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Clinical characteristics of breast cancer in women with a PALB2 mutation

Cezary Cybulski[1], WojciechKluźniak[1], Tomasz Huzarski[1], Dominika Wokołorczyk[1], AnnirudhKashap[1], AnnaJakubowska[1], Marek Szwiec[2], Tadeusz Dębniak[1], BohdanGórski[1], Victoria Sopik[3], Mohammad Akbari[3], Ping Sun[3], Jacek Gronwald[1], Steven A Narod[3] and **Jan Lubiński[1]**
[1]Pomeranian Medical University, Poland
[2]Regional OncologyCenter, Poland
[3]Womens College Research Institute, Canada

Purpose: To estimate the lifetime risk of breast cancer in Polish women who carry a founder mutation in the PALB2 gene and to establish the clinical characteristics of breast cancers in patients with A Palb2 mutation.

Patients and Methods: 12,529 breast cancer patients from Poland and 4,702 controls were genotyped for two deleterious mutations in PALB2 (c.509_510delGA and c.172_175delTTGT).Among breast cancer patients, the ten-year survival of carriers of a PALB2 mutation was calculated and compared with that of non-carriers.

Results: A truncating PALB2 mutation was found in 116 breast cancer patients (0.93%) and in 10 controls (0.21%; OR=4.39; 95% CI=2.3 to 8.4; p<0.0001).The ten-year survival of women with breast cancer and a PALB2 mutation was 49%, compared to 76% for women without a mutation (HR for death=2.14; 95% CI=1.55 to 2.95; p<0.0001).Among the 2,065 patients who died, 38 women (1.8%) carried a PALB2 mutation.

Conclusion: Women with a PALB2 mutation face increased risks of breast cancer and of death from breast cancer.Given the high incidence and case-fatality associated with mutations in this gene, preventive mastectomy should be discussed with unaffected women who are found to carry a PALB2 mutation.

Targeting microtentacles on circulating breast tumor cells to reduce metastasis

Stuart S Martin, Marlene and **Stewart Greenebaum**
University of Maryland, USA

The great majority of current cancer drug development focuses on inhibiting tumor cell growth or local invasion. Comparatively little is known about therapeutic targets in CTCs or the effects of existing chemotherapies on CTCs.Our lab discovered that detached and circulating breast tumor cells generate dynamic membrane microtentacles (McTNs) that arise due to an imbalance between microtubule extension and contraction of the actin cortex specifically in detached epithelial cells. The cytoskeletal mechanism supporting McTNs matches the mechanism by which CTCs bind to blood vessel walls in vivo. Our current studies now show that McTNs are an independent marker of tumor stem cell characteristics.Since large epithelial tumor cells are crushed when pushed through narrow capillaries by blood flow, we are targeting McTNs to reduce tumor cell reattachment and increase the fragmentation of CTCs.Conversely, we have found that the common cytoskeletal drugs, such as the tubulin-stabilizing drug, Taxol, actually enhance McTNs and tumor cell reattachment.Surgery and neoadjuvant chemotherapy can increase CTCs up to 1000-fold, so understanding the CTC cytoskeleton is essential to ensure that cancer drugs do not inadvertently increase metastasis while targeting cell division. Together with engineering collaborators, we have developed a novel microfluidic medical device for imaging cytoskeletal dynamics in free-floating patient tumor cells. Using live-cell confocal microscopy, we have now demonstrated that McTNs are detectable within hours of when tumor cells are recovered from patients.This technology enables immediate testing of patient cells for responses to drugs that could influence CTC reattachment during metastasis.