Letter to the Editor

Cancer Epidemiology, Biomarkers & Prevention

Gestational Diabetes Mellitus and Incident Invasive Breast Cancer—Letter

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In a recent publication, Powe and colleagues (1) focused on the association between the history of gestational diabetes mellitus (GDM) and risk of incident invasive breast cancer (1). They conducted a prospective analysis among parous women in the Nurses' Health Study II, with mean age of 35 years in 1989 (1). They used multivariate Cox proportional hazards models to compare risks of incident invasive breast cancer in women with and without a history of GDM (1). They conclude that the history of GDM is not associated with an elevated risk of subsequent invasive breast cancer, highlighting the need to further investigate GDM's role in breast cancer development (1). GDM accounts for a form of diabetes that is first documented during pregnancy, with no evidence of preexisting type I (T1D) or type II diabetes (T2D; refs. 2, 3). Different forms of diabetes show common pathogenesis characterized by a progressive β-cell demise or dysfunction (2, 3). Functional β-cell mass deficiency in diabetes is connected with imbalanced β-cell death and replication (2, 3). The p21-activated kinase 1(PAK1) has been involved in maintaining β-cell mass (2, 3). PAK1 is a ubiquitously expressed serine/threonine kinase that plays a critical role in cell proliferation (2). In the islet β-cell, chronic exposure to glucolipotoxicity stress impairs PAK1 abundance (3). A paucity of PAK1 in β-cell islets has been associated with T2D (3). Depletion of PAK1 has been described to enhance ubiquitin-mediated survivin degradation in pancreatic β-cells, implying that PAK1 influences survivin expression in islet β-cells (3). Although initially recognized as a cancer gene, survivin is essential for the maintenance of β-cell population (2, 3). It has been detected that either hyperglycemic conditions or a loss of PAK1 trigger the downregulation of survivin in islet β-cells (2, 3). It has been reported that 91 PAK1-related genes are linked to breast invasive carcinoma (4). Overexpression of survivin in breast cancer has been associated with aberrant inhibition of apoptosis, leading to massive proliferation of cancer cells (5). Increased expression of survivin has also been implicated in resistance to chemotherapy (5). Taken together, I hypothesize that the history of GDM does not relate to an elevated risk of subsequent invasive breast cancer as a result of the downregulation of PAK1 and survivin induced by GPT stress, taking into account the promoting effect of increased levels of PAK1 and survivin on breast cancer development and progression. Thus, I propose the existence of a sort of GDM paradox in breast cancer.

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