Two documents pinned to this article provide verifiable proof that shortened telomeres are the primary case of triple negative breast cancer (TNBC). With that said, the issue of how telomeres can be shortened more frequently in African-American women than in white women must be identified.

Supported by numerous studies, stress (anxiety) is a factor for shortening of telomeres. The following is one example.
https://www.sciencedirect.com/science/article/pii/S088915911630023X

How could African-American women have increased levels of stress in comparison to white women?

In our opinion, the list of reasons could be lengthy. However, a large volume of studies identify the existence of epigenetic inheritance of chronic diseases from the mother to offspring as well as from the father to offspring.

Can anyone disprove these points as being the near certain cause that African-American women have dramatically higher instances of TNBC?

http://theconversation.com/why-is-breast-cancer-mortality-higher-for-african-american-women-than-for-white-women-91381?utm_medium=email&utm_campaign=Latest%20from%20The%20Conversation%20for%20February%2023%202018%20-%2095418190&utm_content=Latest%20from%20The%20Conversation%20for%20February%2023%202018%20-%2095418190+CID_b7246d612d85727ec5328fb64b3fd0b7&utm_source=campaign_monitor_us&utm_term=Why%20is%20breast%20cancer%20mortality%20higher%20for%20African-American%20women%20than%20for%20white%20women

Why is breast cancer mortality higher for African-American women than for white women?

February 23, 2018 6.43am EST

Georgia State University provides funding as a founding partner of The Conversation US.

White women in the U.S. are slightly more likely to develop breast cancer than black women – but less likely to die of it. There has been a 35 percent decrease in breast cancer mortality rate from 1990-2012. The breakdown by race over this period, however, shows a different story. Death rates for black women decreased by 23 percent, while the death rates for white women declined by 42 percent.

A big, but not the only, reason for this is that white women tend to more frequently get two subtypes of breast cancers, called ER-positive or HER2-positive, for which we now have very effective targeted treatments.

Black women, however, are two to three times more likely than white women to get an aggressive type of breast cancer called triple negative breast cancer, for which there are still no approved targeted treatments. Researchers do not yet know all the reasons why this is so, but are looking for answers. MCFIP - The document affixed to this article explains the recently identified targeted treatment for TNBC.

Research has vastly improved breast cancer treatments and survival rates over the years, with a five-year survival rate for localized breast cancer at 98.9 percent, but the gap in mortality rates between black and white women has stubbornly persisted.

We study breast cancer, with a special emphasis on health disparities. Here are some of the trends we see.

Disturbing numbers

First, some statistics that lay out the extent of the problem. About 1 in 8 American non-Hispanic white women, and about 1 in 9 African-American women will suffer from breast cancer in their lives.

While breast cancer is slightly less prevalent in African-American women, it is much more likely to be diagnosed at a later stage in them. About 37 percent of white patients and about 47 percent of black patients will have cancers that have spread from their breast to nearby lymph nodes at diagnosis. When the disease has spread, it typically presents a greater treatment challenge. In fact, the five-year survival rate for breast cancer patients with distant metastasis, or disease that has traveled to another organ

such as the liver or bone, is 26.9 percent, as compared to 98.9 percent for those with a localized disease.

In addition, the aggressive triple negative type of breast cancer accounts for 12-20 percent of tumors in white women, but about 20-40 percent in black women. Triple negative breast cancer is particularly hard to treat because it does not respond to targeted treatments that have proven to be effective in treating breast cancers that test positive for certain receptors on cancer cell surfaces.

Internal environment

Beyond triple negative cancer itself, there also seem to be racial differences in what we call the tumor microenvironment of the cancer cells. Tumor microenvironment is the immediate cellular environment of the cancer cells, including surrounding blood vessels, immune cells, signaling molecules and the tissue matrix that surrounds tumor cells (i.e., the extracellular matrix). Since the tumor microenvironment can affect behavior of the tumor cells and their response to treatments, these racial differences could impact tumor biology and disease progression. Studies have also uncovered racial differences in gene expression patterns of cancer cells, in which genes are over-expressed or under-expressed in the tumor cells of black versus white women.

One of the common abnormalities found in cancer cells proliferating within tumors is that they often gain or lose stretches of DNA, which could include multiple genes, or even whole chromosomes that carry hundreds of genes. As a result, cancer cells may harbor higher-than-normal or lower-than-normal copies of genes compared to healthy cells. Daughter cells that arise from such cancer cells form a “clone of cells” that could be genetically different from other such clones within the tumor.

