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**"Metabolic Disease and Malignancy: Investigating Breast Cancer Risk in Diabetes Using the All of Us Database"**

Background: Type 2 Diabetes Mellitus (T2DM) and breast cancer are two of the most prevalent chronic conditions that affect the female population. They may share overlapping metabolic pathways, including insulin resistance, hyperglycemia and chronic inflammation. Since elevated Hemoglobin A1c (HbA1c) levels are the gold standard marker of poor glycemic control and are associated with long-term diabetic complications, it can be used as a representation of average metabolic health of an individual. While T2DM and hyperglycemia have been linked to increased risk of breast cancer progression, the relationship between HbA1c levels and breast cancer development remains less studied.

Objective: To investigate whether high average HbA1c levels prior to diagnosis are associated with an increased risk of breast cancer in retrospective cohort data from the NIH All of Us Research Program.

Methods: Using the NIH All of Us database, we identified female participants with breast cancer and extracted hemoglobin A1c (HbA1c) measurements. A1c measurements for each participant were averaged 12 months and 6 months prior to first diagnosis of breast cancer. Patients without HbA1c data during these time frames were excluded. Glycemic control was defined using standard clinical thresholds (controlled < 6.5% vs uncontrolled ≥ 6.5%). Patients were then further categorized into normal, prediabetes, mild, moderate and severe hyperglycemia within the 6-month group to assess severity of glycemic control as diagnosis of breast cancer approached.

Results: Of 12,091 female participants with breast cancer, 5,971 participants also had complete HbA1c data prior to breast cancer diagnosis. 4,073 had HbA1c data 12 months prior to diagnosis, while 961 had HbA1c data 6 months prior to diagnosis. Using the more adjacent timeframe leading up to diagnosis (6 months), 33.6% of these patients were considered to have uncontrolled hyperglycemia (≥6.5%) while 66.4% were found to have controlled average blood sugar (<6.5%). When broken down into severity, 30.5% were considered to have normal A1c (<5.7%), 35.9% were considered pre-diabetic (5.7 – 6.4), 11.2% were classified as mildly uncontrolled (6.5 - 6.9), 11.7% moderately uncontrolled (7.0 – 7.9) and 10.6% were severely uncontrolled (≥ 8.0%). These results show that a clinically significant number of patients had some degree of hyperglycemia leading up to breast cancer diagnosis.