

Editorial

Methodologic Data: Important Foundation for Molecular and Biomarker Studies

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In this issue of *Cancer Epidemiology, Biomarkers & Prevention (CEBP)*, we have included a Focus section featuring a series of papers with the themes of *Biomarkers, -Omics & Systems Biology* and *Biospecimens & Biorepositories* to highlight the importance and/or emergence of these topics in cancer research. These featured papers, including commentaries, mini-reviews, and data papers, although they vary in format and length, focus on novel and critical concepts or important lessons learned from methodologic studies related to biomarker and genomic research involving biospecimens and biorepositories. Several of these papers include original data from carefully designed pilot studies, including reproducibility and validation studies, that provide unique insights into the value and utility of novel assays and state-of-the-art techniques that have great promise for large-scale epidemiologic studies, with the possibility of forging new research directions. The internal validity of molecular and biomarker studies depends on many factors, including a sound study design, the integrity of the specimens, and the reliability and accuracy of the assays/tools employed in these studies. This is why most epidemiologic studies using novel assays have included rigorous pilot studies to validate new assays prior to incorporating them into the full-scale studies. However, due to limited space, much of the important methodologic data and insights gained from these pilot studies is omitted from the original data paper, thereby limiting opportunities for valuable scientific exchange that could potentially facilitate the application of novel markers in subsequent epidemiologic studies. This is the one of the reasons that methodologic data and issues on biospecimen handling continue to constitute a minor proportion of published manuscripts. In an editorial published in September 2006 *CEBP* (1), we noted that “much of the knowledge

about specific factors that affect biospecimen quality is anecdotal and unreliable.”

Since 2006, the fields of biomarkers and biospecimen research have evolved and advanced at a rapid pace, with many new biomarker assays and genomic platforms. These new technologies, such as a multiplexing assay to measure cytokines, LC-MS to measure steroid hormones and small molecules, and high-density genotyping used for large-scale genome-wide association studies, also create new issues related to the type and preparation of biospecimens and to quality control procedures. Thus, it is our hope that by providing a forum dedicated to the sharing of these important data and insights, including the reproducibility of assays and the intra-person variation of biomarkers as well as the impact of biospecimen collection, processing, and storage on the integrity of the specimens, we can facilitate the application of novel tools in molecular/biomarker epidemiologic research and minimize the costs in time and effort of reinventing the wheel.

An example of a situation where biomarker assays and biospecimen handling issues intersect is the HER2 story. Clinical testing for HER2 status is performed in formalin-fixed paraffin-embedded excised breast tissue, and pathologists use a scoring system to report status. A study by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) found that inconsistent laboratory analyses resulted in an error rate of up to 20%, with millions of dollars in costs for unneeded therapy. Testing problems were found to be due in part to inconsistent tissue processing steps such as fixation time. As a result, in 2007 ASCO and CAP published guidelines to improve specimen handling and testing procedures (2). Similar problems have probably gone undetected due to a lack of carefully validated and published methodologic studies.

To help facilitate development of evidence-based biospecimen standards and approaches, several funding mechanisms are available. For example, the OBBR Biospecimen Research Network was established to provide funding to facilitate biospecimen research that will inform the next generation of biospecimen best practices, and the NCI Early Detection Research Network (EDRN) (3) funds research into the development and validation of biomarkers. An important component of the collaborations

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established through EDNRN funding is the development of "highly sensitive and specific assays" in a variety of biospecimen types. The NCI Innovative Molecular Analysis Technologies (IMAT) Program (4), among other initiatives, provides grants that support "innovative and applied emerging technologies in biospecimen science" that are centered on the development of novel sample preparation technologies suitable for molecular analyses of cancer cells and their host environments. The best practices that have resulted from such initiatives are summarized in this issue of *CEBP* (5). However these international guidelines and policies will need to be updated continuously, based on published advances in biospecimen science and the application of emerging technologies in biomarker assay development and biospecimen management. It is also important for information about optimal biomarker and biospecimen technologies and methods to be published and for an effective forum to be established to highlight the importance of methods studies. Other than the NCI initiatives noted above, there are few funding mechanisms to support methods studies, and publication of methods data involving biospecimens is often not a high priority for investigators.

Recently, issues surrounding methods studies and their publication have been the focus of several workshops that have resulted in more comprehensive instructions for authors. For example, *Molecular and Cellular Proteomics* has published guidelines (6, 7) for authors of manuscripts concerning the collection of specimens for proteomics studies. These guidelines have become the basis for a new effort to establish such authors' guidelines with a broader biospecimen focus. These new recommendations are being established and will be published in 2010 in several journals, including *CEBP*. In 2009, *CEBP* began recommending guidelines for authors concerning the validation of cell lines included among materials in manuscripts (8). Going forward, it will be important for biospecimen quality and methods to be documented in manuscripts in order to avoid problems similar to those that have plagued many studies due to cross-contamination of cell lines.

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To help enhance the validity of biomedical research through improvements in biospecimen handling and integrity of biospecimens, *CEBP* created a special section on Biospecimens and Biorepositories in 2006. With the rapid advancement of molecular/genomic research since 2006, it is time once again to call attention to these important issues. In this Focus issue, we have covered a wide range of topics with various formats to capture important topics such as the application of pathological tools and information in epidemiologic studies, cytokine detection, intra-person variation in circulating vitamin D levels, the impact of sample thawing and refreezing cycles on the reliability of serum melatonin measures, issues related to pooling biological data across studies, use of DNA and RNA extracted from paraffin-embedded formalin-fixed tissue, microRNA detection in various biological samples, using microarrays for gene expression studies, building biorepositories in developing countries, and an ethical framework for the collection and use of human specimens in research. These topics reflect current issues in molecular/biomarker studies and emphasize the fact that ethical and legal issues are as important as technical ones in the laboratory and clinical conduct of research with biospecimens.

With this current Focus issue, the editors are again highlighting the importance of methodologic factors, which do not lend themselves to the most glamorous articles but are crucial to the validity of molecular/biomarker studies. We are fully aware of the fact that this single issue is not likely to capture all relevant topics we face today. Rather, it is our hope that with this Focus issue, we will encourage scientific exchange of these critical data and the publication of such papers. Therefore, moving forward, the editors will consider the publication of short methods studies as a recurring feature of the journal.

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