When this gain or loss occurs at a fast rate, it results in a tumor with astounding clonal diversity. Such tumors are more likely to harbor clones that can spread very efficiently through the body or resist treatments very staunchly, resulting in a higher risk of death for the patient. Scientists have discovered that breast tumors in black women tend to be more clonally diverse, and therefore harder to treat, than those in white women. The discovery of these biological factors is fairly recent, and research is still ongoing.

Beyond tumor biology

Having other diseases, such as diabetes, also could be not only a risk factor for developing breast cancer but also for poorer outcomes, research has shown.

Some statistics point to problems outside of the sphere of medicine, however.

In the U.S., about 23.1 percent of black women live in poverty, compared to 9.6 percent of white women. Studies have shown that a lack of resources makes a huge difference in survival rates, treatment responses, and progression of disease. Poor women are less likely to have good quality health insurance, to get as much information on early detection and screening, and to have access to the best health care and latest treatments.

MCFIP - Could living in poverty increase stress? Could stress from generation to generation cause epigenetic inheritance?

Another factor, that is both biological and environmental, is obesity. According to the National Cancer Institute, fat tissue actually makes the hormone estrogen. Exposure to high levels of estrogen over a lifetime increases the risk of breast cancer.

Further, in the U.S., obesity is strongly linked to poverty, according to the National Institutes of Health. In other words, since black women are more likely to be poor, they are more likely to be obese – which makes them more likely to develop breast cancer.

The higher incidence of poverty among African-Americans also affects access to high-quality, timely care compared to white women.

The search for advances

In future years, we hope we will find specific mechanisms that explain the observed racial differences in breast cancer mortality. Eventually, we believe it will be possible to give each patient customized targeted treatments based on their genetic profile and other factors.

There are many factors that will need to be addressed to create racial equity in breast cancer outcomes. Bridging the gap will require a wide range of experts: clinicians, bioinformaticians, diagnosticians and epidemiologists from the science side, but also social scientists and public health experts. Only by joining together can we make sure that all breast cancer patients get the treatment that is best for them.

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The cellular defense against mitochondrial defects is mitophagy; encapsulation of the organelle in a lysosome where it can be degraded (subjected to ubiquitination) and reassembled through self-assembly based on the principles of particle physics.

Numerous designations exist for the molecule that performs mitophagy; including CTLA4 and the granzyme D (aka GZM-D).

https://medicalxpress.com/news/2018-02-uncovers-therapeutic-aggressive-triple-negative-breast.html

Study uncovers therapeutic targets for aggressive triple-negative breast cancers

February 3, 2018 by Katherine Unger Baillie, University of Pennsylvania

As part of a breast-cancer diagnosis, doctors analyze the tumor to determine which therapies might best attack the malignancy. But for patients whose cancer is triple-negative—that is, lacking receptors for estrogen, progesterone and Her2—the options for treatment dwindle. Triple-negative cancers, or TNBC, also tend to be more aggressive than other cancer subtypes.

While it is known that defects in mitochondria, the cells' energy generators, are associated with the initiation of breast cancers, it is currently unclear whether alterations in mitochondrial DNA or mitochondrial function contributes to TNBC metastasis or to their notorious resistance to chemotherapy.

New findings from a study led by researchers at the University of Pennsylvania have made inroads into a strategy to identify TNBC tumors at risk for metastasis, and eventually target these cancers with drugs. The work, which compared the metabolic profiles of different cancer sub-types, identified patterns associated with aggressive triple-negative breast cancers that point to the possibility for more accurate risk assessment and personalized treatment.

"Currently there is no molecular diagnostic to identify which TNBC patients might be poor responders to available chemotherapies," said Manti Guha, a research assistant professor in Penn's School of Veterinary Medicine. "By identifying unique mitochondrial defects and alterations in metabolic gene expression in the most aggressive subset of tumors, this study provides new molecular biomarkers that could identify the aggressive subset of TNBCs and more importantly offer these patients promising options for treatment."

"The role of mitochondria in disease has been largely overlooked in western medicine," added Douglas Wallace, director of the Center for Mitochondrial and Epigenomic Medicine at Children's Hospital of Philadelphia and a mentor and collaborator of Guha's who was not an author on the paper. "Manti's work is transformative for this particular cancer because by identifying what is different about the mitochondrial energy system in triple-negative breast cancer compared to other, less dangerous forms of breast cancer gives us a real window into how we might intervene."

Guha's coauthors on the study, which appears in the journal BBA: Molecular Basis of Disease, were Penn Vet's Satish Srinivasan, Dawei Dong, Rumela Chakrabarti and Narayan G. Avadhani; Mike Feldman and Russ P. Carstens of Penn's Perelman School of Medicine; the Children's Hospital of Philadelphia's Pichai Raman and Deanne Taylor;

the University of Pittsburgh's Yuefu Jiang and Brett A. Kaufman; Kagohsima University's Yuko Kijima; and Columbia University's Martin Picard.

