Published in final edited form as:

Environ Mol Mutagen. 2010 ; 51(8-9): 774–780. doi:10.1002/em.20607.

Genetics and Women's Health Issues—The Commitment of EMS to Women Scientists and Gender-Associated Disease Topics

Kristine L. Witt^{1,*}, Patricia G. Moorman², Olga Kovalchuk³, Nina Holland⁴, Gladys Block⁴, and Paul R. Andreassen⁵

¹National Toxicology Program, NIEHS/NIH, Research Triangle Park, North Carolina

²Duke University, Department of Community and Family Medicine, Durham, North Carolina

³University of Lethbridge, Department of Biological Sciences, Lethbridge, Alberta, California

⁴University of California Berkeley, School of Public Health, Berkeley, California

⁵Cincinnati Children's Hospital Medical Center, Division of Experimental Hematology and Cancer, Cincinnati, Ohio

Abstract

This manuscript presents an overview of a symposium held at the 2009 annual meeting of the Environmental Mutagen Society (EMS) in St. Louis, MO. The symposium was sponsored by the Women in the Environmental Mutagen Society (WEMS) special interest group, and it covered current molecular genetics technologies and their impact on diagnosis and treatment of diseases that primarily or differentially affect women. Four speakers presented groundbreaking new information from such areas as cancer genetics, gene-environment interactions, epigenetics, DNA repair, and molecular epidemiology. Although cancer was a primary focus of the symposium, other health issues such as obesity and cardiovascular disease were addressed. The rapid evolution in genomic technologies discussed in this symposium should provide new tools to explore some of the critical questions raised by the research projects described in this article. This symposium demonstrates that EMS provides a forum for the presentation, discussion, and extension of the data generated by the investigators featured in this article and other researchers engaged in the study of the molecular mechanisms and gene-environment interactions that impact women's health.

Keywords

ovarian cancer; breast cancer; BRCA1; microRNA; epigenetics; DNA repair; obesity; oxidative stress

INTRODUCTION

The Environmental Mutagen Society (EMS) has recently witnessed the establishment of a new special interest group, Women in the EMS (WEMS), that aims to showcase the role of

*Correspondence to: Kristine L. Witt, National Toxicology Program, NIEHS/NIH, P.O. Box 12233, Mail Drop K2-15, Research Triangle Park, NC 27709, USA. witt@niehs.nih.gov.

This work is a summary report of the WEMS Symposium, EMS Annual Meeting, October 2009, St. Louis, MO.

genetics, gene-environment interactions, and genome-based technologies in the diagnosis, understanding, and treatment of diseases such as breast and ovarian cancers, autoimmune diseases, cardiovascular disease, obesity, and osteoporosis, all of which affect women primarily or differentially. As part of this effort, WEMS sponsored a symposium at the recent (October 24–28, 2009) annual EMS meeting in St. Louis, MO, entitled *Women's Health Issues: Diagnosis and Treatment in the 21st Century*. The theme of this symposium grew out of a desire to explore the changes in medical practice that have occurred as a result of the sequencing of the human genome and remarkable advances in genomic, epigenetic, and other biomarker technologies. These advances have opened the door to the era of personalized medicine: customizing diagnosis and treatment to the genetic profile of the individual patient, thereby identifying optimal treatments and avoiding potentially harmful or ineffective treatments.

Some of the diseases or conditions for which potential applications of the new technologies exist include cardiovascular disease, breast and ovarian cancers, autoimmune diseases, osteoporosis and vitamin D metabolism, and diabetes and obesity. For cardiovascular disease, gender-related diagnostic factors and treatments tailored to oxidative stress status and biomarkers of inflammation are under investigation. Breast cancer treatments in women have evolved recently into more personalized approaches based on specific genetic profiles. Ovarian cancer research has made great strides in the identification of specific gene-environment interactions that predispose to disease and impact prognosis. Enhanced susceptibility to environmental triggers resulting from particular gene variants is being explored in autoimmune diseases. Genotypic differences affecting utilization of vitamin D and bone metabolic processes are now recognized as important factors in the risk for development of osteoporosis. As technical capabilities evolve and knowledge of the roles of gene-environment interactions expands, this list of diseases benefiting from personalized treatments tailored to genetic profiles will surely grow.

