The Warburg Effect Revisited: Does Increased Glucose Uptake in Mammary Cells from African-American Women Predict Aggressive Triple-Negative Breast Cancer?

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Public Abstract:
Why do I want to study sugar (glucose) addiction in breast cancer and pre-cancer cells? My mentor, Victoria Seewaldt MD, and I recently worked with a Nutrition Researcher, Oncologist, and Breast Cancer Survivor to develop a consensus statement about sugar and breast cancer. It became rapidly clear that there was no consensus. One key problem was the absence of data. It is also been known for many years that aggressive breast cancers become “addicted” to sugar (glucose) (AKA the Warburg effect). There is emerging evidence that weight loss and exercise is associated with decreased recurrence of breast cancer. However, there is a lack of data to prove or disprove whether a low sugar diet can 1) prevent breast cancer (primary prevention) or 2) prevent recurrence of breast cancer (secondary prevention). It is important to resolve whether a low sugar diet and/or tight glucose control can prevent breast cancer. Many of my high-risk patients and patients with breast cancer are following a low sugar diet. Another group of my young high-risk patients eat too much sugar, weigh too much, and have gestational diabetes during pregnancy. Serum glucose is an easy target: glucose can be lowered by Metformin, exercise, and diet. If lowering glucose can help prevent breast cancer, then we need to act.

Our Preliminary Data shows that there is high glucose uptake in chemotherapy-resistant triple-negative breast cancer and a subset of precancerous changes in young high-risk women. Activation of a protein pathway, Akt/mTOR, is known to regulate high (abnormal) glucose uptake in cancer cells and predicts poor prognosis in triple-negative breast cancer. Our Preliminary Data provides evidence that 1) chemotherapy-resistant triple-negative breast cancer frequently exhibits high glucose uptake, 2) Akt-signaling is activated in precancerous changes (atypia) from high risk women, and 3) high (abnormal) glucose uptake occurs in atypia from high-risk women. Hypothesis: Here I will test the hypothesis that 1) high (abnormal) glucose uptake (as measured by 2-NBDG fluorescence spectroscopy) occurs in mammary atypia from high-risk premenopausal women and 2) activation of Akt-predicts high glucose uptake in precancerous cells from high-risk women. Based on Preliminary Data, I anticipate that mammary atypia from many young high-risk African-American women and some European-American women will exhibit high glucose uptake. If so, these findings will have important implications. It is unclear whether dysregulation of signaling pathways that predict aggressive triple-negative breast cancer can be detected in mammary atypia. Published data from my mentor provides evidence that p-Akt/mTOR and vimentin is expressed in mammary atypia. Preliminary Data, demonstrates high glucose uptake in mammary atypia from young high-risk women. These findings provide evidence that glucose control may be an important strategy for breast cancer in young women. Aim 1: What is the frequency
of high glucose uptake (Warburg effect) in breast cancer subtypes and pre-malignant breast lesions? Preliminary Data provides evidence that chemotherapy-resistant triple-negative breast cancers have high glucose uptake. Here I will test for high glucose uptake in breast cancer subtypes, chemotherapy-sensitive vs. -resistant triple-negative breast cancers, and mammary atypia from high-risk African-American and European-American women. Aim 2: Does activated Akt predict high glucose uptake (Warburg effect) in live atypical mammary epithelial cells from premenopausal African-American and European-American women? Currently, it is not known whether the high-risk signaling pathways that predict poor prognosis in triple-negative breast cancer can also be detected in pre-cancerous breast disease from high-risk women. This information is critical for designing effective prevention strategies for rapidly progressing, aggressive triple-negative breast cancers. How the project advances our understanding of breast cancer and leads to reductions in mortality: It is assumed that high glucose uptake (Warburg effect) occurs only in advanced breast cancer. Our Preliminary Data provides evidence that the Warburg effect occurs in atypia from young high-risk women. Young African-American women have a high incidence of Type II and gestational diabetes. Obesity has long been associated with increased mortality from breast cancer, regardless of the menopausal status. Information gained from these studies can provide a new target for breast cancer prevention. While pregnancy can protect women against breast cancer for European-American women, pregnancy is not protective for African-American women. Furthermore, for all women, pregnancy increases breast cancer risk for 5 years following childbirth. If my studies show that high glucose uptake is observed in precancerous disease in high-risk women, this argues for efforts to prevent gestational diabetes (diabetes that occur during pregnancy) and provides mechanistic evidence that a low sugar diet may prevent breast cancer. Concerns in the LOI: Random Periareolar Fine Needle Aspiration (RPFNA) will be used to test cells from high-risk women. Do I expect all women to routinely undergo RPFNA? Response: No. RPFNA is being used here as a research tool to gather mechanistic information about early breast cancer. Am I proposing to use 2-NBDG to find small breast cancers? Response: No, imaging of glucose uptake does not find small cancer (not enough resolution). My goal is to use information gathered here to decide whether targeting glucose might be used to prevent breast cancer in African American women.