



**CANCER RESEARCH: Probing the Roots of Race  
and Cancer**

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## CANCER RESEARCH

# Probing the Roots Of Race and Cancer

**African-American women are more likely to develop aggressive breast tumors than are Caucasians. Funmi Olopade is trying to understand why**



**CHICAGO, ILLINOIS**—The breast cancer patients Olufunmilayo Olopade saw as a resident at Cook County Hospital in Chicago reminded her of home. In her native Nigeria, as in the Chicago, Illinois, neighborhoods served by Cook County, the women she saw with breast cancer were often poor, black, unusually young, and very ill. Chicago was a world apart from the Lagos that Olopade had left behind in 1982. She had come to the United States to collect a brother who had dropped out of graduate school. Instead, she wound up settling in this snowy city. Working at Cook County, she became intrigued by the cancer parallels: Often the tumors were aggressive, the patients were young, and, in racially diverse Chicago, they were disproportionately of African descent. “What is this about?” she remembers thinking.

Twenty-five years later, that question anchors Olopade’s expansive and frenetic efforts to unravel the disparities of breast cancer. It’s long been known that black women, although less likely to suffer from the disease than whites, are far more likely to die of it, a difference traditionally attributed to lack of access to health care. But

Olopade and a number of other scientists are finding something else: In more than a dozen studies, they’ve documented that breast tumors in African-American women tend to be more aggressive, less responsive to treatment, and more likely to strike before menopause than breast tumors in whites and other ethnic groups. The differences persist even when statisticians adjust for every variable they can think of, from body weight to education to the cancer treatment given.

Still, the “science of disparity,” as Olopade likes to call it, remains on the periphery of oncology research. Oncologists worry that by focusing on it, they’ll be perceived as dismissive of the very real gulf in access to care. And they’re generally reluctant to seek physiological distinctions between races. “It’s such a contentious issue, and it causes people so much stress to conclude there may be a difference” in biology, says Wendy Woodward, a radiation oncologist who treats breast cancer at M. D. Anderson Cancer Center in Houston, Texas. She recently reported that even when black women with breast cancer receive the same treatment as whites in clinical trials, their

chance of developing incurable metastases is about 20% greater.

Olopade, a commanding presence with a radio announcer’s voice, was one of the first to call attention to these differences in the late 1990s. Today, she treats patients at the University of Chicago (U Chicago), where she also runs a 12-person molecular biology lab and participates in a vast, multimillion-dollar study of the effects of stress on breast cancer susceptibility in mice and people. Her network is growing. Last year, she inspired the founder of Crate and Barrel, the home furnishings retail chain, to help raise \$1 million for the university’s breast cancer research efforts. In 2005, the MacArthur Foundation rewarded her with one of its \$500,000, no-strings-attached “genius” grants.

Olopade, who goes by the nickname Funmi, is using her MacArthur money to trace the biology of disparity to where its roots may lie, in Africa. Her efforts intensified after tumor samples she collected 3 years ago from women in Nigeria and Senegal revealed an even higher rate of aggressive disease than in African-American women—suggesting that genetics may partly explain the difference.

### Troubling differences

Studying disparity was not what Olopade first had in mind. When she arrived at the University of Chicago, she focused on the genetics of leukemia and lymphoma and later on breast cancer. Two genes that conferred a high risk of breast cancer, *BRCA1* and *BRCA2*, had recently been discovered, and Olopade established a clinic to counsel and treat women with *BRCA* mutations and other high-risk characteristics.

Many of the young black women in her clinic who had not inherited *BRCA* mutations, Olopade noticed, nonetheless seemed to develop a form of breast cancer that closely resembled that seen in *BRCA1* carriers. Known as estrogen-receptor-negative (ER-negative) breast cancer, these tumors are not fueled by estrogen and do not respond to drugs such as tamoxifen and raloxifene that cut off their supply of the hormone. They also tend to metastasize and spread more quickly than ER-positive tumors.

As a breast oncologist, “you really get hit in the face with the relatively unique or different cancers that are afflicting women of African background,” says Lisa Newman, director of the breast care center at the University of Michigan, Ann Arbor. Like Olopade, she was struck by the young age of many of her black patients—and indeed, studies have shown that 31% of African-American breast cancer sufferers are under age 50; the comparable figure for white Americans is 21%. Furthermore, systematic surveys have recently confirmed the anecdotal evidence gathered by physicians such as Olopade and Newman: Nearly 40% of breast cancer cases among African-American women are ER-negative, compared with 23% of cases among whites.