The speakers who participated in the 2009 WEMS symposium explored aspects of the current state of the art in understanding the role of genetics and gender-related factors in the diagnosis, treatment, and management of specific diseases and conditions that affect women. In addition, prevention strategies related to specific genetic profiles for some disease states were discussed by some of the participants. Summaries of the presentations follow, and the reader will quickly see the variety of research approaches and disease topics that were addressed and the promise that rapidly evolving genomics and genetics strategies hold for future treatments.

SYMPOSIUM OVERVIEW

Ovarian Cancer—At the Interface of Epidemiology and Genomics

The symposium began with a presentation by Patricia Moorman, Ph.D., an epidemiologist at Duke University, Department of Community and Family Medicine, Cancer Prevention and Control Research Program. Dr. Moorman's research has focused on ovarian cancer, breast cancer, and ovarian function after hysterectomy. Areas of particular interest to Dr. Moorman include the effects of pharmaceuticals and hormonal factors on cancer risk, racial differences in risk factors and outcomes, and genetic markers of cancer risk. She has investigated how

nonsteroidal anti-inflammatory drugs affect the risk for breast and ovarian cancers [Moorman et al., 2003; Schildkraut et al., 2006] and has evaluated how genetic variants may act as possible modifiers of the relationship between certain medications and cancer outcomes [Moorman et al., 2005].

The topic Dr. Moorman selected for this symposium was *Challenges of Epidemiologic Research in the Genomic Era: The Example of Ovarian Cancer*. Her presentation covered a number of advances in genetic epidemiologic studies of this relatively uncommon but highly lethal gynecological cancer. Ovarian cancer is known to be associated with several highly penetrant disease susceptibility genes including *BRCA1*, *BRCA2*, and mismatch repair genes [Permuth-Wey and Sellers, 2009], but it is estimated that only about 10–15% of ovarian cancers are due to inherited mutations in these genes. It is hypothesized that other genetic variants that are more common but less penetrant may contribute significantly to the inherited risk of ovarian cancer.

Over the last decade, there has been considerable effort devoted to identifying genetic polymorphisms associated with ovarian cancer, with most investigators using a candidate gene approach. Similar to what has been observed with genetic association studies of other cancers, many of the variants initially reported to be associated with ovarian cancer risk were not confirmed in subsequent studies [Kavvoura and Ioannidis, 2008; Fasching et al., 2009]. The recognition of the need for rapid validation of genetic associations in other study populations led to the establishment of the Ovarian Cancer Association Consortium (OCAC), a collaboration that now involves more than 25 research groups around the world with data and specimens from more than 15,000 ovarian cancer cases and 20,000 controls [Berchuck et al., 2008]. Through this consortium, collaborating investigators have confirmed associations with some genetic variants [Pearce et al., 2009; Schildkraut et al., 2009], whereas other initially positive associations were not confirmed when additional study populations were genotyped [Palmieri et al., 2008; Pearce et al., 2009].

Work within the OCAC highlights both the challenges and opportunities related to genetic association studies of cancer, including issues related to the strength of the associations, disease heterogeneity, and rapidly changing genotyping technology. The associations between ovarian cancer and individual polymorphisms have tended to be modest in magnitude, and individual studies with typical sample sizes of 500–1,000 cases may have inadequate statistical power to detect these weak associations. This is exemplified by an analysis of single nucleotide polymorphisms (SNPs) in the *TP53* gene region that combined data from 13 case–control studies. Two SNPs, rs2287498 and rs12951053, were shown to exhibit confirmed associations with serous invasive ovarian cancer, whereas statistically significant associations were not apparent in many of the individual studies contributing data to the analysis [Schildkraut et al., 2009].

Analyses within the consortium also highlight the need to consider the heterogeneity of ovarian cancer. Ovarian cancer is known to have distinct histologic subtypes, but most studies have evaluated genetic associations with epithelial ovarian cancer as a single entity. The large number of ovarian cancer cases and controls in OCAC has afforded the opportunity to perform analyses within histologic subtypes. These analyses have shown

evidence of etiologic differences between serous, endometrioid, mucinous, or clear-cell subtypes of ovarian cancer, and they illustrate how stronger associations may be observed when considering more homogeneous subsets of disease [Schildkraut et al., 2009; Song et al., 2009].

The rapid pace of technological developments has shifted the focus of genetic association studies from candidate gene investigations examining variants in a few genes to genome-wide association studies (GWAS) examining hundreds of thousands of polymorphisms. The multistage approach used in GWAS requires thousands of cases and controls at each stage, again necessitating a collaborative multicenter effort. A recently published ovarian cancer GWAS using OCAC cases and controls identified a new susceptibility locus (9p22.2) in an area of the genome not previously suspected to be associated with ovarian cancer [Song et al., 2009]. An immediate challenge related to these findings is to better understand the biological mechanisms by which these variants affect ovarian cancer susceptibility.

