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Summary of PhD thesis

Gene-gene and gene-environment interactions in prostate, breast and colorectal cancer

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Abstract in English

The incidence of cancer in the western world has increased steeply during the last 50 years. For three of the most prevalent cancer types in Denmark, prostate, breast and colorectal cancer (PC, BC and CRC, respectively), only a small fraction (1-15%) of the incidences are caused by highly penetrant single-gene mutations due to their low frequency in the general population. Overall, the contribution from hereditary factors to the causation of BC is only 27%, whereas genetics contributes to 35% and 42% for CRC and PC, respectively. Additionally, immigrations studies point to environmental factors as having strong influence on carcinogenesis. Therefore, very frequent, low effect polymorphisms may have a greater contribution on a population level in combination with environmental factors. Indeed, several dietary and life style factors are now well-established risk factors for different cancer types, such as alcohol consumption, smoking, obesity, inflammation and high meat intake; whereas other factors protect against cancer, such as high intake of dietary fibre, fruits and vegetables, and physical activity. Investigating the interactions between genetic variations and environmental factors, such as dietary and lifestyle factors may provide information about the underlying mechanisms and reveal new biological pathways.

The aim of this PhD thesis was to investigate relevant risk factors in relation to the three major cancer types in Denmark: PC, BC and CRC, respectively. The two major risk factors examined in this thesis are inflammation and alcohol consumption. With regard to inflammation, biological pathways involved in inflammation and the interaction with different dietary and lifestyle factors modulating the risk of CRC (*Paper II-IV*) and PC (*Paper I*), respectively, was examined. Moreover, a possible mechanism in alcohol-related BC in postmenopausal women involving a specific polymorphism in *PPARG* (coding the peroxisome proliferator-activated receptor (PPARγ)) and its interaction with the aromatase (encoded by *CYP19A1*) was investigated (*Paper V-VI*).

The Danish prospective “Diet, Cancer and Health” cohort study was used to examine gene-gene and gene-environment interactions in relation to risk of cancer (*Paper I-V*). A human intervention trial (*Paper V*) was conducted in order to directly examine the effect on concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) and alcohol consumption on circulating female sex-hormones. Finally, *in vitro* assays were performed to study the effect on PPARγ transactivation and sex-hormone concentrations following exposure to other commonly used organic solvents than alcohol (*Paper VI*).

Based on the results from *Paper I*, inflammation did not seem to be a major risk factor for aggressive PC, whereas the results on non-aggressive PC were equivocal. In contrast, *Paper II* and *III* indicated that the immune system is indeed involved in the carcinogenesis of CRC. Carriage of a pro-inflammatory allele of the *NFKB1* gene, was not associated with aggressive PC risk, but was associated to lowered risk of non-aggressive PC, and to increased risk of CRC. Even though none of the results were strong statistically, they demonstrated that cancer is a very heterogeneous disease; and indicated that inflammation may not be a risk factor for (aggressive) PC, but in relation to CRC, inflammation seems important. In *Paper III*, a new possible mechanism involving the ATP-binding cassette (ABC) transporters, the cytokine interleukin (IL) 10

and dietary fibre in relation to protection against inflammation-induced CRC was found. Furthermore, use of NSAIDs seemed to interact with the ABC transporters and IL-10 in relation to CRC.

Paper V illustrated that genetic variations in *CYP19A1* predicts circulating sex-hormone levels in post-menopausal women, and that alcohol intake affects female sex-hormone concentrations in the blood. However, it was not possible to put PPARγ and the aromatase in the same pathway as hypothesized *a priori* in alcohol-related BC; and the possible effect modification of concurrent use of NSAIDs and alcohol consumption was not confirmed. Nevertheless, results from *Paper VI*, indicated that exposure to commonly used organic solvents may act via PPARγ modulating sex-hormone levels. However, whether there is a common mechanism linking the aromatase and PPARγ, and also whether the differences in hormone levels increases risk of BC, still needs to be elucidated. Furthermore, these studies illustrated that acute and chronic alcohol consumption may have different effects on sex-hormone biosynthesis and metabolism, and that it is not straightforward to compare observational studies with experimental studies.

Overall, this PhD thesis has shown that genetic epidemiology can be used to study biological mechanisms in combination with other mechanistic studies, although there are several limitations involved such as missing knowledge of confounders and limited statistical power to study gene-environment interactions.

Future research could establish whether and how dietary fibre, IL-10 and ABC transporters are connected in reducing the risk of CRC; and whether red meat *per se*, specific preparation methods or the life style associated with high red meat intake is carcinogenic. The acquired knowledge would improve the current dietary recommendations.

There also seem to be several yet unknown effects of NSAID usage that need to be clarified. Information of these potential (side) effects would lead to better and safer medication regimens and, hence, improved public health. Also, further knowledge of the harmful health effects related to alcohol consumption, including the potential effect modification with concurrent use of NSAIDs, would lead to improved public preventive strategies.

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