

**Department of Health and Human Services
National Institute of Environmental Health Sciences
National Cancer Institute**

**Minutes of the State-of-the-Science Subcommittee of the Interagency Breast Cancer and
Environmental Research Coordinating Committee**

March 29, 2011

The State-of-the-Science (SOS) Subcommittee of the Interagency Breast Cancer and Environmental Research Coordinating Committee was convened for a meeting on March 29, 2011 at 4:00 p.m. via conference call. The Chair of the subcommittee is Michele Forman, PhD of the University of Texas M.D. Anderson Cancer Center.

Subcommittee Members Present

Christine Ambrosone, PhD

Janice Barlow

Suzanne Fenton, PhD

Michele Forman, PhD

Sandra Haslam, PhD

Neeraja Sathyamoorthy, PhD

Vivian Pinn, MD

NIH Staff Present

Jennifer Collins, MR

I. BACKGROUND

The Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC) is a congressionally mandated body established by the National Institute of Environmental Health Sciences (NIEHS), in collaboration with the National Cancer Institute (NCI). This Committee is comprised of 19 voting members, including representatives of Federal agencies; non-federal scientists, physicians, and other health professionals from clinical, basic, and public health sciences; and advocates for individuals with breast cancer.

The Committee's primary mission is to facilitate the efficient and effective exchange of information on breast cancer research activities among the member agencies, and to advise the NIH and other Federal agencies in the solicitation of proposals for collaborative, multidisciplinary research, including proposals to further evaluate environmental and genomic factors that may be related to the etiology of breast cancer. The Committee serves as a forum and assists in increasing public understanding of the member agencies' activities, programs, policies, and research, and in bringing important matters of interest forward for discussion.

The objectives of the SOS Subcommittee of the IBCERCC are integrated and dependent on the objectives and activities of the other Subcommittees¹ of the IBCERCC and include the following: to summarize the state of the literature (both animal and human research); advances in breast cancer research supported or conducted by Federal agencies relevant to the diagnosis, prevention, and treatment of cancer (and related disorders); and identify research gaps.

The IBCERCC SOS Subcommittee held its second meeting, hosted by NIEHS and the NCI, via webinar on March 29, 2011. Attendees of the meeting included committee members and NIH staff. The meeting agenda included discussion on the following: progress since the last meeting and next steps in addressing the Committee's mandate through the work of this Subcommittee.

II. Discussion

Michele began by reviewing the activities that have happened since the last meeting:

1. A subset of members discussed the criteria for identifying articles for review. They agreed that they would begin with an introduction describing known genetic and environmental risk factors. They would also evaluate the strength of the literature (QC) presented.
2. Members uploaded three "best" review articles regarding breast cancer and the environment to the SharePoint to be used as a "starter pack" for this group. Some individuals are still experiencing issues accessing the SharePoint. Jenny will continue to try and help resolve these issues. She will confirm whether Cheryl Walker is having the same problem as Michele – this will confirm whether it is a firewall/security issue on the MD Anderson side.
3. The Subcommittee members then split into smaller groups to work on the state-of-the-science in the animal research (Sue and Sandy) and epidemiological studies (Christine and Michele).

Sue presented the outline that she has developed with Sandy. They used two sources as they created this outline: a paper that will be coming out very soon in EHP² and the 2007 supplement to *Cancer* by Rudel et al.³

1. Issue of how to identify chemical in environment affecting the breast
 - a. 80,000+ chemicals on market and only 1-2% tested
 - b. Out of 2000+ chemicals tested, 216 affected breast
 - c. Chemicals on market and BC rates still rising
2. Animals as a relevant model for breast cancer research
 - a. Similarity of human and rodent mammary gland – post birth growth

¹ The other Subcommittees of the IBCERCC are the Research Process Subcommittee (Chair, Michael Gould) and the Research Translation, Dissemination, and Policy Implications Subcommittee (Chair, Jeanne Rizzo).

² Environmental Exposures and Mammary Gland Development: State of the Science, Public Health Implications, and Research Recommendations. Ruthann A. Rudel, Suzanne E. Fenton, Janet M. Ackerman, Susan Y. Euling, Susan L. Makris. *Environmental Health Perspectives*. In press, 2011.

