and 5 years), and declines steadily over the remaining life stages. Animal product consumption rates specific to postmenopausal women are not available in the EFH, though combined rates for all persons over 50 are available. Data show that women of premenopausal age consumed approximately 20 % less meat per body weight than the general population, and between 14 % and 28 % less of specific meat types. Animal product consumption rates were highest among non-whites, with consumption rates varying by product-race/ethnicity combination.

In this review, we have identified key limitations that preclude conduct of quantitative dose–response and exposure assessments. As a result, at present, it is not possible to provide a quantitative characterization of risks that result from the use of hormonal drugs in food animal production. As such, understanding the role of dietary hormone exposure in the population burden of breast cancer is not possible at this time. In Table 4, we highlight critical gaps in our understanding of the population burden imposed by hormone use as well as potential opportunities for advancing the science.

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#### Compliance with Ethics Guidelines

**Conflict of Interest** Keeve E. Nachman and Tyler J. S. Smith each declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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# Effectiveness of Policies on Reducing Exposure to Ionizing Radiation From Medical Imaging: A Systematic Review

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## Abstract

**Purpose:** The use of medical imaging has expanded greatly in the past three decades, raising concern about potential unwanted carcinogenic harms associated with exposure to ionizing radiation among patients. This study summarizes evidence of efficacy of interventions that have prompted policies, and structural-level interventions aimed at reducing radiation dose and risk of cancer, especially among women.

**Methods:** Using standard terms, we conducted searches in MEDLINE, Scopus, and Web of Science, and de-duplicated retrieved citations. We hand-searched the reference section of eligible studies and contacted radiology experts to identify studies missed from electronic searches. Two reviewers screened retrieved citations based on predefined eligibility criteria, to identify relevant studies, extract key information from each, rate the quality of evidence, and summarize data in tabular and graphical format.

**Results:** From a total of 1,543 unique citations identified from all sources, 16 were included for data extraction. Half of the studies focused on reduction of ionizing exposure from CT, and half on x-ray or fluoroscopy. Identified interventions were broadly categorized as: policy or structural intervention (two; 13%); multipronged (four; 25%); dose-feedback system (five; 31%); provision of training (four; 25%); and quality-control audit (one; 6%). In general, multipronged programs had a higher range for dose reduction (22%-74%), followed by policy/structural interventions (37%-50%).

**Conclusions:** Existing evidence on the effectiveness of policies aimed at reducing patient radiation dose is disperse and low in quality. Compared with other approaches, multipronged efforts may offer more patient protection.

**Key Words:** Systematic review, health policy, ionizing radiation, medical imaging, medical diagnosis

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## INTRODUCTION

The use of medical imaging technology has become indispensable in modern health care, and its role in diagnostic and therapeutic procedures has expanded greatly in the past three decades. The overall volume of CT procedures, the

most significant contributor to radiation dose, have increased from 3 million in 1980, to 26 million in 1998, to more than 70 million in 2008 [1,2]. Consequently, patient exposure to ionizing radiation has increased significantly. The annual per capita radiation dose was 3.6 (mSv) in the early 1980s, and radiation from medical sources contributed only 0.54 mSv to this dose, with the remainder attributable to cosmic rays, radon, soil, and construction materials. In 2006, medical radiation contributed 3 mSv to the annual dose, which raised the per capita dose to 6.2 mSv, averaged over the US population [1].

Radiation dose for CT is often represented as the “effective dose” and reported in mSv, calculated by multiplying the dose to each irradiated organ by a biologic weighting factor and summing the products for all exposed organs. The effective dose is defined as the dose that, if delivered uniformly to the whole body, would produce the same health consequences caused by a dose delivered to one

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or more specific organs. The effective dose is more usefully viewed as a concept for developing radiation protection standards and setting dose limits for occupationally exposed individuals. The International Commission on Radiological Protection (ICRP) has stated [3]:

Effective dose is intended for use as a protection quantity. The main uses of effective dose are the prospective dose assessment for planning and optimization in radiological protection, and demonstration of compliance with dose limits for regulatory purposes. Effective dose is not recommended for epidemiological evaluations, nor should it be used for detailed specific retrospective investigations of individual exposure and risk.

The ICRP estimates that the incidence risk of cancer in all organs among individuals exposed to ionizing radiation increases by 5% per Sievert [3], although several assumptions are inherent in this estimate, and it has been criticized in other studies as being highly speculative [4]. Risk assessment modeling studies have predicted thousands of radiation-induced cancers and cancer deaths based on such assumptions; in 2007, Brenner and Hall estimated that 1%-2% of all cancers in the United States are caused by CT studies, and Berrington de González et al predicted in 2009 that 29,000 additional cancers and 14,500 cancer deaths are caused by CT examinations each year [2,5].