In an earlier report, Guha and colleagues had shown that, by experimentally inducing mitochondrial dysfunction, breast cancer cells can be reprogrammed towards metastasis.

"We have known for almost a century that, compared to normal cells, tumors have impaired mitochondrial functions and metabolic reprogramming," Guha said. "I was interested in identifying if there were differences in mitochondrial signatures among breast-tumor subtypes and if this variability in mitochondrial genome and functions among patient tumors can help identify cancer patients who are at an increased risk for metastasis."

The researchers made use of tissue samples from patients with different breast-cancer subtypes, defined cancer lines and previously collected genomic data representing 825 breast cancer patients. Screening for mitochondrial DNA copy numbers, they found that patients who had more advanced disease were more likely to have the lowest mtDNA copy numbers. They also found clear patterns in mtDNA copy numbers between breast-cancer subtypes, with triple-negative cancers having the most reduced copy numbers. Additional screening revealed an imbalance in a particular sequence of mtDNA that was prevalent in triple-negative tumors but not in other breast tumor subtypes.

"This particular mtDNA sequence imbalance is fairly unique and has not been reported in cancers," Guha said. "This could potentially be used to stratify patients into different risk categories."

Examining breast-cancer cell lines, they found differences in oxygen consumption between triple-negative and other cancer subtypes, indicating impaired cellular respiration and thus mitochondrial function in those cells.

In a broad screen of 84 genes related to metabolism, a process that mitochondria regulate, the researchers found clear patterns that characterized triple-negative tumors from other breast-tumor subtypes. These genes could serve as potential therapeutic targets for intervention, or as biomarkers to identify breast tumors that are more likely to metastasize, the researchers noted.

"We observed unique mitochondrial aberrations in TNBCs which can serve as a diagnostic marker of TNBC metastasis and be utilized to improved combined chemotherapeutic or individualized approaches," Guha said.

To build on these findings, Guha and colleagues are investigating whether FDA-approved therapies, or those currently in clinical trials, that target metabolic pathways could prove particularly effective against triple-negative breast cancer.

Explore further: **Study identifies potential targets for treating triple negative breast cancer**

More information: Manti Guha et al, Aggressive triple negative breast cancers have unique molecular signature on the basis of mitochondrial genetic and functional defects, *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* (2018). **DOI: 10.1016/j.bbadis.2018.01.002**

Provided by: University of Pennsylvania

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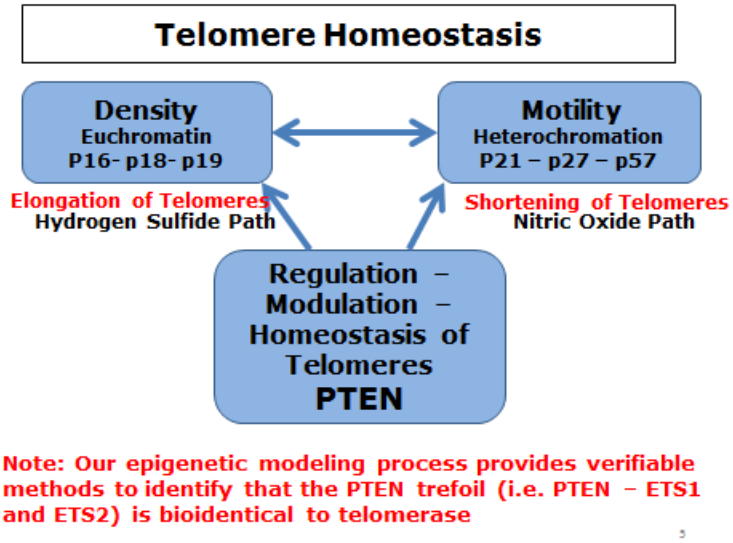
MCFIP - As outlined in the document affixed to this one, Ki67 is an alternative designation for p16, a regulator of telomere length.

Our modeling of TNBC indicates the reason the cancer is triple negative is attributable to the fact that one of the primary causes is telomere abnormalities that are not assayed as a factor.



http://www.oncotherapynetwork.com/breast-cancer-targets/biomarker-african-american-women-triple-negative-breast-cancer-indicates-poor-outcome

Biomarker in African American Women With Triple-Negative Breast Cancer Indicates Poor Outcome

News | March 03, 2017 | Breast Cancer Targets

By Lauren Evoy Davis

Scientists have discovered that African American patients with triple-negative breast cancer (TNBC) who carry a specific biomarker, nKIFC1, experience a dismal prognosis. The scientific community has become more aware that this patient population, due to socioeconomic issues, is diagnosed with later stage breast cancer so this finding is important.