³ Chemicals Causing Mammary Gland Tumors in Animals Signal New Directions for Epidemiology, Chemicals Testing, and Risk Assessment for Breast Cancer Prevention. Ruthann A. Rudel, Kathleen R. Attfield, Jessica N. Schifano, and Julia Green Brody. *Cancer*, 2007.

- b. Hormonal and growth factor regulation
 - c. Structures in puberty and pregnancy similar
 - d. Interaction of epithelium and stroma
 - e. Where do the differences lay – limitations?
- 3. Search for carcinogens
 - a. Define carcinogen – based on mutagenicity or initiation event
 - b. How measured?
- 4. NTP research focused on finding carcinogens
 - a. Info about the testing paradigm used
 - b. Small number of carcinogens identified and not all mammary gland (Rudel et al., 2007)
 - c. Problem – mammary gland not always evaluated; defining what effects on mammary gland are relevant (issue of fibroadenomas)
 - d. Bigger problem- potential for false negatives
 - e. Strain/species issues
 - i. Rat vs. mouse
 - ii. Some strains inappropriate
 - iii. Inbred/outbred
 - iv. More than one strain/species should be tested
- 5. Critical periods of development
 - a. In utero and neonatal – alter development
 - b. Puberty – alter timing and BC suscept.
 - c. Pregnancy – affect lactation and child MG devel; may alter protective effect of pregnancy
 - d. Affect lifelong susceptibility
 - e. Several chemicals ID'd that affect mammary gland development (Rudel et al., 2011)
- 6. New lines of investigation – lifelong susceptibility changes
 - a. Endocrine disruption (can affect any local or systemic mechanism that regulates mammary gland development and function; hormones other than estrogen, growth factors, inflammatory processes)
 - i. Not carcinogenic
 - ii. Stage specific effects
 - iii. Estrogenic effects over emphasized
 - iv. May change lifelong sensitivity to another 'hit'
 - v. Examples of mammary gland as the most sensitive end point assessed (Rudel et al., 2011)
 - b. Developmental reprogramming
 - i. Early life exposures change course of tissue for life
 - ii. Altered receptor and/or stem cell populations; alters other organs and/or tissues that impact mammary gland development (ovary, pituitary, adrenal, immune etc)
 - iii. Methylation changes (epigenetics)
 - c. How are adverse effects defined – new sentinel events for cancer susceptibility?
 - i. Development – permanent effects
 - ii. Lactation impairment

- iii. Hyperplasia/neoplasia – early events
- 7. How to move forward?
 - a. Better testing – changes in 2011 in NTP
 - b. TSCA reform - need to know more about chems before they hit market
 - c. Develop the NCI website on carcinogens - needs an update
 - d. Urgent need for better understanding of reprogramming following early life exposures
 - e. Translational type studies – NIEHS BCERP as example.

The group briefly discussed whether breast cancer rates are actually decreasing. Sandy explained that this decrease is attributable to the reduced usage of combined HRT. Vivian directed attention to an article that recently came out showing that the rates are not decreasing in African Americans⁴. The group agreed that the most up-to-date information should be presented in the report regarding this issue.

Sue suggested that the group needs to be specific about the limitations in rodents because these will be key research gaps. She also felt that it would be useful to describe what the paradigm for testing used to look like because it is not the same now as it was in the last 40 years.

Michele brought forward the need for intermediate markers of exposure in animals and suggested that this point be brought forward in the evaluation of the research areas.

Sandy explained that there is a huge emphasis on using the mouse model, but in fact the rat is probably more relevant. There is a real resistance to publish studies in the rat because of the investment in existing mouse models. This could be another research gap.

In the humans, there is a long *in utero* experience and a long window before puberty. Michele suggested that we provide a chronology for the critical periods of development in which we pinpoint the analogies between the animal and human because this is an underappreciated area. We might want to do a fair bit of work contrasting human/animal in windows of development. Sue has reviews that she has recently written in this area. She explained that there has not been a lot done in humans in the last 30 years – a lot of what we know about human breast development is mainly from the 50's and 60's. Michele was actually referring to the rate of linear growth in girls and referenced a study in Denmark by Mads Melbye et al. where the greatest risk was for girls with high linear growth in ages 5-7.

