Challenges and Opportunities in International Molecular Cancer Prevention Research: An ASPO Molecular Epidemiology and the Environment and International Cancer Prevention Interest Groups Report

Meira Epplein1, Robert M. Bostick2,3, Lina Mu4, Shuji Ogino5,6,7, Dejana Braithwaite8, and Peter A. Kanetsky9

Abstract

The International Agency for Research on Cancer estimates that over half of the new cancer cases and almost two-thirds of the cancer deaths in 2012 occurred in low and middle income countries. To discuss the challenges and opportunities to reducing the burden of cancer worldwide, the Molecular Epidemiology and the Environment and the International Issues in Cancer Special Interest Groups joined forces to hold a session during the 38th Annual Meeting of the American Society of Preventive Oncology (March 2014, Arlington, Virginia). The session highlighted three topics of particular interest to molecular cancer prevention researchers working internationally, specifically: 1) biomarkers in cancer research; 2) environmental exposures and cancer; and 3) molecular pathological epidemiology. A major factor for successful collaboration illuminated during the discussion was the need for strong, committed, and reliable international partners. A key element of establishing such relationships is to thoroughly involve individual international collaborators in the development of the research question; engaged international collaborators are particularly motivated to champion and shepherd the project through all necessary steps, including issues relating to institutional review boards, political sensitivity, laboratory-based assays, and tumor subtyping. Also essential is allotting time for the building, maintaining, and investing in such relationships so that successful international collaborations may take root and bloom. While there are many challenges inherent to international molecular cancer research, the opportunities for furthering the science and prevention of cancer worldwide are great, particularly at this time of increasing cancer incidence and prevalence in low and middle income countries. Cancer Epidemiol Biomarkers Prev; 23(11); 2613–7. ©2014 AACR.

Introduction

In the most recent report released by the International Agency for Research on Cancer, it was estimated that of the 14.1 million new cancer cases that arose in 2012, 57% occurred in low- and middle-income countries. Moreover, almost two thirds of the 8.2 million cancer deaths in 2012 also occurred in low- and middle-income countries (1). As the international burden of cancer continues to grow, collaboration among researchers from around the globe is essential to furthering cancer prevention knowledge and efforts. To begin to address the formidable challenge of these growing international cancer concerns, in the fall of 2012 the U.S. NIH hosted leading cancer researchers from around the world to generate recommendations in all areas of cancer research (2). One major area of concern in a commentary following the meeting and written by Dr. Harold Varmus, Director of the National Cancer Institute (Rockville, MD), was the need for the expansion of the reach of cancer knowledge and efforts. To begin to address the formidable challenge of these growing international cancer concerns, in the fall of 2012 the U.S. NIH hosted leading cancer researchers from around the world to generate recommendations in all areas of cancer research (2). One major area of concern noted in a commentary following the meeting and written by Dr. Harold Varmus, Director of the National Cancer Institute (Rockville, MD), was the need for the expansion of the reach of cancer research, including productive international collaboration in the sharing of data (2). As cancer prevention researchers and molecular epidemiologists, members of the American Society of Preventive Oncology (ASPO) are committed to reducing the burden of cancer worldwide. To discuss the challenges and opportunities in international molecular cancer prevention research, the Molecular Epidemiology and the
Topic 1: Biomarkers in Cancer Research

Sharing biospecimens

Dr. Metra Epplein of Vanderbilt University (Nashville, TN) led the session on the topic of sharing biospecimens in international cancer research where the key challenge concerns country-specific regulatory issues. To begin this discussion, she first reported on her ongoing project to establish a Helicobacter pylori (H. pylori) blood biomarker for gastric cancer risk in East Asia. In phase I of this project, she is seeking to determine whether the initial findings among urban Chinese men of a novel H. pylori biomarker panel to predict gastric cancer risk can be replicated. To do this, she is conducting a nested case-control study composed of eight cohorts from China, Japan, and Korea. Previously collected blood samples from 2,000 gastric cancer cases and 2,000 controls in East Asia are to be selected, aliquoted, and then shipped to the German Cancer Research Center to be assayed by H. pylori multiplex serology. In addition, datasets containing information on baseline as well as outcome variables on the selected cases and controls from each cohort study must be harmonized for analysis. The specific ongoing issues currently encountered in this project include delays in receiving approval by each site’s Institutional Review Board, which may have changed since grant submission; establishing data use agreements legal in two (or more) countries; and the shipping of biospecimens out-of-country.

