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

May 10, 2011

The State-of-the-Science (SOS) Subcommittee of the Interagency Breast Cancer and Environmental Research Coordinating Committee was convened for a meeting on May 10, 2011 at 12:00 p.m. EDT 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
Janice Barlow  
Suzanne Fenton, PhD  
Michele Forman, PhD  
Sandra Haslam, PhD  
Neeraja Sathyamoorthy, PhD

NIH Staff Present
Jennifer Collins, MR  
Laura McGuinn, MPH

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 Subcommittees\(^1\) 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 fourth meeting, hosted by NIEHS and the NCI, via webinar on May 10, 2011. Attendees of the meeting included committee members and NIH staff. The meeting

\(^1\)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).
agenda included discussion on the following: progress since the last meeting and preparation for the May 12-13, 2011 in-person meeting.

II. Discussion

Michele welcomed everyone to the call and said that the main focus of the meeting was to review and provide updates from animal/human research groups and advances and a discussion of key questions (including those that have been a barrier to moving forward). We also need to talk about the slides for the meeting.

Sue Fenton went over current status of animal research. Sandy and Sue have completed a first draft of their chapter. She presented an outline of material:

BC and the Environment – Animal Studies:

1. Utility of Animal Research
   a. What has been learned – gland development and similarities/differences among species.
   b. Carcinogenicity testing
      i. Carcinogen defined
      ii. Carcinogenicity study models

2. Animals as a relevant model for breast cancer research
   a. Similarity of human and rodent mammary gland
   b. Where do the differences lie – limitations
   c. Hormone and growth factor regulation of growth – across species
   d. Inbred/outbred models

3. Chemicals in the environment
   a. Poor tests available
   b. What is known to date?
   c. How to improve – study types and changes to be made.

4. New lines of research
   a. What are EDCs – not carcinogens
   b. Focus on critical windows of development
   c. Fetal programming and multiple generation
   d. Several chemicals ID’d that affect mammary gland development (Rudel et al., 2011)
      i. Estrogenic compounds (pharmaceuticals, phytoestrogens, etc.)
      ii. Pesticides
      iii. Other manufactured chemicals
      iv. Others

5. Moving forward
   a. Better testing of chemicals and various routes and timing of exposures – changes in 2011 in NTP
   b. Need to consider new mechanisms of exogenous hormone exposure (sustained birth control treatment, bioidentical menopausal HRT)
   c. TSCA reform - need to know more about chems before they hit market
   d. Develop the NCI website on carcinogens - needs an update
   e. Urgent need for better understanding of reprogramming following early life exposures
   f. Translational type studies – NIEHS BCERP as example where epidemiological and animal studies are carried out in collaboration to identify exposures in humans, test the effects of the exposures in animal models of mammary development and carcinogenesis and identify potential biomarkers of exposure susceptibility in humans.

6. Important Gaps in our Knowledge:
   a. Animal studies:
      i. Need to define appropriate species and strains for interpretable research.
ii. Should require inclusion of mammary endpoints for federally-funded screening and testing guideline studies in which there is a developmental or critical windows exposure.

iii. Require testing of "grandfathered" and new chemicals entering the market for effects on mammary tissue or cells.

iv. Define cell types (or structures) and signaling events that are altered following exposure to environmental factors during critical periods of growth and development (pre-natal, post-natal, puberty, pregnancy, post pregnancy, peri-menopause), that eventually lead to increased breast cancer risk.

b. Humans (and rodents):
   i. What are the specific physical, chemical, hormonal, and lifestyle exposures that are detrimental and increase breast cancer risk?
   ii. Need to identify and track who was exposed and when (need for time-specific exposure biomarkers). What are children highly exposed to? Add this data to National Health Report.
   iii. Understanding gene environment interactions; impact of genetic background and identity of specific genes involved.
   iv. Need to identify target organs and cells that mediate detrimental effects of environmental exposures.
   v. Need to identify impact of multiple exposures and mixtures of exposures.
   vi. Inadequate testing of chemicals for specific effects on mammary gland development and function.
   vii. Need to define underlying mechanisms of detrimental environmental exposures.

The group discussed mammographic density. Sue reported that to her knowledge there currently is not a model for this (at least not a good one). Sandy said that there is a possibility because MRI can be done on rodents and the rat model has connective and adipose tissue similar to the human breast. She did not feel that anyone has asked this question. Michele said that this is a major risk factor and she felt that if we could identify an appropriate rodent model to measure mammographic density then we could potentially detect differences following environmental exposures (could serve as a biomarker). Sandy said that we need to define what is meant by mammographic density. It has mostly been usual after menopause. It was acknowledged that this could not likely be used across the early periods of a woman’s life, but can be used post-menopause. It may also be possible to extrapolate data to earlier in life exposures. We need to tease out an understanding of exactly what breast density really is and we need the technology to do this. Neeraja reported that there is work going on in this area in the human breast. She will send more information. Sandy asked the group if mammographic density is simply an issue of reduced ability to detect. Michele did not think this was the case. She reported that it is familial and a high risk factor. Sue said that we need to think about this in the context of mammary gland microenvironment (changes in cell ratios in the mammary gland). The consensus was that this is a rich area for research.