Sandy said that the same markers are not readily measureable in animals. This is why Michele thought that the table would be useful. We can contrast and show the similarities.

The group discussed the use of inbred vs. outbred strains. Sandy explained that thinking in the context of human genetic heterogeneity, when you use outbred strains you can lose sensitivity to effects. You will average out potential effects due to those in the population that are not affected. This does not happen when you use inbred strains and you can still assess different

⁴ Breast cancer incidence rates in US women are no longer declining. Carol De Santis, Nadia Howlader, Kathleen A. Cronin, and Ahmedin Jemal. *Cancer Epidemiology, Biomarkers & Prevention*, 2011.

genetic background effects. According to Sue, most studies are done on outbred strains because they want to reflect the heterogeneity in the human population.

The group then discussed the epidemiology outline prepared and presented by Michele and Christine. They used two main review articles: the 2010 State-of-the-Evidence Report from the Breast Cancer Fund⁵ and the 2007 epidemiologic review article by Brody et al.⁶

1. Short introduction regarding what is known about the environment and breast cancer etiology
 - a. Known risk factors (% BC explained)
 - i. Ages at 1st birth, at menarche, at menopause
 - ii. Parity
 - iii. HRT
 - iv. Radiation
 - v. BMI
 - vi. Physical activity
 - b. Genetic factors
 - i. High penetrance genes (BRCA, ATM, etc.)
 - ii. Common variants
 - c. Other factors without consistent association (diet, etc.)
2. Environmental exposures
 - a. Challenges in assessment
 - b. Exposures identified
 - c. Those not assessed so far
 - d. Where do we go from here

Christine listed the criteria that should be considered during review: study design, sample size, laboratory procedures, data analysis, control for confounding, and modeling. She also described some of the issues in exposure assessment including: exposures at work, home, when traveling, and over the life course including windows of susceptibility.

The Brody paper covered organochlorines (PCBs, dioxins, DDT), other pesticides, herbicides, PAHs, drinking water byproducts, solvents, general occupational studies, but it did not address radiation, EMFs, cosmetics (nail products), deodorant, hair products, household products, food packaging materials, sunscreen, diet, etc. The Gray document covered some of those not addressed by Brody.

Michele provided a list of exposures brought forward by the Research Process Subcommittee. Jenny explained that the list was generated from an NIEHS portfolio analysis that went back 15 years in preparation for the September 2010 inaugural meeting.

⁵ <http://www.breastcancerfund.org/assets/pdfs/publications/state-of-the-evidence-2010.pdf>

⁶ Environmental pollutants and breast cancer: epidemiologic studies. Brody JG, Moysich KB, Humblet O, Attfield KR, Beehler GP, Rudel RA. *Cancer*, 2007.

Christine spent time explaining some of the reasons why clear relationships between exposures and disease are seen in animals, but not in humans including combinations of effects, laboratory procedures (biomarker measurements), heterogeneity in tumors (subtypes), heterogeneity in populations (subtypes), genetic susceptibility, and competing risk factors of a protective nature that attenuate risk estimates.

Christine asked whether we should consider clinical exposures – if we include clinical exposures then we should include smoking.

Sandy asked if we are going to make a distinction between what we are voluntarily/involuntarily exposed to. We agreed make a distinction between the nature of the exposure i.e. include voluntary and involuntary.

How do we handle birth control and evolving birth control because some forms of birth control replicate HRT? Bioidentical hormones need to be addressed and considered an area of exposures that are evolving that have not been previously considered. We should also include treatments for hot flashes, etc. If we consider EDCs, then it is difficult to exclude exogenous hormones. The group agreed that this area should be added to “gaps”.

Sue asked if we know the mechanisms for how some EDCs cause endocrine disruption in humans. In a population of humans that have high levels of a given EDC can we use the NHANES to run tests for biomarker assessment (hormone levels)? We should be making better use of the NHANES data. Sue proposed that if we better understood exposures in children then we could potentially understand shifts in pubertal timing or increased risks of cancer in adulthood.

