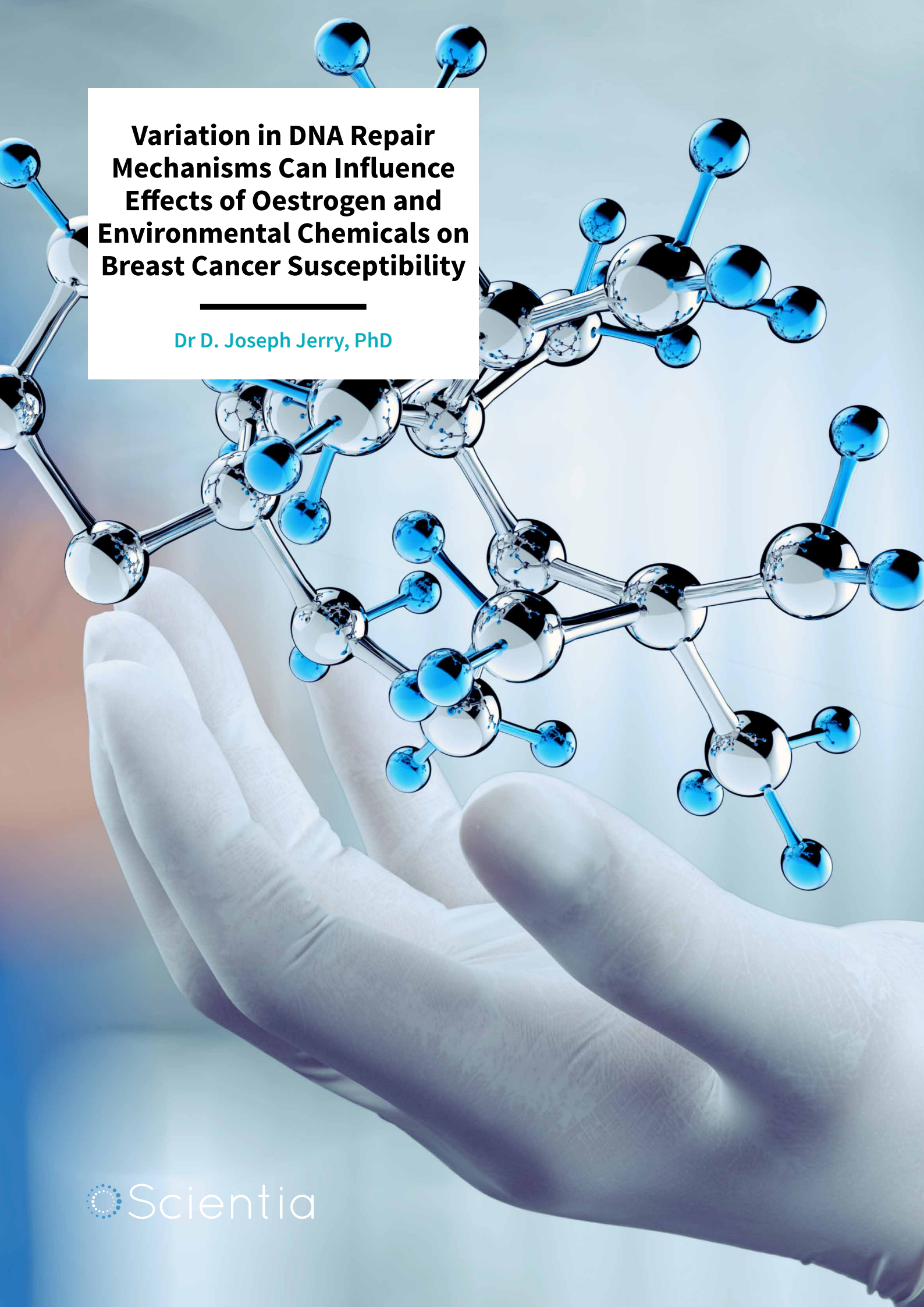

Variation in DNA Repair Mechanisms Can Influence Effects of Oestrogen and Environmental Chemicals on Breast Cancer Susceptibility

Dr D. Joseph Jerry, PhD

Scientia

VARIATION IN DNA REPAIR MECHANISMS CAN INFLUENCE EFFECTS OF OESTROGEN AND ENVIRONMENTAL CHEMICALS ON BREAST CANCER SUSCEPTIBILITY

All women are exposed to oestrogen from puberty through menopause. Oestrogen is a natural hormone that is important for breast development and the maintenance of tissues in women but is also linked to an increased risk of breast cancer. As many as 1 in 8 women in the USA will be diagnosed with breast cancer over their lifetime, and the majority of these breast cancers are sensitive to oestrogen. **Dr Joseph Jerry** and his collaborators at the University of Massachusetts are studying the environmental exposures and genetic differences that alter the consequences of exposure to oestrogens.

