Adult-attained height, early life energy restriction, genetic variation, and cancer risk

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Valorization addendum

Our main objective was to gain a deeper understanding of how adult-attained height is associated with cancer risk later in life. In analogy, we also investigated early-life energy restriction exposures during critical times of growth in relation to height and cancer risk, with cancer risk occurring much later in life. In the meta-analysis conducted in this thesis we observed that severe transient early life energy restriction was associated with a 28% increased breast cancer risk and a 16% increased prostate cancer risk, in the meta-analysis of human observational studies in this thesis. A systematic review conducted in this thesis indicated that moderate energy restriction, as studied in animal experimental and human ecological studies, may be associated with a decreased site-specific cancer risk. With regard to timing of exposure to early life energy restriction, no conclusions could be drawn with regard to breast cancer risk in our meta-analysis. A subsequent meta-regression analysis investigating the effect of the duration and severity of energy restriction on overall cancer risk indicated that duration, rather than severity might result in increased overall cancer risk in women and men, however, this result should be interpreted with caution.

The height-cancer risk association is consistent in the literature and the results presented in this thesis contribute to elucidating plausible mechanisms for this association. We also investigated adult-attained height in relation to the risk of postmenopausal breast cancer by estrogen and progesterone receptor subtypes. Adult-attained height and hormone-receptor positive tumors are thought to share causal mechanisms, specifically hormonal growth factors. In this thesis, adult-attained height and energy restriction before and/or during the growth spurt were both associated with the risk of estrogen- and progesterone receptor-positive subtypes of postmenopausal breast cancer, in the direction as expected, indicating critical exposure windows for hormonal growth-related mechanisms.

Finally, we developed a novel molecular epidemiological approach to identify the underlying mechanisms that may link height to cancer risk. This selection method for genetic variants from GWAS offers a systematic strategy for large-scale prospective cohort studies, interested in studying the underlying mechanisms between multiple phenotypes, such as a quantitative trait (e.g. height) and complex diseases (e.g. breast cancer risk and colorectal cancer risk). We used existing repositories of results from genome-wide association studies (GWAS) to identify adjacently located genetic variants that were associated with adult-
attained height and breast or colorectal cancer. The methodology in this approach relies on the assumption that genetic variants from GWAS found associated with complex diseases or traits are not randomly distributed across the genome, but tend to cluster in regions of low recombination 1. With this approach, we were able to narrow down the large number of genetic variants from GWAS associated with these phenotypes to a limited set of genetic variants clustered to the same gene(s). The genetic variants in these clusters may collectively point to genes in pathways explaining the link between height and cancer risk. The novelty of this method is the comprehensive integration of publically available GWAS repositories, on the basis of which genetic variants associated with multiple associated complex traits and diseases can be identified. The past decade has seen a large number of wide-scale genetic studies in identifying genetic variants that may modify individuals’ predisposition to common diseases.2 The GWAS catalog3 has now grown to contain tens of thousands of SNPs associated with hundreds of common diseases. However, the interpretation of these variants lags far behind.2 Efforts such as the method introduced in this thesis, may allow using this data to systematically select genetic variants in large-scale epidemiological studies investigating disease aetiology. Existing strategies prioritise genetic variants related to exposure in cases and controls 4 or genetic variants related to the outcome 5, in which genetic variants are prioritised based on a genome-wide scan in the own study population. The selection approach for genetic variants presented in this study is of particular interest for application in large-scale studies with exhaustive bio-samples, e.g. DNA from nails, in which a genome-wide scan within the own study population is not feasible.

In this valorization addendum, the results of this thesis will be discussed in the light of, “value for society” and “value for science”.

**Value for society**

**Attention for timing of exposure**

With regard to the results in this thesis, it is obvious that adult-attained height in itself cannot be the target of future interventions. Adult-attained height can be seen as a result of exposures to growth factors. It is a marker for genetic, environmental, including nutritional factors, and hormonal factors affecting growth during the period from preconception to completion of linear growth. Energy restriction is one of the environmental factors that may negatively influence energy balance and thereby may oppose the effects of exposure to growth factors. When energy restriction occurs early in life, it could therefore reduce cancer risk in
adulthood. Yet, it seems that a differentiation with regard to energy restriction occurring early in life and cancer risk later in life has to be made based on the timing of exposure to early life energy restriction, particularly during periods of rapid growth and development, such as during the pubertal growth spurt, and its subsequent effect on adult-attained height and cancer risk. These periods also coincide with the timing of breast tissue growth and maturation. If this theory is true, this may hold implications for lifelong prevention of cancer. When starting primary prevention of cancer early in life instead of in adulthood, the effectiveness of prevention might be larger than currently anticipated. Our study suggests that primary prevention of cancer is a lifelong goal that has to start early in life covering critical times of growth and development.

