

Ratio of blood Zn/Cu levels as a marker of survival in breast cancer patients

Marek Szwiec¹, Wojciech Marciniak², Róża Derkacz², Tomasz Huzarski³, Jacek Gronwald³, Cezary Cybulski³, Tadeusz Dębniak³, Anna Jakubowska^{3, 4}, Marcin Lener³, Michał Falco⁵, Józef Kładny⁶, Piotr Baszuk³, Jerzy Duszyński⁷, Joanne Kotsopoulos^{8,9}, Steven A Narod^{8,9}, Jan Lubiński^{2,3}

1. Department of Surgery and Oncology, University of Zielona Góra, Zyty 28, 65-046 Zielona Góra, Poland.
2. Read-Gene S.A., 72-003 Grzeczynica, Poland.
3. Department of Genetics and Pathology, International Hereditary Cancer Center, Pomeranian Medical University, 71-252 Szczecin, Poland.
4. Independent Laboratory of Molecular Biology and Genetic Diagnostics, Pomeranian Medical University in Szczecin, 71-252 Szczecin, Poland.
5. Regional Oncology Centre, 71-730 Szczecin, Poland.
6. Department of General and Oncological Surgery, Pomeranian Medical University, 71-252 Szczecin, Poland.
7. Nencki Institute of Experimental Biology, Polish Academy of Sciences, 3 Pasteur Street, 02-093 Warsaw, Poland.
8. Women's College Research Institute, Women's College Hospital, University of Toronto, Toronto, ON M5G 1N8, Canada.
9. Dalla Lana School of Public Health, University of Toronto, Toronto, ON M5T 3M7, Canada.

Abstract

Recently, there are more and more articles assessing the relationship between the level of micronutrients in the serum and the risk and prognosis of patients with breast cancer. Numerous observational studies and metaanalysis have shown decreased serum zinc level and increased copper levels in women with breast cancer. There are no clear data assessing the relationship between serum zinc, copper level and their ratio (copper/zinc) and the prognosis of breast cancer patients. In this study, we investigate serum level of zinc, copper and their ratio and survival after a diagnosis of breast cancer. We obtained a blood sample from 538 women diagnosed with a primary invasive breast cancer between 2008 and 2015 in the region of Szczecin, Poland. Blood was collected after diagnosis but before starting treatment. Serum zinc and copper level was quantified by mass spectroscopy and each patient was assigned to one of four categories (quartiles) based on the distribution in the entire cohort. After calculating the copper to zinc ratio, patients were also assigned to one of four categories (quartiles). Patients were followed from diagnosis to death over a mean follow-up of 9.97 years. Vital status was obtained by linkage to the Polish National Death Registry. We observed a relationship between serum zinc levels and ratio (copper/zinc) and overall survival. The 10-year overall survival was 64.9 % for women in the lowest ($\leq 762.7 \mu\text{g/L}$) and 79.9 % for those in the highest ($\geq 920.3 \mu\text{g/L}$) quartile of serum zinc level ($p = 0.004$), and was 58.3 % for women in the highest (≥ 1.563) and 82.1 % for those in the lowest (≤ 1.160) quartile of serum copper/zinc ratio ($p < 0.001$). The multivariate hazard ratio (HR) for death was 1.74 (95%CI 1.07–2.04; $p = 0.02$) for patients in the lowest quartile of serum zinc, compared to those in the highest, was 2.26 (95% CI 1.38–3.69; $p = 0.001$) for patients in the highest quartile of serum copper/zinc ratio, compared to those in the lowest and was not significant for serum copper levels. The 10-year breast cancer-specific survival was 73.8 % for women in the lowest ($\leq 762.7 \mu\text{g/L}$) and 84.3 % for those in the highest ($\geq 920.3 \mu\text{g/L}$) quartile of serum zinc level ($p = 0.009$), and was 67.2 % for women in the highest (≥ 1.563) and 84.9 % for those in the lowest (≤ 1.160) quartile of serum copper/zinc ratio ($p < 0.001$). The multivariate hazard ratio (HR) for breast cancer death was 1.85 (95%CI 1.02–3.37; $p = 0.04$) for patients in the lowest quartile of serum zinc, compared to those in the highest, was 2.07 (95% CI 1.17–3.63; $p = 0.01$) for patients in the highest quartile of serum copper/zinc ratio, compared to those in the lowest and was not significant for serum copper levels. There is evidence that the serum zinc level and copper/zinc ratio provides an independent predictive value for overall survival and breast cancer specific survival after breast cancer diagnosis.