In recent years, many policy interventions have been developed at various levels, including institutional, state, and federal, to improve radiation reporting in health care, limit medical radiation dose to certain thresholds, and develop industry-level standards. For example, major academic medical centers and hospitals typically require employees who may be exposed to radiation to monitor and report their radiation exposure, with a typical annual limit of 50 mSv [6]. Many states now require formal reporting of radiation dose when patients undergo procedures that expose them to ionizing radiation. Most prominently, a California law that was enacted on July 1, 2012 requires the reporting of certain dose parameters for all diagnostic CT examinations in the radiology report [7].

Federal regulations regarding the quality (and dose limits) for mammography have long been in place, formalized by the Mammography Quality Standards Act (MQSA), which became law in October 1992 [8]. Finally, guidelines have been created at the level of professional societies, such as the ACR's Appropriateness Criteria<sup>®</sup>, which are evidence-based guidelines to assist physicians in making the most-appropriate imaging or

treatment decision for a specific clinical condition, while taking dose into prominent consideration [9].

In many cases, the efficacy of these institutional and government policy interventions in reducing ionizing radiation exposure is not known. This review seeks to summarize the effectiveness of policy interventions that are aimed at reducing ionizing radiation exposure resulting from diagnostic imaging, as currently reported in the literature, with a focus on breast cancer, using standard systematic review methods. Another purpose of the review is to potentially inform a research-funding initiative by the California Breast Cancer Research Program (CBCRP) aimed at reducing environmental sources of exposure to carcinogens [10].

## METHODS

### Protocol Development

We generally applied standard systematic review methods for our data collection process. For protocol development, we first created a detailed protocol for searching, extracting, and analyzing the data. We applied the PICO (population, intervention, control, and outcome) framework to inform our protocol development. Although the primary objective of this review was to assess the evidence of effectiveness of interventions in the context of breast cancer among women, our initial database searches led us to conclude that our search strategies should be expanded beyond breast cancer among women. Thus, we defined our **PICOs** of interest to reflect that concept: **P** (populations at risk of exposure to ionizing radiation, owing to medical imaging for diagnostic purposes); **I** (policies or interventions with potential policy implications aimed at reducing risk of exposure to ionizing radiation associated with medical imaging); **C** (no intervention, existing policies, or standard of care); and **O** (health endpoints, measure of exposure, quality improvement).

### Search for Relevant Studies

The data collection process began with identification of relevant studies using three sources: (1) electronic databases; (2) references cited in relevant citations; and (3) radiology experts. First, a medical librarian, in consultation with the authors, created a PubMed search designed to locate articles from both MEDLINE and the portion of PubMed not in MEDLINE. The search strategy contained MeSH (main subject heading) keywords reflecting radiation exposure sources (eg, "diagnostic imaging," "ionizing radiation"); patient protection (eg, "patient safety"); and radiation exposure (eg, "radiation

injury,” “radiation dose”). Equivalent searches were created for Scopus and Web of Science. Selective keywords were used to search in Google for the grey literature. Results from all sources were collected, and duplicates were removed, using EndNote. No language, geographic setting, or date restriction was applied.

Given the scarcity of studies in this field, the search was enhanced by applying a selective combination of keywords in Google to identify relevant gray literature. Additional citations were obtained from references of relevant citations by entering titles of eligible citations into Scopus to identify electronic versions of cited documents and exporting them into an EndNote library. Finally, radiology experts were consulted, by obtaining e-mail addresses of the first, second, and last authors of relevant studies, and contacting them to solicit input on identifying the gray literature, as well as any study that might have been missed because of a limitation of the search strategy or a publication time lag. Experts were asked to provide the names of at least three other radiologists with expertise in radiation safety that could be contacted for the same purpose.

### Study Screening

Two reviewers independently applied a list of inclusion criteria corresponding to PICO of interest to screen titles and abstracts of all retrieved citations, to identify relevant studies. We included studies with firsthand quantitative data and sufficient technical information for the assessment of quality of evidence. If studies were relevant based on all other eligibility criteria, but were missing certain critical information (eg, abstract), we would include the study and contact authors to obtain the information. Given this paper's focus on policy interventions, we excluded studies that focused on merely the evaluation of the effect of a specific mechanical or technologic alternation, the superiority or equivalency of one radiology technology compared with another, interventions implemented to reduce ionizing radiation from therapeutic procedures, and those that did not deal with ionizing radiation.