Michele reported that she has been working with Laura on the state of the science in human epidemiology chapter. Michele presented the strategy for epidemiology review. They have initially focused on incidence and exposure to carcinogens and promoters. They began with summary articles in 2007 and identified the resources including organizations that might have been sponsored reviews and they set criteria for which reviews to use. The reviewed studies since 2007 from both the quantitative and qualitative literature and set criteria based on the following parameters:

- Design
- Sample size
- Methods: Data and biospecimen collection; Lab analysis; Data analysis; Confounders;
- Results
• Contributions
• Limitations

The general outline was presented:

**BC and the Environment – Human Epidemiology Studies:**

1. **Known risk factors**
   a. Identification of known environmental exposures
      i. By source
      ii. Not tested or identified
   b. Critical windows of susceptibility across the life course (Michele presented a table of
      Integrated child-life stage for NICHD pediatric terminology as mapped to existing
      medical terminologies that demonstrated the complexity of this)
      i. Infancy – period of weight gain & age at puberty
      ii. Childhood – linear growth & age at menarche/BC risk
   c. Kinetics of exposure
      i. Persistence
      ii. Dosage
      iii. Intra and inter-individual variation in exposure
   d. Methodologic issues
      i. Exposure assessments
         1. Self-reported – v. inconsistent findings
         2. Blood values - variable laboratory procedures and handling/prep of specimens
      ii. Exposure validation
         1. Optimal:
         2. Soil to biospecimen correlation; biospecimen to hormone correlation
         3. Household biospecimen and BC risk
         4. Requires knowledge of critical period of exposure
      iii. Models of data analysis
         1. Sample size limitations
         2. Multiple comparisons
         3. Inadequate adjustment for confounders

2. **Gaps**
3. **How do we move forward?** Interface of and collaboration of animal and human research.

The groups appear to be on the same paths. The two chapters will be mirror-image like. We are still stymied by the definition of environment and what we mean by estrogenic, etc. Sandy thought that we were still very estrogen-centric.

Michele also thought that we are talking about critical WOS and she sees all phases of the life cycle as a critical window that might be best identified by which exposures influence what dynamics of development. For example, if weight gain in infancy, then which exposures have an influence on weight gain/puberty/menarche association?

Sue said that we should look for opportunities to get extra samples from ongoing studies. Michele proposed a call for us being very directive of NCS. We could take a subsample of NHANES and then a NCS sub-cohort and then think about the optimal design of the sub-cohorts, what kind of exposure assessments would we want to conduct and how do we want to validate them and then see if there is replication.

Sandy asked how we going to overcome averaging out effects in human studies. She also said that racial ethnicity issues are missing in the SOS. This was noted as a gap.
Janice did not have an update on the summary of advances. She has reached out but has not received any direction. Is the identification of the subtypes really an advance? She thought that we could include a glossary of subtypes or even a type like the one in the New England Journal of Medicine. Janice needs more support in this area of the report. The timeline discussed just covered treatment.

Michele reviewed her draft presentation for May 12. She will list the subcommittee members, restate the objectives of the SOS, describe the scope of the SOS, review the delegation of activities, and present a timeline.

Michele asked Sue/Sandy which criteria would be used for the animal. They will specify their criteria in their section.

Sandy noted that the slide on progress was missing reduced HRT as preventative agent.

Information regarding intrinsic subtypes in animal models is needed. Knockouts are created and then not placed in the context of subtypes.

Michele asked if there were overall questions/areas for clarification from this group to the larger Committee. The group listed the following:
- Definition of environment
- Definition of mammographic density
- Definition of stroma
- Clarifying what constitutes an advance/progress (the group thought it would be good to understand how clinicians and breast cancer survivors define an advance – Janice suggested that advocates look at from the perspective of advances in treatment because it has the most impact on them directly)
- Are the issues of exposure validation so vast that we are not ready to make recommendations for translation?
  - Concept of precautionary principle - we need to be less stringent as had been done in other countries.
  - We could have an IACR-like set of standards that can be met that leads us to the precautionary principle. They do not rely totally on epidemiological evidence. Once you get sufficient evidence (certainty) in animals, why not then adopt the precautionary principle. This would be one way to deal with the enormous complexity/challenge.
  - Inadequate testing to get to a precautionary principle.
  - There are two definition of precautionary principle. Birnbaum disagrees with the very broad definition. She feels that it must be based on scientific evidence. We could lean towards the more stringent one based on animal research.

We need to develop the exposure validation procedure – especially when thinking about mixtures. One thing to consider is potential biomarkers. You might not be able to measure the actual exposure, but you can measure the biomarker.

There is already a preponderance of descriptive studies. There needs to be more mechanistic studies. We need to get to the next level.

Everyone will edit their slides based on the discussion today. Michele will do overview and then present epidemiology. Sue will present animal and then they will close with presenting integrated human/animal gaps.
III. Adjournment

The meeting adjourned at 2:00 on May 10, 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)