IOM Report on Breast Cancer and the Environment

CHE Breast Cancer Call

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Critical Roles of Animal Models in BC Research

- Providing solid evidence for early life ‘stages’ or ‘windows’ of susceptibility or sensitivity to environmental risk factors (genistein, steroids, BPA, dioxin)
- Understanding the importance of protecting the rapidly dividing duct ends from further environmental exposures (carcinogen-induced models)
- Defining the role of steroid hormones in development, regulation and dysregulation of breast cells (epithelia, stroma, fat, immune)

Recommendation 8

The research and testing communities should pursue a concerted and collaborative effort across a range of relevant disciplines to determine optimal whole-animal bioassay protocols for detection and evaluation of chemicals that potentially increase the risk of human breast cancer.

- Even though much of the media portrayed this report as 'limited evidence' for the role of the environment in breast cancer, the Silent Spring perspectives statement (see their website) got it right. They suggest a 'desperate need' for increased testing of the over 86,000+ chemicals on the U.S. market and improvements to the Toxic Substances Control Act (TSCA) that will enable risk assessors to act on the mounting evidence of the environment in breast cancer risk.
- NTP changes were implemented in 2010 to include early life chemical exposures, responsive strain of rat, and more relevant dosing strategies
- Current NTP studies that include early life exposures are collecting mammary gland whole mounts – addresses issue raised on page 199 that developmental assessment, evidence for endocrine disruption, functional consequences and late life outcomes need to be examined in concert
  - "The degree to which changes in mammary structure that result from early exposures signal increased sensitivity to mammary tumor development is an area for study to increase the usefulness of these assays for detecting potential breast carcinogens."
- Role of environment for altered breast developmental timing did not receive enough attention. What role does this significant developmental timing shift in girls of all ethnicities have in the current high incidence of breast cancer?

Recommendation 8 (cont.)

The need for '**concerted and collaborative effort across a range of relevant disciplines'** is not happening at all government agencies.

POSITIVE:

- The NTP and a branch of the FDA – the NCTR (National Center for Toxicology Research) have been working in conjunction for many years now to evaluate the effects of chemicals on mammary tissue (genistein, ethinyl estradiol, BPA)
- The NIEHS and NCI (and Avon in the past) have funded the Breast Cancer and the Environment Research Program – outreach, epidemiology, and animal biology specialists working in collaboration, and cross-country epidemiological comparisons (multiple ethnic/SES/BMI comparisons).

Recommendation 8 (cont.)

NEGATIVE:

- Within the last few weeks, the US EPA National Coordinator to the global OECD (Organisation for Economic Co-operation and Development) program, Christine Olinger, announced that the EPA has withdrawn their recommendation to include mammary gland evaluations in a global chemical testing effort. The specific guideline study (meaning that everyone that used this design to test their chemical would do it the same way) to which mammary tissue would be a required end point uses early life exposures, evaluates more than one generation, and is meant to give early indications of effect, but may be extended if a specific tissue is suspected of being affected. It is called the EOGRTS – Extended One-generation Reproductive Toxicity Study. This startling display of disregard for breast health is on the heels of nearly two years of work by individuals within the OSCP (EPA EDSP) and the NTP, working in conjunction with mammary biologists in the Danish Technical Institute, to provide validated methods for use within the OECD EOGRTS. This recommendation came at the request of the Office of Pesticides Program, with reported input from their senior leadership - Vickie Dellarco, Jack Fowle, Steve Bradbury, and the Office of Science Coordination & Policy.
- Primary reasons given for the recommendation withdrawal were:

  1. "…. EPA has serious concerns that the animal and logistical costs of adding the mammary gland whole mount technique to the EOGRT test guideline would result in minimal benefit."

  2. "…whole mount technique has not yet been proven to be a sensitive screening tool for the mammary gland…."

  3. "….addition of this work intensive endpoint during the weaning period may compromise the collection of the other critical measures taken at this time."

Recommendation 9

a. **The research and testing communities should ensure that new testing approaches developed to serve as alternatives to long-term rodent carcinogenicity studies include components that are relevant for breast cancer**

Excellent suggestions:

- Mammary carcinogen-challenge studies assess changes in susceptibility due to early life stage exposures – can test in about 8 months vs 2 yr (assesses altered risk to tumor induction, not frank carcinogenicity of a chemical – These are 2 DIFFERENT questions, both of significant importance)
- Tox21 Collaboration: excellent idea in theory, but must include models that are relevant to the complex make-up of breast. Important to consider multiple cell type models and breast and tumor-specific aromatase promoter identities. Should not use just a "tumor cell" model – will seriously limit interpretation of effect.
  - California Breast Cancer Research Program (CBCRP) has recently funded the development of several novel research models that may show great utility in the future.
- Novel rodent models (gene modified) that more accurately reflect the tumor types in human breast (have to be careful not to use mice to assess male breast cancer – limited or no epithelium forms in male mice – not mentioned in report)

Overall Thoughts

- Extensive overview – kudos to writing team for in depth literature review
- Specific comments on Recommendations 8 and 9; good overview of the state of the science and the limitations of the science
- Recommendation #3 – population cohorts – use animal data to inform/extend study designs
- Life Course Approach – Outstanding focus
  - IF FOLLOWED, THIS APPROACH SHOULD CONSIDERABLY ENHANCE OUR UNDERSTANDING OF BREAST CANCER RISK FACTORS
  - TIMING OF EXPOSURE TO RISK FACTORS IS CRUCIAL