We excluded qualitative studies, case reports, and modeling data. Review studies focusing on interventions relevant to our review were restored as a potential source of studies. Disagreements between the two reviewers at the level of title and abstract review underwent a reconciliation process. Full text was obtained for citations that passed initial screening, and these citations underwent the next level of sequential review by both reviewers. Reviewers discussed disagreements and reconciled decisions to select the final list of studies for data extraction.

### Data Extraction

Data extraction was performed by first extracting key technical data from eligible studies into a spreadsheet, including: author and year, geographic setting, intervention recipients, intervention and control content, intervention duration, intervention settings, outcome measures, effect size, sample size, and study design. A senior researcher conducted a thorough review of extracted data for all fields, and double-extracted outcome measures to ensure accuracy. We contacted study authors to obtain key data that were not reported by studies. Outcome data were transformed from absolute dose reduction (eg, dose-area product or effective dose) and frequency of exposure to percent reduction in dose and frequency, respectively. Finally, we conducted descriptive quantitative analysis and plotted data points using bar charts. Due to the heterogeneity of outcome metrics, various imaging technologies, and heterogeneous target populations and settings, pooled data were not analyzed using meta-analysis methods.

### Assessment of Quality of Evidence

Two reviewers independently applied the Qualitative Assessment Tool for Quantitative Studies developed by the Effective Public Health Practice Project (EPHPP) to assess the quality of studies [11]. The EPHPP tool and accompanying instruction can be found online (<http://www.ephpp.ca/tools.html>); assessment of the reliability and validity of the tool has been described elsewhere [12]. In brief, the tool consists of eight study-design and risk-of-bias characteristics, six of which are applied to rank studies: (1) selection bias; (2) study design; (3) confounders; (4) blinding; (5) data collection methods; and (6) withdrawal and dropouts.

Following the tool's instructions, reviewers independently responded to detailed guiding questions for each domain, and followed a decision-making algorithm to rate each domain using a three-level ordinal ranking system (weak, moderate, strong), in which weak corresponded to shortcomings in that domain. In aggregate (global rating), reviewers rated studies as strong, if no weak rating was available in the domain level; a rating of moderate was used if only one domain had a weak rating; and a rating of weak was used if two or more domains were rated as weak. Domains with discordant ratings between the two reviewers underwent a reconciliation process to arrive at the final rating.

## RESULTS

From a total of 1,543 unique citations identified from all sources, a total of 16 citations met our eligibility criteria and were included for data extraction. [Figure 1](#) illustrates

the number of citations remaining after each screening step. From 16 included studies, 15 were peer-reviewed manuscripts, and one was a conference poster. Authors from only two of nine studies with missing key data responded to our inquiries. Table 1 contains a summary of included studies. We classified relevant studies into five categories: two (13%) were policy or structural interventions; four (25%) were multipronged; five (31%) were dose-feedback system; four (25%) were provision of training; and one (6%) was a quality-control audit.

Studies were conducted between 1995 and 2014. Twelve (75%) studies were conducted in the United States. Studies utilized interventions to reduce ionizing exposure in the context of various radiologic technologies, including: eight (44%) CT; five (31%) x-ray; three (19%) fluoroscopy; and one (6%) mixed. Most interventions were conducted at the individual level (eleven [69%]); the remaining five (31%) were conducted at the institutional level. Half of the studies (eight) were implemented at academic hospitals; the other settings comprised three (19%) mixed, two (13%) medical practice, and one provider network, one research institute, and one integrated health system.

As summarized in Table 2, the vast majority of studies (ten) used a single-arm pre-post design to assess the effect of interventions, except for three studies with time series, two with only post-intervention data, and one double-arm design. Using the EPHPP quality assessment tool, in aggregate (global rating) only one study was rated as moderate in the three-level system (weak, moderate, strong); the rest were rated as weak. For quality domains

within each study, ratings of strong were rare, and the distribution of the weak rating across various domains was as follows: twelve were selection bias (75%); two were study design (13%); fourteen were confounding (88%); eight were blinding (55%); thirteen were data collection method (81%); and four (25%) were withdrawals and dropouts. Results of individual rating by each reviewer are available from the corresponding author.