The group discussion around these issues acknowledged that although much effort has been expended on establishing standards for biospecimen collaboration and storage, collaborating with international groups who have precollected samples presents other challenges, particularly relating to regulatory issues. One suggestion by the group was to establish a protocol to ship biospecimens to an established company, rather than to an individual’s academic institute, to provide a neutral third party. Another discussion point was the potential for transferring technology to the collaborating country, although this can be quite difficult when complex methodologies are involved. Also suggested, moving forward was an openness to mechanisms for specific projects to be included on an as-needed basis, so that this process would be eased in the future.

Another issue raised by SIG members during the discussion was the need to engage the individual international collaborators more thoroughly in development of the research question itself, as well as in the process necessary to complete such a project, so that they can champion and shepherd it through all necessary steps in each collaborating institution, a particularly challenging process when biospecimens are involved. In addition, the concept of custodianship was raised, which has been advanced as a framework for collaborations involving biospecimens. Custodianship incorporates ethical with legal principles in an attempt to create a clear understanding of the responsibilities of the biobanking community and minimize conflict among stakeholders, all while focusing on the goal of best practices in medical research. An individual who ideally is neither the research investigator nor the funder is designated as the biospecimen custodian, and abides by a governance plan established before the start of the project that includes the collection of biospecimens. However, even for already existing biobanks, establishing a custodian can enable greater transparency and committed caretaking of biospecimens. A strong international collaboration might in fact require both of these concepts together—a scientific advocate committed to the research question along with a custodian of the biospecimens who oversees the ethical and legal means for sharing of resources.

Assay validity

This discussion, led by Dr. Roberd (Robin) Bostick of Emory University (Atlanta, GA), was focused on factors involved in biospecimen collection, handling, storage, distribution, and analysis that can affect assay validity. Although the potential for adverse influences, such as errors and inconsistencies, on this multiphase process in any study is large, the potential is greater in multcenter studies, and even greater in international multicenter studies. Guiding principles for dealing with this potential include recognizing it and creating agreed upon systems with detailed instructions and forms and conducting standardized, rigorous training to reduce the chances of errors and to minimize the small, but potentially cumulative and difficult to measure adverse inconsistencies. The process generally begins with the investigators and key staff across all centers discussing and agreeing on the procedures to be followed. The next step is to develop a detailed, step-by-step, essentially “cookbook” style manual of operations containing the protocols for carrying out every phase of the process, along with corresponding tracking and quality assurance/quality control (QA/QC) forms (collectively referred to as the manual of operations). A way to think about the protocols and manual of...
operations is that they should be foolproof to use by someone who is suddenly thrust into fulfilling a particular role, but who is both unfamiliar with the study and less qualified for their position than the person for whom they are substituting. In developing the manual, it is advisable to make no assumptions and to be culturally sensitive as different cultures may have unique approaches to meeting study goals, interpreting protocols, or dealing with problems. Active communication is key. Once the first draft of the manual is written, the next steps include obtaining input from all investigators and key staff across all centers and an iterative process of revising and testing the manual until it is proven that all works well and that all investigators and study teams are fully on board with all the processes and forms for the duration of the study.

Several considerations about designing biospecimen protocols were discussed. The first involves decisions about centralized versus distributed protocol components, such as initial processing and aliquotting, biospecimen storage, and conducting assays. Weighing the potential for error and introducing extraneous variability should inform the decisions about the balance between centralizing and distributing protocol functions. For distributed functions, attention should be paid to standardizing equipment and supplies. For biospecimen storage, splitting samples and storing them in different locations can provide protection against catastrophic specimen loss. If specific assays must be conducted across multiple centers, specific assay controls, such as using National Institute of Standards and Technology (NIST) standards and/or pooled quality control samples, can be used for calibrating assays across sites and minimizing within-center variability. A specimen collection/handling and assay control that can be used to assess the reliability of the entire process of collecting, handling, and assaying samples is collecting duplicate samples on some proportion of study participants (e.g., every 10th person) and blinding the laboratory to the fact that different samples are from the same person (i.e., blinded duplicate quality control samples). For assays that may be especially prone to batch variation, in addition to including replicate samples, running the assays in large batches, balancing on comparison groups, and, for clinical trials, including a subject’s baseline and follow-up samples, can be helpful. When analyzing data from specific assays conducted across multiple centers, methods such as calculating site-specific categorization cut points, stratified analyses, batch standardization, or calibrating values across centers can be used. Finally, regardless of whether most procedures are handled centrally or not, a sound QA/QC and associated data management system are crucial. For example, in the manual of operations, specify acceptable lengths of time between various steps (e.g., between venipuncture and centrifugation, between centrifugation and aliquotting and freezing) and record and continuously monitor data on these times. With continuous monitoring, deviations from agreed upon protocol standards can be detected, remedied, and where necessary, accounted for in the data analyses. For further commentary on this topic, a number of extensive reviews have been published (7–9).