Another major challenge is the development of novel statistical techniques to analyze the vast amounts of data generated from GWAS studies. When considering associations with hundreds of thousands of polymorphisms, statistical methods must account for the possibility of false discoveries due to the huge number of associations examined. However, associations between individual genetic variants and ovarian cancer are likely to be only the beginning of the story. The genesis of ovarian cancer is very probably a result of gene-gene or gene-environment interactions. The identification of such interactions is an enormous epidemiological, computational, and statistical challenge that will rely on the development and application of innovative statistical methods.

Despite the challenges, significant advances have been achieved in genetic epidemiologic studies of ovarian cancer in the recent years. Still, many important questions remain to be answered, especially in relation to gene-environment interactions. Better understanding of these interactions will have a direct impact on future prevention strategies for this lethal disease.

Epigenetics in Early Detection and Prognosis of Breast Cancer

Olga Kovalchuk, M.D., Ph.D., a molecular biologist and Canadian Institutes for Health Research Chair in Gender and Health at the University of Lethbridge, Alberta, Canada, presented the second talk of this symposium. Dr. Kovalchuk's research focuses on the role of epigenetic dysregulation in the developmental processes of carcinogenesis, and epigenetic regulation of the cancer treatment responses, with a specific focus on epigenetic events and microRNAs involved in breast cancer [Kovalchuk et al., 2007]. She is also engaged in studies exploring radiation epigenetics and the role of epigenetic changes in genome stability and carcinogenesis. Other areas of interest include radiation-induced oncogenic signaling, and radiation-induced DNA damage, repair, and recombination.

In her talk, *Novel Epigenetic Biomarkers for Early Detection of Breast Cancer and Prediction of Treatment Responses: From Bench to Bedside*, Dr. Kovalchuk presented results from her research in the area of breast cancer and epigenetic mechanisms. She focused on interindividual differences in DNA repair capacity and the delineation of novel,

characteristic variants in microRNAome profiles associated with epigenetic changes in carcinogenesis as well as in breast cancer resistance to common therapeutic agents.

MicroRNAs have been shown to be critically important in breast cancer chemoresistance, and research is currently underway to investigate their potential application in reversal of drug-resistance phenotypes [Kovalchuk et al., 2008; Filkowski et al., in press]. The role of microRNAs as novel biomarkers for the early detection of cancer in women and for prediction of breast cancer treatment responses was initially studied in a rat model of estrogen-induced breast carcinogenesis (Pogribny et al., in press). Epigenetic changes and alterations in the microRNAome have been shown to be important in several key processes associated with breast cancer development, including the etiology and pathogenesis of the disease, as well as in treatment responses. These epigenetic changes have recently been shown in an ACI rat model to occur before carcinogenic transformation.

At present, radiation, including diagnostic X-ray exposure, is the only genotoxic agent that is causally and conclusively linked to breast cancer induction. In the ACI rat model, co-administration of estrogen and radiation results in a synergistic effect on breast cancer development. In the transformed rat cells, dramatically altered microRNA genes that are involved in regulation of the expression of apoptosis-, DNA repair- (e.g., *BRCA1*), and other DNA damage-related genes have been identified. Identification of the affected genes and elucidation of the cellular pathways in which they are active may provide a promising strategy for developing novel gene therapy approaches to breast cancer treatment. The translation of laboratory findings such as these into enhanced and targeted applied therapeutic management of a devastating disease that affects primarily women will be a major initiative in the future.

Biomarkers of Oxidative Stress and Cardiovascular Disease in Obese Populations

The third symposium speaker was Nina Holland, Ph.D., a geneticist and molecular epidemiologist from the School of Public Health at the University of California, Berkeley. The main focus of her research is on the effects of environmental exposures on pregnant women and children using biomarkers of genetic damage, oxidative stress, and genetic susceptibility [Holland et al., 2006; Chen et al., 2007; Huen et al., 2010].