The group then discussed whether the available epidemiological consortia (Cohort and the Case/Control consortia) have been underused to this point. Christine pointed out that the issue is not underutilization, but rather it is really a feasibility issue (referencing the Nurses’ Health Study samples). Many of the chemicals are not lipophilic and may not remain in specimen. Sandy suggested that data collection is happening at the wrong time (in adults) – not when the timing of exposure is critical. The group agreed that this was another gap for consideration. The group could recommend the identification of critical periods and then call for agencies to indicate whether there are studies in these areas and determine what resources are available from them.

Michele asked whether it would be more useful to develop a matrix of animal and human studies to put this all together including some criteria for level of evidence/quality of the research to put all animal/epi studies together or is it better to have an animal chapter, a human chapter, and a chapter that puts together a series of recommendation.

Sandy suggested that all we can do is to identify the criteria for level of evidence that were used in each of the reports. The group did not want to spend a lot of time developing weight of evidence, but thought that they could address what differences exist between criteria used in various reports. The group can make recommendations about criteria. It is more important to move forward and identify gaps and what recommendation would be.

Other considerations discussed included natural experiments that have occurred (Japan at Hiroshima and now) and older longitudinal studies.

The group discussed other issues including the committee's mandate to address advances in prevention, diagnosis, and treatment of breast cancer. The group agreed that progress was a more appropriate term instead of advances and discussed limiting to the last 10 years.

One advance discussed was the identification of the intrinsic breast cancer subtypes. Janice sent around a paper by Lisa Carey about biological advances in the last 10 years. This paper focused on the subtypes. Sandy suggested that it addressed diagnosis and direction of treatment, not advances in treatment or prevention.

Prevention strategies for high risk women include use of SERMS i.e. tamoxifen and aromatase inhibitors. These act like a chemoprevention. Christine made the point that it depends on what you mean by prevention. It starts with epidemiology and what causes breast cancer. We know that physical activity reduces risk and alcohol increases risk (and maybe cruciferous vegetables – as per Michele, diet has been varied enough to determine this). How do you get people to act on this information? People don't want to consider this prevention – they want something like a pill before they consider it as prevention. Dissemination/translation of epidemiological finding to the community is a big issue and a clear gap. This is tied in to the third subcommittee.

Diagnosis has been approved with imaging technologies and subgroup identification. What are major improvements in treatment? There should be a least a paragraph on this.

Michele wanted to get some agreement on the exposures to focus on – we are a limited group with limited amount of time to do this. She suggested that we use examples of some of the information on chemicals that we already know about such as dioxin and DDT. Dioxin is carcinogen, but DDT is not necessarily considered a carcinogen. We could use as examples and then focus on the gaps in these areas. We should coordinate examples and share them with each other and then address the gaps.

Action Items

- Jenny will continue to try and help resolve these issues. She will confirm whether Cheryl Walker is having the same problem as Michele – this will confirm whether it is a firewall/security issue on the MD Anderson side.
- Janice will begin developing a paragraph for the progress (advances) section.
- Both the epi and animal research groups will flesh out their agendas.
- Everyone will revisit the strategy of this group with the goal of identifying gaps and new approaches.
- Jenny will schedule additional calls from May – September and send the group a listing of confirmed meetings. She will also find out what is involved in canceling a meeting that has been advertised in the Federal Register if it is not needed.

III. Adjournment

The meeting adjourned at 5:45 p.m. on March 29, 2011.

CERTIFICATION

I hereby certify that, to the best of my knowledge, the foregoing minutes and attachments are accurate and complete.

/Michele Forman/

Michele Forman, PhD

Chairperson

State-of-the-Science Subcommittee

Interagency Breast Cancer & Environmental Research Coordinating Committee

/Gwen W. Collman/

Gwen W. Collman, PhD

Executive Secretary

Research Process Subcommittee

Interagency Breast Cancer & Environmental Research Coordinating Committee

Proper signatures

Treat as signed, § 1.4(d)(2)