Topic 2: Environmental Exposures and Cancer

Dr. Lina Mu of the University at Buffalo (Buffalo, NY) led the discussion on the topic of international collaborative research on environmental exposures and cancer. Exposure to heavy environmental pollution, especially in developing countries, has been drawing increasing attention from scientists from multiple disciplines. In the past decade, increasing number of international collaborative projects has been developed in this field to advance our understanding of cancer development and survival in relation to environmental exposures. Dr. Mu shared her experiences on several of her international research projects, including studies on water pollution and three upper-gastrointestinal cancers, indoor air pollution, and lung cancer among Chinese women, and biologic response to air quality changes pre-, during-, and post-Beijing Olympics.

A few common challenges in most international epidemiologic studies were discussed. First, scientists often have difficulty in accessing environmental monitoring data. When conducting cancer-related epidemiologic studies, investigators often need retrospective environmental data to estimate past exposure levels. However, many developing countries either have not collected monitoring data in the past few decades, or they do not make those data available to scientists (10). This situation limits certain study designs and testing of the hypotheses. Scientists also often face challenges of quality control when projects are conducted in another country (11, 12). Although most investigators seek to be in the field when the study is initiated and to visit the field often and periodically, it is difficult to make frequent and prolonged visits to provide constant supervision. As a result, study procedures can often deviate from protocol, which might have a significant unintended impact on the validity of the study. In addition, environmental issues are often politically sensitive (13), resulting in numerous unexpected barriers and hurdles related to the individual country’s political system.

Having realized the many challenges in this type of research setting, the group agreed and emphasized that there remain very good opportunities for investigators to conduct international epidemiologic studies on cancer. First, high environmental exposure in some countries creates special opportunities for environment-related research, such as for the topic of indoor air pollution (14). Investigators should take advantage of those special environmental issues to advance the science in this research area with potential public health applications. Second, there is increasing research support in many countries. China, as a good example, has seen research funding significantly increased over the last 8 years (15).
The increased investment in research will enable better infrastructure, stronger research teams, more well-trained professionals, and a better collaborative environment. All these improvements create great opportunity to build long-term international research partnerships. We all believe strongly that long-standing partnerships can benefit all sides of a collaboration in many ways, including technology exchange, data sharing, as well as improvement in quality control for international studies.

**Topic 3: Molecular Pathologic Epidemiology**

Finally, Dr. Shuji Ogino of Harvard School of Public Health (Boston, MA) presented tenets for the practice of MPE. Accumulating epidemiologic evidence indicates that exposures influence disease pathogenesis. Exposures vary from person to person, and a disease process in each individual seems to differ from that in any other individual and manifests as a combination of a unique set of molecular alterations (i.e., the unique disease principle; refs. 16, 17). To integrate disease heterogeneity and pathogenesis into epidemiologic research, “MPE” has emerged as a functional union of molecular pathology and epidemiology (18). The premise of MPE is that disease subtyping based on similarity in molecular disease signatures can better link exposures to disease processes. With such a disease subtyping effort, MPE can strengthen epidemiologic research via linking an exposure to specific molecular changes, refining strengths of associations with specific molecular subtypes, enhancing causal inference, and identifying potential molecular disease biomarkers for clinical translation (17, 19).