In her presentation, *Obesity, Vitamin Supplementation and Biomarkers of Oxidative Stress and Cardiovascular Disease*, Dr. Holland described a novel research study, led by UC Berkeley epidemiologist Dr. Gladys Block, investigating the effects of vitamin C and E supplementation on oxidative stress in relation to obesity and cardiovascular disease in women [Block et al., 2008, 2009]. As background, Dr. Holland discussed the latest data on obesity in the United States, emphasizing the enormous public health problem that this condition represents. According to the Centers for Disease Control and Prevention, the frequency of obesity in the United States has been increasing rapidly during the last 20 years, and now all states, but Colorado, have obesity prevalence above 20%. Two diseases strongly associated with obesity, cardiovascular disease and cancer, are the leading causes of death in the United States [Higdon and Frei, 2003]. Thus, the obesity epidemic is a public health problem of critical proportions and one that especially affects women.

Because of the relationship between obesity and oxidative stress [Block et al., 2002; Keaney et al., 2003; Vincent and Taylor, 2006], and with an ultimate goal of finding a simple approach to begin to slow the rise in obesity-related disease in the United States, the effects of two supplemental dietary antioxidants, vitamin C and vitamin E, on biomarkers of oxidative stress were investigated. In a 60-day intervention trial in healthy non-smokers (259 women and 137 men) who were recruited in the San Francisco Bay Area, CA, vitamin C (1,000 mg/day) was shown to reduce the level of oxidative stress biomarkers, F₂-isoprostanes and malondialdehyde, whereas no effect on the levels of these two biomarkers was seen with vitamin E supplementation (800 IU/day of all-natural mixture of RRR d- α -tocopherol) [Block et al., 2008]. Levels of both biomarkers were directly correlated with levels of C-reactive protein (CRP), and elevated CRP levels are a strong predictor of an increased risk for cardiovascular disease [Buckley et al., 2009]. Additionally, CRP levels have been shown to increase with increasing body mass index [Block et al., 2009]. A 60-day course of vitamin C supplementation resulted in a 35% reduction in CRP levels in individuals who had above-normal levels at the start of the study [Block et al., 2008]. Furthermore, in the study cohort, BMI and levels of CRP and F₂-isoprostanes were all higher in women than in men. This observation is consistent with several other large studies that found that women have higher levels of oxidative stress than do men [Coudray et al., 1997; Block et al., 2002; Keaney et al., 2003; Gross et al., 2005]. These findings suggest that women might benefit more than men from antioxidant vitamin supplementation.

The results of these dietary intervention studies underscore the importance of a healthy diet, one that includes a large proportion of fruits and vegetables (sources of antioxidant vitamins), to sustained good health. However, for some sub-populations, such as obese people or people with a genetic predisposition to elevations in oxidative stress or inflammation, a healthy, balanced diet may not be sufficient to prevent disease. For people in this latter category, vitamin supplementation may be necessary to ensure good health.

Discerning the Functional Link Between BRCA1 and BRCA2 in DNA Repair Pathways

Paul Andreassen, Ph.D., a molecular biologist at the University of Cincinnati College of Medicine, Cincinnati Children's Research Foundation, completed the presentations by discussing results of recent groundbreaking investigations into the functional link between the *BRCA1* and *BRCA2* tumor suppressor genes, a research focus of his for the past several years. *BRCA1* and *BRCA2* are the genes identified most prominently as being mutated in inherited breast cancer [Venkitaraman, 2001; Turner et al., 2004]. Furthermore, *BRCA1* is frequently silenced epigenetically in sporadic cases of the disease [Catteau and Morris, 2002].

In his talk *PALB2 Physically and Functionally Connects BRCA1 and BRCA2 into a Pathway of Homologous Recombination*, Dr. Andreassen first presented background information from earlier studies of the associations between *BRCA1* and *BRCA2* with DNA repair and breast cancer, and then presented the results of recent studies definitively connecting these two genes. The proteins encoded by the *BRCA1* and *BRCA2* genes both function in DNA repair processes, and deficiency for either protein is associated with hypersensitivity to ionizing radiation or DNA interstrand crosslinking agents, such as

mitomycin C (MMC) [Venkitaraman, 2001]. Thus, these proteins are potentially important modifiers of the outcome of radio-therapy or chemotherapy used to treat breast cancer or other malignant diseases. Mutation of *BRCA1* or *BRCA2* also results in spontaneous chromosome instability and defective homologous recombination. Although the *BRCA1* and *BRCA2* proteins would appear to have similar functions in DNA damage responses based upon the phenotypes associated with deficiency for either protein, the question of whether these proteins are functionally related has remained elusive until recently. Resolving this issue has been a critical need for understanding the etiology of breast cancer and could have important implications for personalized treatment of the disease. Furthermore, integration of *BRCA1* and *BRCA2* into a cohesive cellular pathway could identify other important genetic determinants of therapeutic outcome.

