



PETER BAKER

## Investigating Disparities in Breast Cancer Outcomes

Lajos Pusztai, MD, DPhil

A few years ago, a group of Yale physicians and researchers drew upon the massive National Cancer Database to see if race played a role in how women with breast cancer responded to pre-surgical chemotherapy. The answer turned out to be yes, for some types of breast cancer. For instance, African-American women with triple-negative breast cancer (TNBC, also called HER2-negative) were significantly less sensitive to chemotherapy, meaning that their cancer was more likely to survive treatment. That increased the likelihood that their cancer would return, spread, and become fatal despite best current therapies.

What accounts for this racial disparity? That's the question being explored by several of those same Yale scientists in a new project. They already know, based on research done by themselves and others, that there is one strong

molecular feature that can predict response to chemotherapy in TNBC, regardless of race.

“And that marker is the number of immune cells in the cancer microenvironment,” said Lajos Pusztai, MD, DPhil, Professor of Medicine and Co-Director of the Genomics, Genetics and Epigenetics Program, and also the project's primary investigator. “The more immune cells there are, the more likely the cancer will respond to treatment. So maybe the reason why African-American women with triple-negative breast cancer don't respond as well to chemotherapy as other races is that they have fewer, or less active, immune cells in the cancer.”

Chemotherapy works by killing or damaging cancer cells. It is widely believed that chemotherapy-damaged cells get finished off by swarms of immune cells that respond to the tissue damage. But if the number of immune cells in the microenvironment is low, some of the damaged cancer cells can elude the attackers, recover, and resume growing. That's what Dr. Pusztai and his colleagues suspect is happening among African-American women, and it's the hypothesis they are testing in the new project, whose three components are now underway.

“First we need to establish that the lower response rate of African-American women is due to lower immune activity in the microenvironment,” said Dr. Pusztai. They are investigating that with data from The Cancer Genome Atlas (TCGA), comparing immune gene expression patterns in TNBC among African-American women and non-African-American women.

Second, they are validating those findings in an independent cohort with tissue taken from women with TNBC treated at Smilow Cancer Hospital. The patients in the cohort are being matched for many variables, such as age, time of diagnosis, tumor size,

and tumor grade. One of Dr. Pusztai's research partners, David Rimm, MD, PhD, Professor of Pathology, Director of Pathology Tissue Services, and Director of Translational Pathology, is collecting the tissue from 50 African-American women with TNBC and 50 non-African-American women.

The third component is a clinical trial. African-American and non-African-American women will receive the standard pre-operative chemotherapy, but also immunotherapy

cancer survival in other countries, with very different racial composition than the U.S., you will find that people with lower socioeconomic status have poorer outcomes. This suggests a major role for socioeconomic factors in health care disparities. Indeed, African-Americans in the U.S. also have a higher rate of dying from prostate cancer, lung cancer, colon cancer, breast cancer, diabetes, kidney failure, and many other diseases which would be hard to explain solely

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in the form of a PD-L1 inhibitor called durvalumab. The drug stimulates the immune system.

“We want to see whether the weaker response to chemotherapy among African-American women with TNBC can be overcome by adding an immune-boosting drug,” said Dr. Pusztai.

If these studies confirm the hypothesis that African-American women with TNBC have fewer immune cells in the tumor's microenvironment, the next question is, why?

“One possible hypothesis is that there is some sort of shared racially-inherited genetic driver of lesser immune response to the cancer,” said Dr. Pusztai. “Another, perhaps more likely possibility, is chronic stress related to socioeconomic circumstances. If you look at breast

based on genetic predisposition.” However, socioeconomic status can have measurable effects on human physiology. “So, the next thing to study,” continued Dr. Pusztai, “is whether socioeconomic stresses can alter the immune system in the cancer tissue environment.” That could be tested by measuring stress hormones in the blood of people who are chronically stressed compared with people who aren't and correlate this with immune activity in the cancer microenvironment.

But at the moment he is focused on investigating whether boosting the immune system can improve outcomes for African-American women with triple-negative breast cancer. If so, then immune-stimulating drugs such as durvalumab may soon become standard of care and correct the disparity that is currently costing women their lives. ☺