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Circulating concentrations of soluble Receptor Activator of Nuclear Factor κβ and Osteoprotegerin in relation to risk of breast cancer and mortality after a breast cancer diagnosis

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Murine models have established that Receptor Activator of Nuclear Factor κβ ligand signaling mediates progesterone-induced proliferation in the normal breast, and plays a role in development, progression, and spread of breast cancer. Circulating concentrations of Receptor Activator of Nuclear Factor κβ ligand and its decoy receptor, Osteoprotegerin, have been found to be dysregulated in Breast Cancer 1 and 2 gene mutation carriers, who have a high lifetime risk of breast cancer. Yet, epidemiologic evidence on concentrations of both proteins in the general population is limited. With denosumab – a humanized antibody that blocks Receptor Activator of Nuclear Factor κβ ligand – showing benefit for cancer patients in clinical trials, there is increasing interest in Receptor Activator of Nuclear Factor κβ ligand as a target for prevention and treatment of breast cancer. This thesis presents the first results on Receptor Activator of Nuclear Factor κβ ligand and Osteoprotegerin concentrations and breast cancer risk and mortality by estrogen receptor status in humans.

The overarching aims of this study were to investigate associations between soluble Receptor Activator of Nuclear Factor κβ ligand and Osteoprotegerin concentrations and risk of breast cancer and mortality after a breast cancer diagnosis, as well as to characterize determinants of circulating concentrations of both proteins in healthy women. These three aims were investigated in a large, well-characterized case-control study (n=2023 case-control sets) nested within the European Prospective Investigation into Cancer and Nutrition cohort. Serum concentrations of soluble Receptor Activator of Nuclear Factor κβ ligand and Osteoprotegerin were measured in pre-diagnosis blood samples, and women were followed up for breast cancer incidence and subsequent mortality.

Higher pre-diagnosis circulating soluble Receptor Activator of Nuclear Factor κβ ligand was positively associated with risk of hormone receptor positive breast, but not hormone receptor negative disease. Among breast cancer patients, pre-diagnosis concentrations of soluble Receptor Activator of Nuclear Factor κβ ligand were not associated with risk of mortality. These results on breast cancer risk are in line with those from experimental studies, showing soluble Receptor Activator of Nuclear Factor κβ ligand induced autocrine proliferation in hormone receptor positive breast (cancer) cells. However, reproducibility of soluble Receptor Activator of Nuclear Factor κβ ligand concentrations over 14 years was relatively low (r=0.38); thus, a single serum measure, as included in this study, may not represent longer-term concentrations.

Higher pre-diagnosis circulating Osteoprotegerin was positively associated with risk of hormone receptor negative breast cancer, but not hormone receptor positive disease. This can most likely be attributed to its role as a decoy receptor for Tumor Necrosis Factor-Related Apoptosis-Inducing ligand, which induces apoptosis, preferentially in hormone receptor negative breast cancer cells. Contrary to pharmacological inhibition of Receptor Activator of Nuclear Factor κβ ligand with denosumab, higher pre-diagnosis circulating Osteoprotegerin was associated with increased mortality risk in women diagnosed with hormone receptor positive breast cancer. The role of Osteoprotegerin in breast cancer is complex, as it may both inhibit proliferation and apoptosis, and results from this study suggest that the role of Osteoprotegerin in breast cancer may be different in tumor initiation and progression.

In line with previous studies, results presented in this thesis indicate concentrations of soluble Receptor Activator of Nuclear Factor κβ ligand and Osteoprotegerin were not associated with lifestyle or reproductive factors, or endogenous sex hormone concentrations

The case-control study presented in this thesis is the first large-scale epidemiologic investigation to report on the Receptor Activator of Nuclear Factor κβ-axis and risk of breast cancer and mortality after a breast cancer diagnosis, and supports a, potentially diverse, role for Receptor Activator of Nuclear Factor κβ ligand and Osteoprotegerin in risk of and mortality following hormone receptor positive and negative breast cancer.

Following the results presented here, several additional lines of research are required to more fully describe the role of the axis in breast cancer risk and survival. First, these results suggest that Osteoprotegerin does not influence breast cancer risk and survival solely by inhibiting Receptor Activator of Nuclear Factor κβ ligand signaling, and future studies should evaluate

interactions between circulating Osteoprotegerin and both Receptor Activator of Nuclear Factor κβ ligand and Tumor Necrosis Factor-Related Apoptosis-Inducing ligand in associations with breast cancer risk and survival. Secondly, this study investigated pre-diagnosis concentrations and risk of death after a breast cancer diagnosis. It is plausible that concentrations at diagnosis are more informative in relation to breast cancer survival; this should be investigated in well-defined patient cohorts. Thirdly, Receptor Activator of Nuclear Factor κβ ligand and Osteoprotegerin are expressed by a number of tissues (including bone, lung, and breast), and a better understanding of how circulating concentrations relate to expression in the breast is needed. Finally, considering the role of Receptor Activator of Nuclear Factor κβ ligand in normal breast development and established associations between pregnancy, parity, and breast cancer risk, it would be of interest to evaluate how concentrations of Receptor Activator of Nuclear Factor κβ ligand and Osteoprotegerin in pregnancy relate to breast cancer risk in the mother following pregnancy.