Ten studies from four intervention categories reported data that could be transformed to percent dose reduction: *multipronged*: Antypas 2011 [13], Fetterly 2012 [14], Rehani 2012 [15], and Zhang 2012 [16]; *policy and structural*: Lipoti 2008 [17] and Alcaraz 2010 [18]; *dose-feedback system*: Miglioretti 2014 [19] and Wilson 2014 [20]; and *provision of training*: Stein 2010 [21] and Frederick-Dyer 2013 [22] (Figure 2). In general, multipronged programs had a higher range for dose reduction [22% (FSD, Fetterly 2012) [14] to 74% (DAP, Zhang 2012)], followed by policy/structural interventions [37% (Alcaraz 2010) [18] to 50% (Lipoti 2008)] [17]. However, all studies in these two intervention categories used single-arm pre-post design to assess the effect of interventions, except for, Lipoti 2008 (time series). Provision of training yielded a reduction in dose ranging from 20% (Stein 2010) to 35% (Frederick-Dyer 2013) [22]. The range of dose reduction was lower for the dose-feedback system, compared with other interventions [14% (Miglioretti 2014) [19] to 19% (Wilson 2014)] [20]; however, percent reduction for one of these for Miglioretti 2014 [19] represents relative measures adjusted for dose reduction in two control conditions (double-arm study).

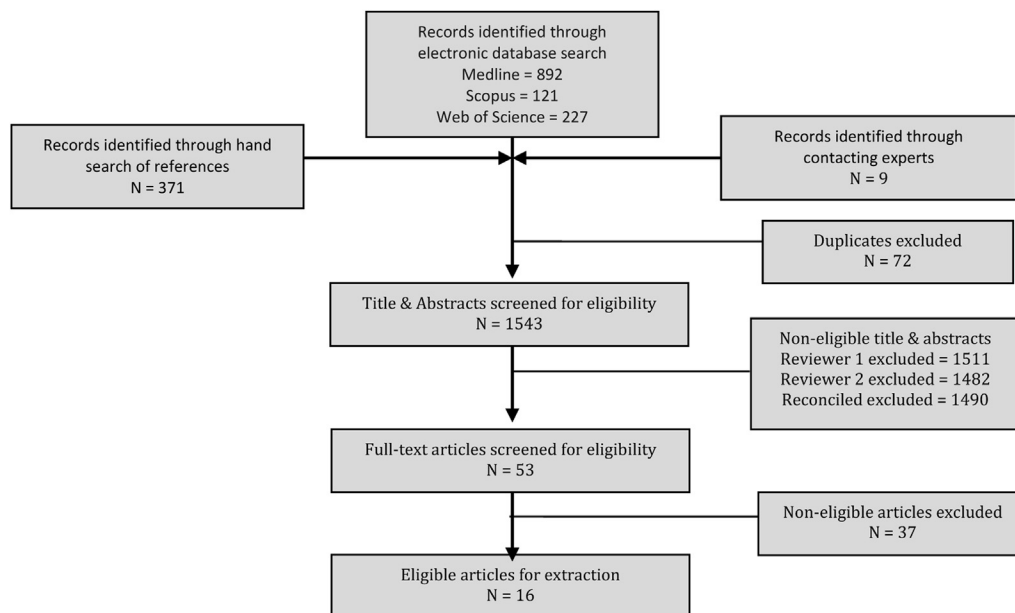


Fig 1. Number of citations by screening step.

Table 1. Summary of Programs Aimed at Lowering the Risk of Ionizing Radiation Exposure From Medical Imaging (n = 16)

Author (Year)	Location & Setting	Study Design (Implementation Year) & Sample Size	Intervention Type and Summary	Intervention Level/Recipient	Technology Type	Outcome Type	Key Findings
Structural level (regulation/policy)							
Alcaraz (2010)	Spain; dental practices	Observational time series (retrospective) (1996-2007) 19,079 radiology reports from 25% total Spanish dental practices	Annual quality control requirement for all Spanish dental practices; to European Union Medical Exposure Directive	Facility/dental practices	X-ray (dental)	Radiation dose (mGy) % reduction	37% reduction in the radiation dose necessary to obtain an image of an upper second molar in normal working conditions from 1996
Lipoti (2008)	United States; hospitals, medical offices, chiropractic offices	Observational time series (1994-2001) 2,667 imaging facilities	Adoption of quality assurance programs for medical diagnostic x-ray installations	Facility/imaging units	X-ray (mixed types)	Entrance skin exposure % reduction	Entrance skin exposure dose reduction for various modalities: chest x-ray 46%, AP lumbar spine 34%, foot x-ray 66% 22% improvement in x-ray quality
Multipronged programs							
Antypas (2011)	United States; hospitals	Experimental, single arm (2010) One institute; 40-60 trial cases	Radiation safety program: no unnecessary CTs, adjust scan parameters, protocol revision, shielding & dose monitoring, computer-based dose modulation software, technologist training	Patients undergoing CT-PE protocol	CT	Radiation dose (dosimetry) % reduction	35% dose reduction by reducing kVp in CTs on patients with BMI < 30 28.4% breast dose reduction with use of Bismuth shields in chest CT 31% thyroid dose reduction with use of Bismuth shield in neck and c-spine CT



