Zinc and Breast Cancer Survival

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Zinc is an essential mineral incorporated into at least 300 enzymes, and is involved in numerous signaling pathways important for, e.g., cell proliferation and differentiation, cell cycle regulation, apoptosis and redox regulation. Zinc has been reported in preclinical studies to trigger an interplay of G protein estrogen receptor with insulin-like growth factor receptor I (IGF-IR) and epidermal growth factor receptor, which results in the activation of important transduction pathways and biological responses such as proliferation and migration in breast cancer cells.

Keywords: zinc ; breast cancer ; survival

1. Background

Zinc is an essential mineral incorporated into at least 300 enzymes, and is involved in numerous signaling pathways important for, e.g., cell proliferation and differentiation, cell cycle regulation, apoptosis and redox regulation [1]. While some reports exist on zinc levels and breast cancer risk [2][3][4], little is known about zinc regarding its potential effect on breast cancer survival. Although the potential role of zinc in breast cancer survival is not well-known, many possible biochemical mechanisms have been discussed [5]. Zinc has been reported in preclinical studies to trigger an interplay of G protein estrogen receptor with insulin-like growth factor receptor I (IGF-IR) and epidermal growth factor receptor, which results in the activation of important transduction pathways and biological responses such as proliferation and migration in breast cancer cells [6]. Furthermore, it has been shown that tamoxifen-resistant breast cancer cells have increased levels of zinc and zinc transporter ZIP7, leading to increased growth and invasion [7]. In addition, ZIP10 is involved in invasive behavior and metastasis of breast cancer cells [8].

One important aspect to consider when studying any essential nutrient is the possible interactions with other nutrients. Phosphorus, in the form of phytate, is common in vegetarian sources of zinc and has been shown to inhibit zinc absorption [1][9]. In addition, the balance between the trace element selenium and zinc has been suggested to play an important role in the onset of cancer [10]. Consequently, phosphorus and selenium levels may be important to take into consideration when studying zinc and breast cancer survival.

To the researchers' knowledge, no previous study on the potential effect of zinc levels on breast cancer survival has been conducted. However, several prospective epidemiological studies investigating the relationship between zinc and all-cause mortality reported either an inverse association [11][12][13][14] or no association at all [15][16]. Regarding cancer-specific mortality, Wu et al. (2004) found that cancer mortality was negatively related to serum zinc levels [14]. In contrast, Shi et al. (2017) found a positive association between relative zinc intake and cancer mortality [17].

2. Zinc and Breast Cancer Survival

Previous studies investigating the relationship between zinc and all-cause- or cancer-specific mortality have rendered mixed results. A study of a national cohort from the United States, including 6244 individuals, found that serum zinc was negatively related to cancer mortality [14]. In addition, the Paris Prospective Study 2, including more than 4000 men, suggests that a combination of low serum zinc and high serum copper or low magnesium results in an increased cancer- and all-cause mortality risk [11]. In contrast, a study in Finland among 344 elderlies found no association between serum zinc and all-cause mortality; however, these results might be limited by the relatively low number of participants [15]. Moreover, a study in Jiangsu Province, China, including 2832 adults, found a positive association between zinc intake and all-cause and cancer mortality [17]. Consequently, similarly to the results, previous research suggests that there might be a potential association between zinc and breast cancer prognosis, even though the evidence remains inconclusive.

It is well–known that phosphorus, in the form of phytate, inhibits zinc absorption by forming insoluble complexes in the gastrointestinal tract that cannot be absorbed due to the absence of intestinal phytase enzymes [1][9]. Indeed, a meta-analysis by Bel-Serrat et al. (2014), including 30 studies, revealed an overall reduction of fractional zinc absorption by

45% of the control meals when the phytate/zinc molar ratio of the diet was greater than 15 [18]. In addition to phosphorus, other factors have been identified to have a possible effect on serum/plasma zinc levels, such as time of day [19], albumin levels [20] and infection [21]. It can be hypothesized that an effect of zinc on breast cancer prognosis might be seen only when zinc levels are reduced by external factors. Since the research was the first to take phosphorus intake into account when evaluating the association between zinc and breast cancer survival, future studies should consider the possible interaction between zinc and phosphorus, as well as other factors affecting zinc levels.