As technologies advance, clinicians are identifying cancers by more precise signatures. Last June, for example, a team of U.S. and Canadian researchers published results in *The Journal of the American Medical Association* from the Carolina Breast Cancer Study, which examined the prevalence of different breast cancer subtypes among 496 breast cancer patients. The researchers were particularly interested in a high-risk “basal-like subtype.” These “triple-negative” tumors—negative for estrogen receptors, progesterone receptors, and human epidermal growth factor receptor-2 (HER2)—tend to spread quickly. And because they don’t respond to targeted new drugs, they can be hit only with traditional chemotherapy.

### Breast Tumors: More Common in Whites, Deadlier in Blacks

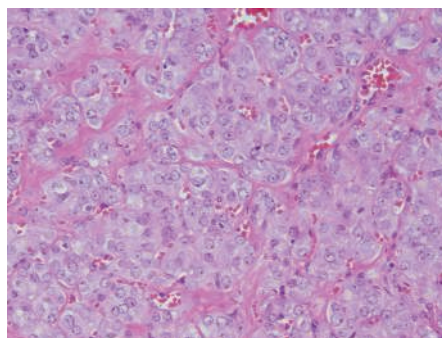
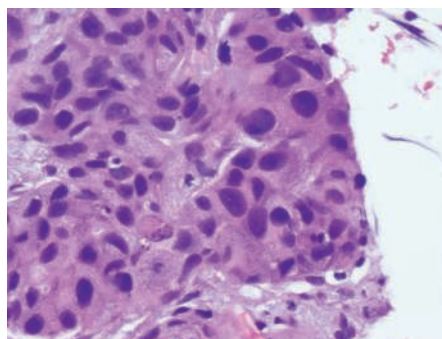
	Breast cancer incidence	Survival*	Under age 50	ER-negative	High grade
Caucasians	134/100,000	90%	21%	23%	41%
African Americans	118/100,000	77%	31%	39%	57%

\* Five years after diagnosis.

Triple-negative tumors, it turns out, are also unusually prevalent in young African-American women. Of the 97 premenopausal African Americans in the Carolina Breast Cancer study, 39% had this subtype. Among postmenopausal African Americans, the number was 14%, whereas in the 300 non-African Americans, regardless of age, it held steady at 16%. “The question is how much is nature, how much is nurture, how much is something else?” says Lisa Carey, a breast oncologist at the University of North Carolina, Chapel Hill, who helped conduct the study.

### Back to Africa

“I started off thinking that it was all genetics,” explains Olopade. On a frigid December day in Chicago, she’s striding between campus buildings after a meeting with members of the National Institutes of Health. Three officials are in town for the day to evaluate the university’s \$9.7 million Center for Interdisciplinary



**Triple jeopardy.** Breast tumors negative for three key markers (*top*) are tougher to treat than the triple-positive variety (*bottom*); in one study, 39% of young African Americans had triple-negative tumors, compared to 16% of Caucasians.

Health Disparities Research, which Olopade helped launch with her next-door neighbor and U Chicago colleague, biopsychologist Martha McClintock, and social scientist Sarah Gehlert. Olopade, in a black suit with thin white stripes and a black coat with fur trim, shows no signs of fatigue despite having left the hospital at midnight the night before, after admitting two seriously ill African-American breast cancer patients. Word among her colleagues is that she rarely sleeps.

She’s also one of a tiny handful of breast cancer experts turning to Africa to help explain racial disparities. After confirming that fewer than 10% of the women in a group of patients from Nigeria had inherited a *BRCA* mutation, Olopade found that a startling 77% of 378 samples from Nigeria and Senegal were ER-negative. This contrasts with 39% in African Americans and 23% in Caucasians. Although many of the African women were young, and younger breast cancer patients are more prone to have ER-negative tumors, the numbers were still off the charts. “This just blew us away,” she says. Those results, which Olopade and her colleagues presented at a cancer meeting in 2005 and are readying for publication, led her to believe that aggressive breast cancers in blacks are driven by an interplay of genes and environment.

These days, Olopade is joined in Africa by Newman, who is recruiting breast cancer patients in Kumasi, Ghana, in collaboration with Ghanaian investigators. “A lot of the slave[s] came through” Ghana before traveling to America, notes Newman, who hopes that by comparing samples from Ghanaian women with those from African Americans and whites, she’ll develop a better understanding of what’s driving aggressive, ER-negative disease.

Like others in the field, Newman has encountered concern about turning back to “an era of practicing race medicine, where you get one type of care if you’re black and another if you’re white,” she says. Newman, who’s African-American herself, decries that view. “We’re talking about a cancer-control issue,” she says. “Getting a better sense of the hereditary issues ... has implications for women worldwide.”