The relevance of understanding biological mechanisms for prevention

Another aspect to consider when developing prevention strategies may be that risk factors for postmenopausal breast cancer differ by hormone receptor-positive and hormone receptor-negative subtypes. Generally, in contrast to hormone receptor-negative subtypes, hormone receptor-positive breast cancer tumours, i.e. estrogen- and progesterone hormone receptor-positive tumours, have been associated with modifiable (hormonal) growth-related risk factors, which can be a target for prevention at a young age. Given that approximately 80% of all breast cancer tumours in the population of the Netherlands is estrogen hormone receptor-positive, of which 65% is also progesterone receptor-positive, breast cancer prevention strategies aimed at modifiable (hormonal) growth-related risk factors may be particularly promising in reducing the incidence of hormone receptor-positive breast cancer. Our results suggest that when estimating the potential for prevention it is advisable to take the molecular subtypes of tumours reflecting biological mechanisms into account. The knowledge and insight into potential biological mechanisms provided in this thesis may contribute to the justification of prevention policies aimed at modifiable early life exposures.

Value for science

It is important to understand which aspects of growth relate to cancer risk as it might expand our knowledge about the pathways that lead to cancer development. Height is a reflection of absolute linear growth, and while it may be the outcome of the entire growth curve, it does not reflect the entire growth curve well when it comes to the timing, duration, and velocity of growth, hormonal changes influencing growth, and exposure to general growth factors. In addition,
height does not provide information on the contribution of leg length relative to trunk length. This information could give important clues given that a short height due to relatively short legs is generally associated with different early life exposures, particularly with exposures related to a social adverse environment, compared to exposures associated with a short height due to a relatively short trunk length. Likewise, early life energy restriction is just one factor associated with the negative end of the spectrum of energy balance, which, as a whole, is associated with different factors among which can also be discerned nutritional status, physical activity, and body composition. Early life energy restriction was operationalized through very specific historical events in this thesis, which generally represented extreme circumstances. Nevertheless, studies focusing on the negative end of the energy balance spectrum are important, as most epidemiological studies and also prevention have focused on the positive end of this spectrum, i.e. childhood obesity, and cancer risk.

More insight into factors contributing to growth that lead to cancer development by investigating the determinants of adult-attained height, e.g. by investigating the growth curve and components of height as well as which aspects of energy restriction link height to cancer risk, as described in Chapter 5 of this thesis.

Further clues with regards to the mechanisms underlying the height-cancer association may be found using the framework of the collaborative effort between WCRF and Bristol University for systematic reviews of mechanisms underpinning exposure-cancer associations. This collaboration has led to the development of a novel two-stage framework on the mechanisms underpinning the association between exposure and cancer risk that provides: (stage I) an overview of mechanistic pathways wherein results from human (i.e. epidemiologic), animal, and cell studies are integrated and (stage II) a systematic review of the literature for identifying biologically plausible mechanisms underlying these exposure-cancer associations. While there are well-established methodologies for systematic reviews of epidemiologic data, this framework offers guidelines for performing a systematic review of mechanistic evidence underlying well-known epidemiologic associations, which has not been proposed previously. Both the selection method for genetic variants from GWAS described in this thesis and the mechanistic framework from Bristol University mentioned above can be used to identify potential mechanisms for underpinning exposure-cancer associations with regard to timing, duration and growth velocity, and for hormonal and growth factors. With respect to adult-attained height, genome-wide associations and
Longitudinal analyses have already linked genetic loci to pubertal height growth, pubertal timing and childhood adiposity.\textsuperscript{13,14}

The research conducted within this thesis is part of a larger molecular epidemiological research line at the Department of Epidemiology and the GROW-School for Oncology and Developmental Biology at Maastricht University. This research line focusses on exposures related to energy balance, including body size and gene-environment interactions, and molecular characteristics of tumours. The aim is to further elucidating the contribution of energy balance-related risk factors to cancer risk, including energy balance-related risk factors in early life, and the pathways underlying these associations. Next to cancer cohorts such as the Netherlands Cohort Study, birth cohort studies with cancer follow-up into old age with detailed data on linear growth and genetic data could yield valuable insights, but these studies are scarce. Likewise, epidemiologic data regarding the mechanisms underlying an association between early-life energy restriction and human site-specific cancer risk are scarce because exposure to energy restriction is rarely available in observational studies and few studies are large enough to allow for subgroup analyses for molecular and histological specific endpoints. Birth cohort studies with cancer follow-up into old age and detailed data on growth and energy balance in early life (with attention to the full spectrum of energy balance) are promising, but such studies are not mature enough yet.

In the meantime, identifying potential mechanisms linking height to cancer should be pursued and these mechanisms could be identified and investigated with respect to the height-cancer risk association in ongoing prospective cohort studies.

To conclude, the results of this thesis point to critical exposure windows for hormonal growth-related mechanisms for postmenopausal breast cancer. Generally, early life determinants of growth, particularly during critical periods of growth, seem to be relevant to cancer that occurs after 55 years of age. Understanding how height is related to cancer is important for public health prevention strategies in childhood and for expanding our knowledge about the pathways to cancer development.
References