MDCS is a large and well-characterized population-based prospective observational study with a relatively long follow-up. Moreover, data on tumor characteristics were collected, which enabled adjustment for many potential confounders, even though residual confounding cannot be ruled out.

Concerning the risk of a potential selection bias, the participation rate for women in the MDCS was 43%, but previous analyses have shown that the MDCS had sociodemographic characteristics and prevalence of obesity and smoking similar to those of the overall background population [22]. In addition, the mean total daily zinc intake in the research (12.1 ± 0.2 mg/day) was close to the mean total daily zinc intake for women in the National Health and Nutrition Examination Survey in the US 2011–2014 (13.4 ± 0.4 mg/day) [20].

Another strength is the use of two different indicators of zinc status. The modified diet history methodology used in the MDCS was especially developed to reflect the usual intake of individuals, and the relative validity and reproducibility of this methodology has proved to be high [23][24]. In the validation study, a slightly different dietary assessment method (a 2-week food record and a 130-item questionnaire) was compared against a reference method of 18-day weighted food records collected over 1 year. The energy-adjusted correlation coefficients for zinc and selenium were 0.44 and 0.44, respectively [23]. Furthermore, a sensitivity analysis excluding women reporting substantial diet changes prior to baseline did not alter the results notably. In addition, the inter-batch coefficients of variation for the serum analyses were 3.3% for zinc, 3.0% for phosphorus and 3.4% for selenium, which increased the reliability of researchers' measurements. Taken together, these points show there is a low risk of misclassification bias regarding the exposure variable, zinc status.

Besides using two different indicators of zinc status, the Swedish Cause of Death registry is a high-quality, virtually complete register on the event of death, and 96% of individuals in the registry have a specific underlying cause of death recorded [25]. Furthermore, the registry has been shown to be correct in approximately 90% of cases where malignant neoplasms were the cause of death [26]. Consequently, data regarding cause of death in Sweden are expected to be both complete and correct to a large extent.

One limitation of the research is that serum sampling was only performed once, from a single blood sample taken pre-diagnostically. Thus, circumstantial factors, such as a zinc-enriched meal, time of day, albumin levels and infection, might affect the acute zinc status. However, it has been suggested that strong homeostatic mechanisms exist to prevent deviations in serum zinc when dietary intakes fluctuate, which might help in maintaining long-term ranking between individuals [20][27].

Although serum/plasma zinc concentration and dietary zinc intake are recommended as biomarkers of zinc status by Biomarkers of Nutrition for Development (BOND) Zinc Expert Panel, the search for a more reliable indicator for zinc continuous [1]. Several potential emerging biomarkers of zinc status have been identified, e.g., concentrations of zinc metalloenzymes and zinc-binding proteins, plasma zinc turnover rates and zinc concentrations in nail, hair and urine. However, further research is needed before those biomarkers can be used to determine the zinc status of individuals or a population. Moreover, researchers' results from a previous study of the MDCS showed a poor agreement between serum zinc and zinc intake with a kappa value of 0.03 (p = 0.02) [4]. This is in line with the National Health and Nutrition Examination Survey 2011–2014, including 4347 individuals in the US, showing that serum zinc levels were not related to zinc intake [20].

Further limitations include the risk of type I errors due to multiple comparisons. However, the analyses with zinc intake pointed in the same direction as the analyses with serum zinc, which strengthens the evidence that the findings could be due to a true effect rather than chance. In addition, researchers did find significant results in the interaction analyses indicating that the power was high enough to detect a difference. The risk of a type II error must also be considered, as the statistical power in some of the stratified analyses, and some sensitivity analyses, was limited. This is also a problem considering that researchers included a long time period, and at the end of the period, survival curves will be less reliable due to the low number of patients and events.

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