Oestrogen Signalling and the Link with Breast Cancer

At some point in their lifetime, 1 in 8 women in the USA will be diagnosed with breast cancer. Genetic factors and exposure to endogenous (i.e., internal) and environmental hormones can both influence the development of the breast epithelium and affect susceptibility to breast cancer. There is a large body of evidence demonstrating that breast cancers are sensitive to the actions of oestrogen in the majority of cases. Oestrogen is a natural hormone that has an important role in breast development and the maintenance of tissues in women. For a subset of women who are sensitive to endogenous or environmental oestrogen exposures, this may be associated with the subsequent development of breast cancer. Overall, however, the majority of women do not develop detectable breast cancers in their lifetime.

Dr Joseph Jerry, and his collaborators from the Department of Veterinary and Animal Sciences at the University of Massachusetts, the Pioneer Valley Life Sciences Institute and Baystate Medical Center, are working on an ambitious research plan. They are outlining how genetic variation in the general population affects the role played by oestrogen in the early stages of breast cancer. Then, by understanding the molecular basis for premalignancy in the human breast, they aim to develop diagnostic tools that can identify the women who are at high risk. Importantly, this identification of at-risk women would allow the provision of appropriate hormonal therapies at an earlier, more effective timepoint than currently possible.

The Effect of Dietary and Environmental Oestrogen on DNA Damage

Dr Jerry and his colleagues have worked extensively on the hypothesis that environmental chemicals mimicking the effects of oestrogen exacerbate or prolong the damaging effects of oestrogen in women who are sensitive. It has long been observed that exposure to oestrogen-like compounds available in the diet or the formulation of cosmetics can trigger the activation of oestrogen receptors. An abundance of

Elevated Risk

Low Risk

these receptors in breast cells may make them susceptible to DNA damage by exogenous (i.e., external) oestrogen-like compounds. Critically, DNA damage in epithelial breast tissue can contribute to the formation of malignant tumours.

The team published an article in 2020 reporting on the experimental observations of the effects on the DNA in mice and on human breast cancer cells following treatment with benzophenone-3 (BP-3) and propylparaben (PP), environmental chemicals that can mimic oestrogens referred to as environmental xenoestrogens. BP-3 is an ultraviolet filter used extensively in personal care products (such as sunscreens, cosmetics and lotions), while PP is commonly used as an antimicrobial agent in food and personal care products.

The study concluded that exposure to PP and BP-3 induced DNA damage in mammary glands of mice at concentrations relevant to acute oestrogen exposure in humans. PP and BP-3 also affected the DNA stability of cultured breast cancer cells and could cause DNA damage in the breast tissue of susceptible individuals. According to the researchers, the DNA damage in breast epithelium was caused by the formation of oestrogen receptor-dependent R-loops, a specific type of DNA damage that could in future be used as a sensitive endpoint for the screening for potentially harmful chemicals.

Genetic Variation Affects the Risk of Developing Breast Cancer

While all women are exposed to endogenous and environmental sources of oestrogen, it is important to remember that 7 in 8 do not go on to develop breast cancer and furthermore, there are reports that oestrogen may have a protective effect against breast cancer, for some women, at least. The strikingly different responses to oestrogen exposure among women prompted Dr Jerry's team to investigate if the variation in the responses among individuals could be related to small changes, known technically as polymorphisms, in specific genes. The team analysed human breast tissue samples from female donors undergoing reduction mammoplasty surgery to examine the DNA integrity following exposure to oestrogen.

The results of the study confirmed that responses are highly variable among women, suggesting that genetic polymorphisms could result in significant differences in intracellular signalling pathways among individuals. These differences may be important for identifying groups of patients who might be more at risk of developing breast cancer following prolonged exposure to endogenous and environmental oestrogens.