But in tackling the genetics behind breast cancer disparity, researchers must also address what race, a crude construct, really means. “Race is not a scientific category,” says Harold Freeman, a cancer surgeon and medical director of the Ralph Lauren Center

for Cancer Care and Prevention in New York City. While he praises Olopade's work, he is skeptical about performing research on populations whose distinctions he considers socially determined. And even if biological differences are relevant, Africans and African Americans "come from the most genetically diverse continent in the world," says Lovell Jones, who conducts health disparities research at M. D. Anderson Cancer Center. It's important to specify race according to place of origin and not rely on vague identities, he says. He's beginning a study of Nigerian immigrants in Houston, their relatives who remain in Africa, and African-American women, to determine whether susceptibility to breast cancer differs as a way of estimating the importance of environmental factors.

Olopade is taking a closer look at environment herself. Several years ago, she launched another Nigerian project, now funded by the U.S. National Cancer Institute, for which she's recruiting 2000 women, half with breast cancer and half without. She and her colleagues are gathering information about their environment, family history, and, if relevant, their tumors. Members of her lab are also now studying African-American breast tumors for patterns of methylation—regulatory alterations in DNA—in the *BRCA1* gene. Olopade wonders whether an altered form of the normal *BRCA1* gene could account for more aggressive tumors in some blacks.

DNA methylation can be brought about by environmental factors, agrees Lieutenant Colonel Larry Maxwell, director of the gynecologic disease program at Walter Reed Army Medical Center in Washington, D.C.

His work focuses on uterine cancer, in which black women more often fare worse than whites. Maxwell is studying methylation patterns to discern differences in the tumors of African Americans and Caucasians.

In the Chicago health-disparity center to which Olopade devotes a slice of her time, another environmental driver may be emerging. Co-Director McClintock has shown that when rats are socially isolated early in life, increasing stress and vigilance and prompting immune system changes, they develop breast tumors 40% earlier and four times

more often than do animals housed in groups. The isolated rats also display larger, more aggressive tumors.

Now the center is recruiting hundreds of African-American women with breast cancer in Chicago to begin assessing whether social isolation and stress-hormone levels predispose to cancer. "The whole idea is to elevate it to a science," says Olopade of disparity research.

### Branching out

The field seems to be gaining momentum. In October, the American Association for Cancer Research (AACR) hosted 30 researchers in



**Sleuthing for answers.** Olopade, with one of her patients, is adamant that the black-white survival gap isn't due only to inadequate access to health care.

Philadelphia, Pennsylvania, to discuss the science of cancer disparities and plan a large meeting on the subject for the end of 2007, which Olopade will co-chair. "It's been understudied," admits Margaret Foti, chief executive officer of AACR, of disparity science.

Kathy Albain, a breast oncologist at Loyola University Medical Center in Maywood, Illinois, has been poring over data from decades of clinical trials. Among 19,400 patients, 12% of whom were African American, differences in survival by race emerged for ovarian, breast, and prostate

cancers. Despite uniform treatment, blacks fared worse, on average, than whites, even after adjusting for differences in tumor type and other factors. But no comparable survival differences surfaced for other cancers, including lung cancer, leukemia, colon cancer, and multiple myeloma. "There must be something else going on pertaining to molecular biology, pharmacogenetics, hormonal issues," says Albain, who presented her most recent data, an in-depth analysis of more than 6000 breast cancer patients, at a meeting last December in San Antonio, Texas. She and her colleagues are looking more closely at a number of other variables in the different cancers, from white blood cell counts to drug doses.

Even as disparity research draws more scientists, it remains a touchy topic. It's "a very loaded area," says Timothy Rebbeck, who studies prostate cancer disparities at the University of Pennsylvania. "You can imagine saying, 'There is a genetic basis to health disparities.' It's something you have to say very carefully so it doesn't get misinterpreted."

Some cancer researchers also worry that disparity research could lend support to racial stereotyping. "If you listen to some folks, ... it sounds like they're talking about blacks having weaker genetics," says Otis Brawley, deputy director of the Emory Winship Cancer Institute in Atlanta, Georgia. Brawley believes that studying the science of disparities has distracted from focusing on disparities in treatment and access to care. "I'm not the only one who feels this way," he adds, although "I may be the loudest."

Olopade the straight talker responds forcefully to such criticisms, arguing that the aggressive disease she so often sees is not due only to poverty and lack of access to care. And she has strong defenders, especially among colleagues such as Rebbeck, who has collaborated with her for many years. "She's very outspoken and forceful and direct in a good way," he says.

Olopade says that her patients are the ones who really remind her how broad disparities research should be. Visiting the hospital room of a 50-year-old African-American breast cancer sufferer, who initially declined treatment and whose triple-negative disease has spread through her chest, she touches the woman gently on the shoulder, inquires about her family, and asks her to please listen to her doctors. "It keeps me thinking—that woman, why is she in the position she's in?" she wonders later. "If I don't have the experience of seeing patients like that, who walk in, and I studied disparities," she says, "I would never get it."

—JENNIFER COUZIN