During the session, examples of recent MPE research and its implications were discussed. Colonoscopy is associated with lower risk of colorectal cancer, but the preventive effect of colonoscopy seems to be reduced for the Cpg island methylator phenotype (CIMP)-high subtype compared with the non-CIMP-high subtype (20); these findings can lead to a more personalized approach for prevention; in this example, individuals known to be susceptible to the development of CIMP-high cancer (e.g., current smokers; ref. 21) may need to increase frequency of colonoscopy or find alternate screening strategies. Another example focused on data suggests that aspirin may be especially useful for P1K3CA-mutated colorectal cancer, but not for P1K3CA wild-type cancer (22, 23), which can have a direct impact on cancer patient management. Thus, introduction of MPE strategies to identify specific exposure-molecular subtype relationship can potentially enable us to improve risk–benefit performance in not only each individual, but also in the overall healthcare system. This MPE paradigm has been increasingly utilized around the world (24–28).

However, there are challenges to incorporating MPE methods into research protocols, especially in international research. One of the challenges is the paucity of interdisciplinary experts and education programs. A second hindrance is the lack of international research guidelines (which can be termed STROBE-MPE guidelines; ref. 29), that would offer a broadly accepted schema within which to incorporate MPE activities into research. A third challenge, which was also discussed in Topic 1, above, is standardization of, and quality assurance procedures for, tumor molecular tests and other surrogate marker tests, which is even more challenging in international studies.

In the discussion surrounding MPE, it was agreed that opportunities in this field research are numerous. Molecular diagnostic tests are now routine in clinical practice in the United States, and in many other countries around the world. We expect that molecular testing will become routine clinical practice in many parts of the world in the near future. Hence, considerable amounts of disease molecular signature data will accumulate in hospitals and pathology laboratories around the world and can be utilized in epidemiologic research (30). Finally, in a continued attempt to build collaborations, gather interdisciplinary experts and address these challenges, The Second International MPE Meeting will be held on December 4–5, 2014 in Boston, MA.

**Summary**

There are many inherent challenges in engaging in international molecular cancer prevention research, including but not limited to those relating to biospecimen sharing and assay validity, studies of environmental exposures, and disease subtyping, as presented above. The opportunities, however, for furthering the science and prevention of cancer worldwide are even greater, particularly at this time of increasing cancer incidence and prevalence in low- and middle-income countries. Successful collaboration in international molecular research involves numerous factors, but as consistently illuminated in the discussion among members of the ASPO Molecular Epidemiology and the Environment and the International Issues in Cancer SIGs, strong, committed and reliable international partners are a must. A key element of establishing such relationships, as identified by group members, is thoroughly engaging the individual international collaborators in the development of the research question, so that they are particularly motivated to champion and shepherd the project through all necessary steps in each collaborating institution, including issues relating to Institutional Review Boards, political sensitivity, laboratory-based assays, and tumor subtyping. Also essential is allotting time for the building, maintaining, and investing in such relationships so that successful international collaborations may take root and bloom.

**Acknowledgments**

The authors thank all of the members and attendees of the ASPO Special Interest Group Breakfast on Molecular Epidemiology and the Environment & International Issues in Cancer for their active participation and insightful comments during this session of the 2014 Annual ASPO Meeting, held March 9–11, 2014, in Arlington, Virginia.
Grant Support
M. Epplin was supported by the National Cancer Institute, NIH (K07 CA151792 and R01 CA174853). S. Ogino was funded in part by the National Cancer Institute, NIH (R01 CA151993). R.M. Bostick was supported in part by the National Cancer Institute, NIH (P30 CA138320). L. Mu was funded by the National Institute of Environmental Health Science, NIH (R01 ES018846).

Received July 21, 2014; accepted July 29, 2014; published OnlineFirst October 2, 2014.

References
Challenges and Opportunities in International Molecular Cancer Prevention Research: An ASPO Molecular Epidemiology and the Environment and International Cancer Prevention Interest Groups Report

Meira Epplein, Roberd M. Bostick, Lina Mu, et al.

Cancer Epidemiol Biomarkers Prev 2014;23:2613-2617. Published OnlineFirst October 2, 2014.

Updated version Access the most recent version of this article at:
doi:10.1158/1055-9965.EPI-14-0848

Cited articles This article cites 27 articles, 9 of which you can access for free at:
http://cebp.aacrjournals.org/content/23/11/2613.full#ref-list-1

Citing articles This article has been cited by 4 HighWire-hosted articles. Access the articles at:
http://cebp.aacrjournals.org/content/23/11/2613.full#related-urls

E-mail alerts Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.