Fetterly (2012)	United States; practice based	Observational Single arm (retrospective) 2008-2011) 9,877 coronary angiography procedures	Comprehensive: 6,000 mGy internal reporting, 3,000 mGy reporting, include air-kerma in final report, compulsory fellow training, standardize protocols, reduce fluoro dose and frame rate	Adults undergoing invasive cardiac procedures	Fluoroscopy	Entrance surface air kerma, acquisition skin dose, and fluoroscopy skin dose % reduction	37% reduction in mean entrance surface air kerma 42% reduction in acquisition skin dose 22% reduction in fluoro skin dose 40% reduction in cumulative skin dose over 3 years for all procedures
Rehani (2012)	Syria & Thailand; hospitals	Experimental, single arm (2006-2011) Thailand (9 rooms); Syria (12 rooms)	Comprehensive: survey equipment & technology, utilization of safety practices, frequency reporting high-dose exams, dose level optimization for multiple modalities	Hospitals in Syria and Thailand	Multimodal: CT and x-ray	Entrance surface air kerma % dose reduction	Thailand: 85% dose reduction for chest x-ray; 34% for AP skull x-ray Syria: 20% dose reduction for chest x-ray, 10% for lumbar spine x-ray, 28%-38% for skull x-ray
Zhang (2012)	China; research institute	Experimental, single arm (2004) 100 patients	Comprehensive: complete calibration & adjustment of imaging equipment, reducing exposure field, training for radiographers and patients	Patients referred for routine diagnostic radiography	X-ray	ESD, DAP % dose reduction	65% (Range: 33-79) for ESD 74% (Range: 50-84) for DAP
Dose/exposure feedback system Birnbaum (2008)	United States; community hospitals	Experimental, single arm (post only) (2005-2008) 158 patients	Identification of patients at risk of frequent imaging using specified criteria to reduce # of CTs	Individual patients (who had received >5 CTs)	CT	N/A	54 high-risk patients identified over 3 years, and additional 104 patients identified since the installation of RIS & first helical CT scanner in 1998

(continued)

Table 1. Continued

Author (Year)	Location & Setting	Study Design (Implementation Year) & Sample Size	Intervention Type and Summary	Intervention Level/Recipient	Technology Type	Outcome Type	Key Findings
Duke (2012)	United States; medical centers, imaging centers, multispecialty clinics	Experimental, single arm (post only) (2011) 33,372 patient visits	CT imaging record to track episodes of radiation exposure	Individual ED patients	CT	CT frequency reduction	13.3% reduction in CT frequency (cancelled studies due to discovery of prior images) Low patient compliance (<2%)
Duncan (2013)	United States; hospitals	Experimental, single arm (2008-2012)	Record FT and monthly feedback using patient-based reporting system	Individual patients	Fluoroscopy	Dose metric and FT	Protocol revision resulted in a 2-fold reduction in average exposure per procedure
Miglioretti (2014)	United States; integrated health care system	Experimental, double arm (2010-2011) 3,129 CT studies	Personalized dose audit report; technologist educational seminars on dose reduction strategies Two intervention facilities and one control facility	Individual; imaging technologists	CT	Dose-length product, % reduction	3%-12% dose reduction for abdomen CT 7%-12% dose reduction for head CT (at only one of two intervention facilities)
Wilson (2014)	United States; health care facility	Experimental, single arm (2014) 44,826 total CT studies	Review of detailed CT radiation reports	Providers; radiologists, physicists, and technologists	CT	Effective dose, % reduction	10%-20% dose reduction in chest CT 10%-30% dose reduction in abdomen CT No marked dose reduction in head CT
Provision of training Bussieres (2013)	United States; chiropractic providers	Experimental, time series (2008) 15,000 chiropractors	Web-based dissemination of spine imaging guidelines for chiropractors	Individual; chiropractic providers	X-ray	Spine x-ray frequency reduction	5.26% relative in spine x-ray after guideline dissemination