In another article, Dr Jerry and his co-authors reported that oestrogen signalling appears to be increased in the earliest stages of breast cancer and it is involved in benign or pre-malignant breast lesions known as atypical hyperplasias (AH). Understanding how AH lesions form could provide valuable insights into the molecular changes that cause breast epithelial cells to become malignant. The authors found that some genes can act as a 'signature' that discriminates the histologically normal tissue from AH tissues in 8 out of 10 cases. The genetic profiles associated

with AH breast lesions revealed variations in the oestrogen receptor levels among others. Monitoring the genetic profiles of patients presenting with AH lesions could help identify early changes in the epithelium that could be linked to an increased risk of cancer.

Genetic Polymorphisms Can Undermine DNA Repair Mechanisms

Dr Jerry's team is aiming to understand the cellular mechanisms promoting breast cancer in the oestrogen-sensitive subgroup of women, while at the same time trying to ascertain what factors contribute to cancer resistance in the majority of the population.

The group has recently published a manuscript in which they identify genetic polymorphisms in mice that alter DNA replication and repair pathways. Here, the researchers demonstrated that genetic polymorphisms were responsible for susceptibility to mammary tumours in a strain of rodents and resistance in another. The inherited polymorphisms interfered with DNA damage repair in all tissues, however, the development of tumours occurred most often in the breast epithelium. This suggests that the breast epithelium is especially reliant on DNA damage repair to maintain its genomic integrity.

The team is currently working on unpublished data that provide further evidence on oestrogen-induced DNA damage. They show that the damage is elevated among mice and rats that are susceptible to mammary tumours. Furthermore, the researchers speculate that alterations affecting the DNA repair pathways could exacerbate the risk of breast cancer in humans. Preliminary data confirm that the sensitivity to 'pathogenic actions' of oestrogen is also higher in women with an inherited risk of breast cancer compared to the general population. Given that urinary concentrations of environmental oestrogens suggest that more than 20% of women are exposed to levels that are sufficient to stimulate DNA damage, it is important to identify individuals who might be more susceptible to these adverse effects of environmental oestrogens.

Future Perspectives

Dr Jerry and his collaborators argue that it is vital to understand and map out the cellular mechanisms that control the levels of DNA damage in most women. Once those pathways are identified, they can be used as therapeutic targets for treating or preventing breast cancer in the subset of women who are most at risk. Biomarkers of DNA damage in breast cancers would provide tools to assess the risk of progression and to identify specific therapies. This means that it would be beneficial to observe specific patterns of gene expression among women and whether those would provide the medical profession with suitable biomarkers for the identification of risk among the general population.

Preliminary data from Dr Jerry's current research show that specific molecular probes can identify DNA damage in the nuclei of cells by emitting fluorescence. These probes could be employed for the analysis of tissue obtained from core biopsies. The prevalence of the DNA damage caused by oestrogen be used to define thresholds associated with increased risk of breast cancer.

Dr Jerry and Dr Grace Makari-Judson are Co-Directors of the Rays of Hope Center for Breast Cancer Research, a collaboration between the University of Massachusetts, Baystate Medical Center and the Rays of Hope charity. Through the generosity of women, the Center has worked with advocates, scientists and clinicians to create a unique repository of normal human breast tissues. This resource is allowing researchers to get closer to a breakthrough in this important field of medicine. The Rays of Hope Center has helped lay the groundwork for the research on chemicals in cosmetics and sunscreens that may contribute to the cause of breast cancer for a subset of women.

More research is needed to understand the impact of Dr Jerry's findings. Most critically, we need to better elucidate the health risks posed by chemicals in personal care products and identify individuals for whom the chemicals pose a significant hazard.

Meet the researcher

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Dr D. Joseph Jerry obtained his PhD in Nutrition in 1987 from The Pennsylvania State University. After postdoctoral training in genetics (Jackson Laboratory) and molecular virology (Baylor College of Medicine), he joined the University of Massachusetts Amherst in 1993, where he is currently Professor of Veterinary & Animal Sciences. Since 2011, he has been Co-Director at the Rays of Hope Center for Breast Cancer Research. The Rays of Hope project has established a Breast Research Registry with more than 1,200 individuals enrolled as of June 2020. The resource provides lifestyle data as well as tissue specimens and breast cell cultures from donors. Dr Jerry and the team of collaborators have shown that oestrogen and environmental xenoestrogens stimulate DNA double-strand breaks that are mediated by oestrogen receptors. Their studies using human breast explants indicate that the pathogenic effects of oestrogen may be enriched among individuals who are susceptible to breast cancer.

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FURTHER READING

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