Co-immunoprecipitation and co-localization of *BRCA1* and *BRCA2* was reported more than a decade ago [Chen et al., 1998]; but at the time, there was little or no evidence that these proteins interacted directly. The fact that no direct binding between these two proteins had been demonstrated in yeast two-hybrid assays, coupled with the estimation that no more than 5% of the pool of either protein, interacted with the other, suggested that *BRCA1* and *BRCA2* might interact via an intermediate [Venkitaraman, 2001]. *PALB2* was recently identified as a *BRCA2*-interacting protein [Xia et al., 2006]. Importantly, *PALB2* was a candidate linker of *BRCA1* and *BRCA2*, given that *PALB2* has also been identified as a breast cancer-associated gene [Erkko et al., 2007; Rahman et al., 2007] and that deficiency for *PALB2* yields cellular phenotypes similar to those resulting from deficiency for *BRCA1* or *BRCA2* [Xia et al., 2006, 2007].

Recent experimental evidence has now definitively demonstrated how *PALB2* links *BRCA1* and *BRCA2*, both physically and functionally. This work was published recently [Zhang et al., 2009a] along with similar reports from other groups [Sy et al., 2009; Zhang et al., 2009b]. *PALB2* has a coiled-coil domain and four WD40 motifs at its N- and C-termini, respectively. To test for co-immunoprecipitation of these proteins, truncated mutants were expressed transiently in T-antigen transformed HEK 293 cells. Results of these experiments demonstrated that the coiled-coil domain of *PALB2* directly binds to *BRCA1*, whereas the C-terminal WD40 repeats of *PALB2* interact with *BRCA2*. Dr. Andreassen also presented evidence that *BRCA1* and *BRCA2* do not bind directly to each other, but instead, they associate using *PALB2* as an intermediate.

Additional experiments have recently shown that the assembly of *PALB2* into DNA-damage foci is deficient in a breast cancer-derived cell line that expresses mutant *BRCA1*, but not the full-length protein [Zhang et al., 2009a,b]. In addition, results of experiments in which *PALB2*-deficient cells were reconstituted with different forms of *PALB2* demonstrated that *BRCA1* is required to localize *PALB2* to nuclear foci in a process mediated by the N-terminus of *PALB2*. *BRCA1* thereby functions upstream of *PALB2*, which in turn functions to localize *BRCA2*. Ultimately, the interaction of *PALB2* with both *BRCA1* and *BRCA2* is necessary for recruitment of the *RAD51* recombinase, which plays a major role in DNA double-strand break repair [Zhang et al., 2009a].

Further evidence that PALB2 functionally links BRCA1 and BRCA2 derives from the observation that homologous recombination and resistance to MMC require the interaction of PALB2 with each protein [Sy et al., 2009; Zhang et al., 2009a]. Genetic instability resulting from a mutation anywhere in the BRCA1-PALB2-BRCA2-RAD51 pathway might explain the common connection of BRCA1 and BRCA2 to breast cancer. These findings provide one more example of bench research that holds the promise of translation into enhanced and targeted applied therapeutic management of a disease, breast cancer, which affects primarily women.

CONCLUSION

The 2009 WEMS-sponsored symposium at the annual EMS meeting served to introduce the audience to the many roles and promises of new genomic and genetic technologies in diagnosis, treatment, and prognosis of diseases in women that have strong genetic components or critical gene-environment interactions. Ovarian cancer, breast cancer, cardiovascular disease, diabetes, and obesity all fall into this disease category, and all are important public health issues that affect women disproportionately or exclusively. As the role of WEMS within the EMS matures over the Society's next 40 years, encouragement and support of women scientists and scientists who are exploring gene-environment interactions associated with diseases and conditions that impact women's health will be an important facet of EMS's mission. The rapid evolution in genomic technologies should provide new tools to explore some of the critical questions raised by the research projects described in this article. In the future, EMS will continue to provide a forum for the presentation and discussion of the science that impacts women's health.

Acknowledgments

The preparation of this manuscript was funded in part by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences; Grant sponsor: NIH; Grant numbers: R01-CA76016, R01-DK062378, R01-ES012503, PO1-ES009605, NCI MO1-RR01271; Grant sponsor: EPA; Grant numbers: R826886, R82670901; Grant sponsors: the Canadian Breast Cancer Foundation, the Alberta Cancer Research Institute, the Canadian Institutes for Health Research grants.

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