Frederick-Dyer (2013)	United States; hospitals	Experimental, double arm (2012) 2,545 total exams	Online training modules; physics, biology, radiation safety	Individual; radiology residents	Fluoroscopy	DAP, % dose reduction FT	38% reduction in DAP across all procedures performed by first year residents Significant reductions in FT for barium enema, cystogram, defecogram, and esophagram procedures ( $P < .001$ )
Stein (2010)	United States; hospitals (EDs)	Experimental single arm (2006-2007)	Introducing an imaging algorithm to reduce CT-PE protocol utilization	Individual; ED patients suspected of PE	CT	Effective dose, % reduction CT-PE frequency reduction	Overall 20% dose reduction (34% for age <40 y and 32% for women) 19% frequency reduction
Strother (2013)	United States; hospitals	Experimental, single arm (2009-2012) 358 total CT exams	QI project to educate clinicians and radiologists on ACR recommendations	Individual; referring clinicians and radiologists	CT	CT frequency reduction	54% overall frequency reduction for head CT 14% reduction in CT studies that did not meet ACR criteria (not indicated)
Auditing Hirvonen-Kari (2009)	Finland; academic and community hospitals	Experimental, single arm Single facility	Clinical audit of radiograph quality of diagnostic units	Facility; radiologists and technologists	X-ray (mix types)	Improvement in audited questions and recommendations	66% reduction in quality problems

Note: AP = area product; DAP = dose-area product; ED = emergency department; ESD = entrance surface dose; FT = fluoro time; N/A = not applicable; PE = pulmonary embolism; RIS = radiology information system.

**Table 2.** Quality Assessment of Studies Included in Systematic Review (n = 16)

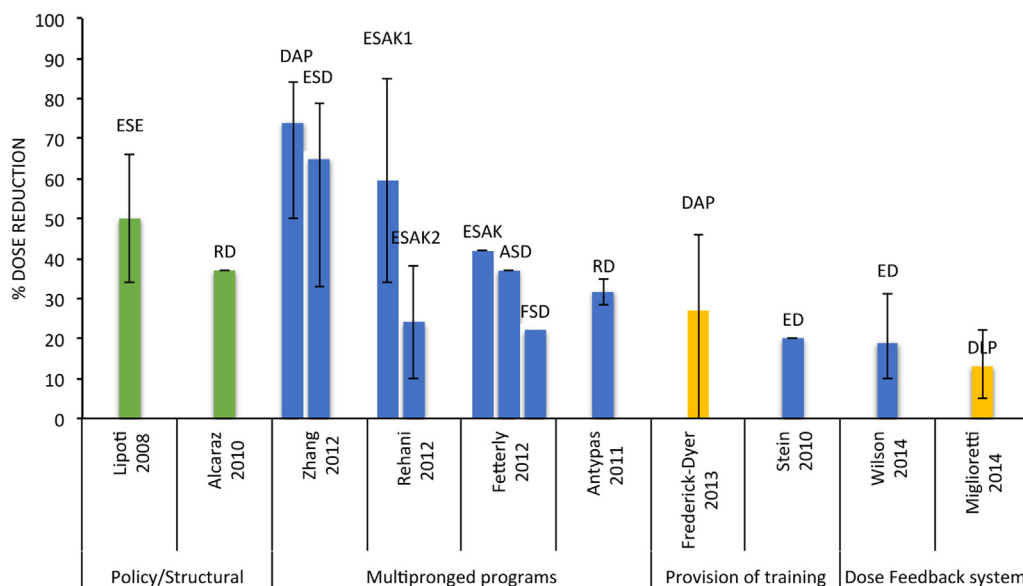
Author/Year	Selection Bias	Study Design	Confounders	Blinding	Data Collection Method	Withdrawals & Dropouts	Global Rating
Alcaraz 2010	Moderate	Moderate	Weak	Moderate	Weak	Moderate	Weak
Lipoti 2008	Strong	Moderate	Weak	Moderate	Weak	Moderate	Weak
Antypas 2011	Weak	Moderate	Weak	Weak	Strong	Moderate	Weak
Fetterly 2012	Weak	Moderate	Weak	Moderate	Weak	Moderate	Weak
Rehani 2012	Moderate	Moderate	Weak	Weak	Strong	Weak	Weak
Zhang 2012	Weak	Moderate	Weak	Moderate	Strong	Moderate	Weak
Birnbaum 2008	Weak	Weak	Weak	Moderate	Weak	Moderate	Weak
Duke 2012	Weak	Weak	Weak	Weak	Weak	Weak	Weak
Duncan 2013	Weak	Moderate	Weak	Moderate	Weak	Moderate	Weak
Miglioretti 2014	Moderate	Moderate	Moderate	Weak	Weak	Weak	Weak
Wilson 2014	Moderate	Moderate	Weak	Weak	Weak	Weak	Weak
Bussieres 2013	Moderate	Moderate	Moderate	Moderate	Weak	Moderate	Moderate
Frederick-Dyer 2013	Weak	Moderate	Weak	Moderate	Weak	Moderate	Weak
Stein 2010	Weak	Moderate	Weak	Weak	Weak	Moderate	Weak
Strother 2013	Weak	Moderate	Weak	Weak	Weak	Moderate	Weak
Hirvonen-Kari 2009	Weak	Moderate	Weak	Weak	Weak	Moderate	Weak

Note: For Global Rating: strong (no weak ratings); moderate (one weak rating); weak (two or more weak ratings). Ranking direction: weak corresponds to shortcomings in study design and higher risk of bias.

