

## The role of whole grains and lignans in lifestyle diseases – emphasis on prostate cancer and type 2 diabetes and their risk factors

### Abstract

Whole grains are rich in dietary fibre and bioactive compounds and have consistently been associated to improved health and lower mortality. Whole-grain rye is rich in fermentable fibre and lignans, that are converted to enterodiol and enterolactone by the gut microbiota. Enterolactone has been studied widely for several suggested beneficial health properties. In this thesis, the role of whole grains and lignans in cardio-metabolic health and mortality from type 2 diabetes and prostate cancer was studied.

Whole-grain rye and lignans did not affect glucose response assessed by an oral glucose tolerance test in men with metabolic syndrome after 8 wk intervention. Whole-grain rye improved lipid profile by lowering LDL-cholesterol compared to whole-grain wheat, whereas high-dose lignan supplementation had no effect on any of the investigated cardio-metabolic outcomes. Baseline microbiota enterotype appeared to explain some of the difference in response to treatments. Lipid profile was improved in the *Prevotella* enterotype by whole-grain rye diet and in the *Bacteroides* enterotype by whole-grain wheat diet. Lifestyle intervention with high intake of whole-grain rye and physical activity was feasible to implement in a group of men with non-aggressive prostate cancer. However, a full-scale trial is needed to investigate the potential of whole-grain rye in prostate cancer progression. Lastly, plasma enterolactone was investigated in two observational studies based on data from the population-based Diet, Cancer and Health cohort. Enterolactone concentrations were inversely associated with mortality among persons with type 2 diabetes, whereas no association with mortality was observed in men with prostate cancer.

Overall, the findings from this thesis highlights that whole-grain rye has beneficial health properties related to lipid profile, that long-term dietary interventions with high intake of whole-grains are feasible among middle-aged men with metabolic syndrome or prostate cancer, and that plasma enterolactone is associated with lower mortality among persons with type 2 diabetes. Furthermore, the finding of no association between enterolactone and prostate cancer mortality contributes to the existing evidence from observational studies that does not support the findings of a protective role from cell, animal and a few human interventions.

*Keywords:* whole-grain rye, lignans, enterolactone, metabolic syndrome, human intervention, type 2 diabetes, prostate cancer, cohort study, prognosis

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## List of publications

This thesis is based on the work contained in the following papers, referred to by Roman numerals in the text:

- I Anne Kirstine Eriksen\*, Carl Brunius, Mohsen Mazidi, Per Hellström, Ulf Risérus, Kia Nøhr Iversen, Rikard Fristedt, Li Sun, Yi Huang, Knud Erik Bach Knudsen, Natalja Nørskov, Cecilie Kyrø, Kirsten Frederiksen, Anne Tjønneland, Anja Olsen, Johan Dicksved, Rikard Landberg (2019). Effects of whole-grain rye and lignan supplementation on cardio-metabolic risk factors in men with metabolic syndrome are associated with baseline gut microbiota enterotype: a randomized cross-over trial (manuscript)
  
- II Anne Kirstine Eriksen\*, Cecilie Kyrø, Natalja Nørskov, Knud Erik Back Knudsen, Kirsten Frederiksen, Kim Overvad, Rikard Landberg, Anne Tjønneland and Anja Olsen (2019). Pre-diagnostic plasma enterolactone concentrations are associated with lower mortality among individuals with diabetes: a case-cohort study in the Diet, Cancer and Health cohort. Accepted 27 February *Diabetologia*
  
- III Anne Kirstine Eriksen\*, Rikke Dalgaard Hansen, Michael Borre, Ryan Godsk Larsen, Jeppe Munthe Jensen, Kristian Overgaard, Mette Borre, Cecilie Kyrø, Rikard Landberg, Anja Olsen and Anne Tjønneland (2017). A lifestyle intervention among elderly men on active surveillance for non-aggressive prostate cancer: a randomised feasibility study with whole-grain rye and exercise. *Trials* Jan 13;18(1):20
  
- IV Anne Kirstine Eriksen\*, Cecilie Kyrø, Natalja Nørskov, Anne Katrine Bolvig, Jane Christensen, Anne Tjønneland, Kim Overvad, Rikard Landberg and Anja Olsen (2017). Prediagnostic enterolactone concentrations and

mortality among Danish men diagnosed with prostate cancer. *Eur J Clin Nutr*: 71(10), 1235-1240.

Papers *II-IV* are reproduced with the permission of the publishers.

\* Corresponding author. Associated papers not included in this doctoral thesis:

- V Elin Hålldin, Anne Kirstine Eriksen, Carl Brunius, Andreia Bento da Silva, Maria Bronze, Kati Hanhineva, Anna-Marja Aura and Rikard Landberg (2019). Factors explaining inter-personal variation in plasma enterolactone concentrations in humans. *Mol Nutr Food Res*, Feb 28:e1801159. doi: 10.1002/mnfr.201801159.