This was first published in the journal *Nature*.
The expression was assessed by immunohistochemistry in 163 African American and 144 white TNBC tissue microarrays (TMAs) pooled from four hospitals. The nKIFC1 biomarker correlated significantly with Ki67 in white TNBCs, but not in African American TNBCs, suggesting that nKIFC1 is not just a surrogate for proliferation in African American TNBCs. High nKIFC1 weighted index (WI) was associated with significantly worse overall survival (OS), progression-free survival (PFS), and distant metastasis-free survival (DMFS) (hazard ratios [HR], 3.5, 3.1, and 3.8, respectively; $P = .01$, .009, and .007, respectively) in multivariable Cox models in African American TNBCs, but not white TNBCs.

"We looked at the levels of nuclear KIFC1 in their tumors, and interestingly, we found that African American women had slightly higher levels, but it was only within African American patients that the levels mattered for their outcome," saidAngela Ogden, lead author of the study and a PhD candidate in Dr. Ritu Aneja's laboratory in Georgia State's Biology Department. "African American women with high nuclear KIFC1 levels tended to do poorly, whereas in white women, it didn't matter if they had high or low levels. It had no effect on their outcomes."

The researchers further investigated why the biomarker only seems to matter in African American patients by studying triple-negative breast tumor cells from African American and white patients.

"We found that if we silence the KIFC1 gene, it had a greater impact on the migration of the African-American cells than it did on the white cells," Ogden said. "It may be that for whatever reason, in African-American breast cancer tumors, KIFC1 helps the cells to migrate and spread to other parts of the body. And for reasons that we currently don't know, that's not the case in white tumors. Ultimately, it may even be that African-American patients could potentially be treated with a KIFC1 inhibitor to help prevent metastasis, but that's for future studies."

TNBC accounts for 15% to 20% of all breast cancers, and is more prevalent in African American and Hispanic women, and women younger than 40 years of age. This oftentimes deadly cancer is also likely to metastasize early. These findings may lead to biomarkers that could identify differences in tumor biology between racial groups to predict risk and to help lessen health disparity in African American women who have this diagnosis.

Although it is not completely clear about whether African American women with TNBC is a molecularly distinct disease or whether African American women have a higher incidence of aggressive biology driven by disparities. However, it is important to learn how biology and disparities affect survival rate of African American women with TNBC.

MCFIP - If its alternative designations were used, it would be known immediately as a long standing biomarker for cancers; i.e. refer to studies to verify Ki67 as being bioidentical to p16 and CDKN2A.

http://www.techtimes.com/articles/148905/20160410/scientists-identify-molecular-marker-in-healthy-tissue-that-may-help-predict-breast-cancer-risk.htm

Scientists Identify Molecular Marker In Healthy Tissue That May Help Predict Breast Cancer Risk

By Ted Ranosa, Tech Times | April 10, 8:52 AM

Scientists from the Harvard Stem Cell Institute (HSCI), the Brigham and Women's Hospital (BWH) and the Dana-Farber Cancer Institute (DFCI) have discovered a biomarker that exists in the normal breast tissue of women, which can be used to determine whether they are at high risk of developing breast cancer later in life.
In a study featured in the journal *Cancer Research*, researchers Kornelia Polyak from the HSCI and Rulla Tamimi from the BWH led their colleagues in identifying new ways to find out the susceptibility of certain individuals to developing breast cancer.
Their paper builds on Polyak's earlier work where she found that women with a high risk to develop cancer and those who did not have a baby before they turned 30 years old had high amounts of progenitor cells in their mammary glands.

Polyak, Tamimi and their team examined data collected from 302 women diagnosed with benign breast disease who took part in the Nurses' Health Study and the Nurses' Health Study II. They compared tissue samples taken from 69 participants who had cancer to tissue samples from the rest of the group who did not develop the malignancy.

The team discovered that participants who had high levels of a molecular marker known as Ki67 were five times more susceptible to developing cancer. Ki67 was found in mammary epithelium cells, which are located in the lobules and mammary ducts of women. Most types of breast cancers are known to begin in these particular tissues.

While doctors already use levels of Ki67 present in breast tumors to help them determine the appropriate treatment for patients, this latest study is the first instance where medical researchers were able to associate the molecular marker to healthy tissue, which can be used to predict the likelihood of individuals to develop cancer.

Tamimi pointed out that doctors currently have a difficult time in finding out if a patient has a low or high risk of developing breast malignancies. Being able to identify those who are at a high risk for the cancer would allow researchers to come up with individualized screening as well as strategies on how to lower these risks.