Four studies reported on radiation frequency reduction, one in the “dose-feedback system” category Duke 2012 [23], and three in the “provision of training” category Bussieres 2013 [24]. Stein 2010 [21], and Strother 2013 [25] (Figure 3). Studies were heterogeneous in terms of outcome metrics, study design, and technology used. The

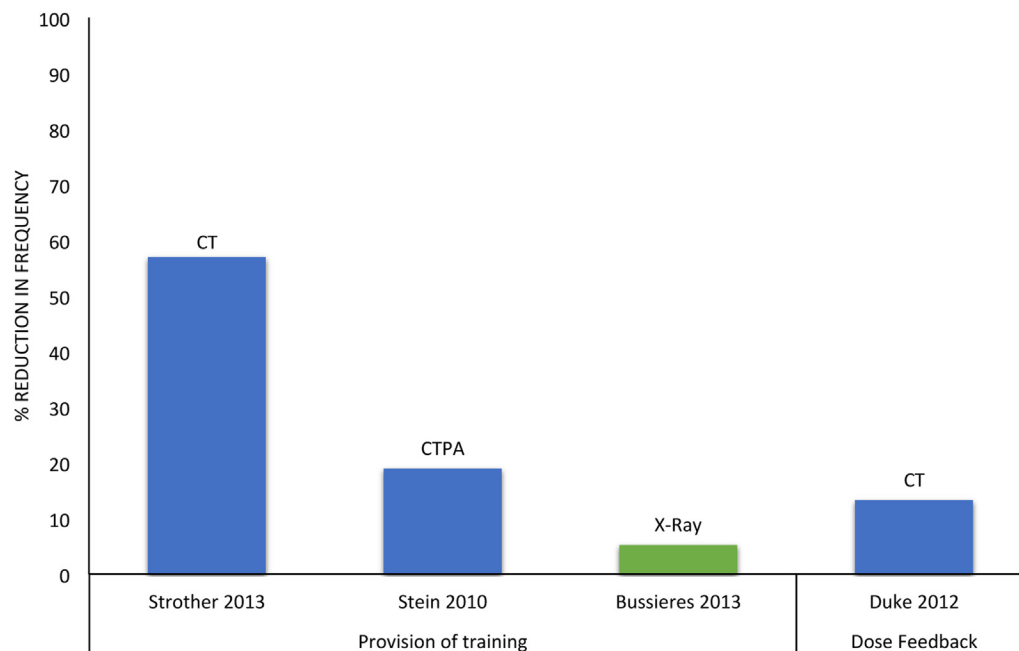
range of frequency reduction varied from 5.25% (Bussieres 2013, double arm) to 57% (Strother 2013).

Additional extracted citations included: Birnbaum 2008 [26] and Duncan 2013 [27] which utilized a dose-feedback system to identify patients at risk of increased radiation exposure for CT and fluoroscopy, respectively, and Hirvonen-Kari 2009 [28] that employed



**Fig 2.** Percent reduction in radiation dose by intervention type (n = 10). Blue (single arm); green (time series); orange (double arm). Uncertainty lines represent range of dose reduction, and heights of bars with uncertainty lines represent midpoint or average. ESAK1 is from Thailand; ESAK2 is from Syria. ASD = acquisition skin dose; CSD = cumulative skin dose; DAP = dose area product; DLP = dose length product; ED = exposure dose; ESAK = entrance surface air kerma; ESD = entrance surface dose; FSD = fluoroscopy skin dose; FT = fluoroscopy time; ESE = entrance skin exposure; EAK = entrance air kerma rate.





**Fig 3.** Percent reduction in frequency of radiology exams by intervention type (n = 4). *Blue* (single arm); *green* (time series); CT = computed tomography; CTPA = CT pulmonary angiogram.

a clinical audit of x-ray units to improve diagnostic quality (Tables 1 and 2).

## DISCUSSION

Studies included in this systematic review represent a cross-section of efforts across various populations, health care and geographic settings, provider roles, imaging modalities, and intervention types, to reduce ionizing radiation from medical imaging. Outcome measures were equally diverse, and generally could be classified into two broad categories: percent dose reduction and exam frequency reduction.

In sum, all studies included in the review were effective in reducing radiation dose, exam frequency, or both, to some extent. Multipronged programs produced overall superior results, as the programs combined various interventions, including reductions in unnecessary exams, individual education and training, evaluation and modification of technical protocols, and dose reporting and monitoring. Studies that isolated only one of these techniques seem to be less effective. However, although multipronged interventions seem to provide a relatively large effect size, which intervention component might have contributed most is unclear. Online training, although it demonstrates a modest effect size, is a relatively easy and inexpensive intervention that can be tested in larger trials.

These studies have several limitations: Many lacked proper controls or sufficient power, leaving the possibility of confounding variables. In respect to quality of evidence,

only one study was rated as moderate, and the rest as low. For example, Miglioretti et al studied the effect of providing radiology technologists with dose audit feedback on CT examinations. However, baseline characteristics, of both technologists and patients, were dissimilar between the intervention and control arms. Duke et al studied the effect of a patient CT dose record, which showed good results, but very low patient compliance (2%).

An additional limitation is the wide variability regarding measurement of radiation exposure (eg, dose-length product versus effective dose) and reporting of outcomes. Finally, external validity and applicability of findings reported in this review are limited, as more than half of studies were implemented in academic/research settings, which may be different than community facilities, to measure and implement dose-reduction practices. Furthermore, quality of data reporting, as distinct from quality of evidence, was poor for some studies, particularly studies in the “provision of training” category, and most did not report at least one key methodologic finding.

These drawbacks limit applicability of these studies to inform research practice and policy. Note that studies that focused on mechanical or technologic advances and the superiority or equivalency of one radiology technology compared with another were excluded, as they were outside the scope of this article, which aimed to review policy-level interventions. Studies that were identified and excluded on these criteria are available as a [supplemental list](#). Recent

technologic advances in CT, such as tube current modulation, automatic exposure control, and iterative reconstruction techniques, have successfully reduced patient dose and are often routinely used [29].

Only two studies were identified that were specifically designed to assess the effect of macro-level policy changes on radiation reduction, and only one was conducted in the United States. Given the previously discussed rapid rise of the use of diagnostic medical imaging in the United States, a more thorough investigation of the efficacy of state and federal guidelines to limit exposure is warranted to assess their impact. However, our systematic review produced two non—peer-reviewed reports from the United Kingdom that review recent trends in CT [30] and x-ray/fluoroscopy [31] patient doses, in the context of national reference standards utilized as patient quality and safety tools.

These national standards may be viewed as macro-level policy, and the resultant trend data are worthy of mention here. For x-ray, survey data were collected between January 2006 and December 2010, at 320 hospitals throughout the United Kingdom, representing one quarter of all hospitals with diagnostic x-ray facilities. On average, reference doses reported in the 2010 survey were approximately 10% lower than corresponding doses in the previous 2005 survey, and approximately one half that in the original survey from the mid-1980s [31].

For CT, dose details on some 47,000 individual patients, representing approximately one third of all United Kingdom CT scanners, were surveyed. In contrast to x-ray, dose levels (determined primarily by dose-length product) were relatively stable (within 10%), compared with prior reviews or national practice, and they actually represented an increase compared with 2003 (increases of approximately 20% for CT dose index volume, and 40% for dose-length product). These United Kingdom survey data provide an approximate benchmark by which to assess future macro-level policy in the United States, should national- or state-level benchmarks be developed and measured.

Overall, data represented in this systematic review reflect the heterogeneity in reporting of patient dose for various ionizing procedures, the varied nature of interventions utilized in dose reduction, and the spectrum of trend data available in peer-reviewed and gray literature. Highlighted in this review is the general effectiveness of multipronged programs for dose reduction, and the noticeable lack of national reference standards and consistency of dose reporting in the United States. Furthermore, this review illuminates the disperse nature and low quality of existing evidence, further emphasizing the need for patient quality and safety standards,

and research on the most effective methods to reduce exposure and prevent harm related to ionizing radiation dose.

## TAKE-HOME POINTS

- Patient exposure to ionizing radiation from medical imaging has expanded greatly in the past three decades, prompting institutional, state, and federal policy interventions to protect patients from potential unwanted carcinogenic harms.
- The nature of interventions is broad, and includes policy/structural interventions, dose-feedback systems, provision of training for medical professionals, quality control audits, and multi-pronged approaches.
- Existing evidence on the effectiveness of policies aimed at reducing patient radiation dose is disperse and low in quality. Compared to other approaches, multi-pronged efforts may offer more patient protection.
- There is a lack of national reference standards and consistency in radiation dose reporting, emphasizing the need for patient quality and safety standards, and research on the most effective methods to reduce exposure and prevent harm due to medical ionizing radiation.

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## ADDITIONAL RESOURCES

Additional resources can be found online at: <http://dx.doi.org/10.1016/j.jacr.2015.06.033>

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