

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

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## English summary

Our main objective as introduced in **Chapter 1** was to gain a deeper understanding of how height is associated with cancer risk later in life. Increased adult-attained height has been consistently associated with increased cancer risk in the literature, yet plausible mechanisms remain to be further elucidated. Although there is a broad understanding of how early life environmental and genetic processes contribute to adult-attained height, there is still little evidence on how these factors might link to cancer risk. As it has been observed that height increases the risk of a number of different types of cancer and because relative risk estimates in relation to height are very similar across different cancers and in different populations, a common mechanism might be at play. From an environmental perspective we aimed to study these underlying mechanisms by investigating how early life energy restriction during childhood and adolescence influences both adult-attained height and cancer risk. Early life determinants of growth are presumably associated with cancer risk later in life in a direction as expected based on analogy with the height-cancer association.

We also aimed to specifically study height in relation to the risk of postmenopausal breast cancer by hormone receptor subtypes. Breast cancer includes hormone-sensitive tumors, which may be susceptible to hormonal growth factors influencing adult-attained height and cancer risk. Finding an association between height and hormone receptor-positive breast cancer indicates involvement of hormonal growth factors as plausible mechanisms.

Furthermore, a SNP selection approach was applied to identify genetic variants and genes that may link height to cancer risk. We focused on postmenopausal breast cancer and colorectal cancer. Both types of cancer share a subset of risk factors and height has been identified as a convincing risk factor for these cancers according to the World Cancer Research Fund. Germline genetic variants are useful as markers of shared mechanisms between adult-attained height because these are time-independent markers of pathway involvement.

**Chapter 2** consists of a systematic literature review and meta-analysis of human observational studies in which the evidence on the association between early life energy restriction and site-specific cancer risk is investigated. Furthermore, specific aspects of early life energy restriction are discussed, such as the timing, duration, and severity of exposure, which may determine whether exposure is

associated with an increased or decreased risk of cancer. The systematic review indicated that moderate continuous energy restriction, as studied in animal experimental and human ecological studies, was generally associated with a decreased site-specific cancer risk. The meta-analysis of human observational studies indicated that severe transient early life energy restriction was associated with a 28% increased breast cancer risk and a 16% increased prostate cancer risk, though some of the underlying studies showed null results. The evidence for an association between severe transient early life energy restriction and risk at other cancer sites, *i.e.* colorectal-, stomach-, pancreas-, ovarian-, and respiratory cancer was either limited or studies were too heterogeneous for pooling. 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. With regard to timing of exposure to early life energy restriction, no conclusions could be drawn with regard to breast cancer risk.

In **Chapter 3** associations of adult-attained height and early life energy restriction with postmenopausal breast cancer risk are studied according to estrogen and progesterone receptor status within the Netherlands Cohort Study on Diet and Cancer. The Netherlands Cohort Study is a prospective cohort study among 120,852 participants, of which 58,279 men and 62,573 women and has data available on adult-attained height and the rather unique exposure of early life energy restriction. Adult-attained height was significantly positively associated with postmenopausal breast cancer risk, in particular with hormone receptor-positive subtypes. Of the three exposures to energy restriction investigated, *i.e.* exposure to energy restriction during the Hunger Winter (the winter of 1944-45), the War Years (1940-44), and the Economic Depression (1932-40), only exposure to energy restriction during the Economic Depression was related to a shorter stature (an almost 2 cm reduction) in female subcohort members. Energy restriction during all three periods of exposure, provided that the exposure occurred before and/or during the growth spurt, was associated with a significantly decreased risk of hormone receptor-positive breast cancer subtypes. Interestingly, energy restriction during the Hunger Winter increased the estrogen receptor-negative breast cancer risk regardless of the timing of energy restriction. Taken together, the observation that both height and early life energy restriction taking place before and/or during the growth spurt were associated with reduced hormone receptor-positive breast cancer risk seems to suggest possible common underlying mechanisms and critical exposure periods in life.

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In **Chapter 4**, an approach for the selection of genetic variants is presented, which was developed to select genetic variants to identify shared mechanisms linking height to postmenopausal breast- and colorectal cancer risk. The selection method for genetic variants is based on the assumption that genetic variants from GWAS associated with complex diseases or traits tend to co-segregate in regions of low recombination, harboring functionally linked gene clusters. This phenomenon allows for selecting a limited number of genetic variants. This selection approach for genetic variants is of particular interest for large-scale studies with exhaustive bio-samples, *i.e.* DNA from nails, in which a genome-wide approach is not feasible, and will reduce the costs of genotyping and the chance of false-positive findings. The novelty of this method is the comprehensive integration of publically available GWAS repositories, on the basis of which genetic variants associated with complex traits and diseases can be identified, as these are hypothesized to cluster in regions of low recombination. Genomic regions including genetic variants for height and cancer may indicate pathways underlying height-cancer associations. Such genetic variants can serve as time-independent biomarkers of pathway involvement that may mechanistically explain the established associations. Using our selection method for genetic variants, we identified clusters of genetic variants derived from GWAS data that were associated with adult-attained height and the risk of postmenopausal breast cancer and/or colorectal cancer. This systematic approach identified a limited number of clustered genetic variants, which pinpoint potential shared mechanisms (*i.e.* Indian Hedgehog signaling) that may link together the complex phenotypes height, postmenopausal breast cancer risk and/or colorectal cancer risk.

Finally, **Chapter 5** concludes the thesis with a discussion of the main findings as well as the challenges of and insights offered by (molecular) epidemiology on studying the height-cancer association. The findings reported in this thesis require confirmation in other studies, but our observations support the growing body of evidence that the factors that contribute to a greater longitudinal growth, reflected by a greater adult-attained height, are associated with postmenopausal breast cancer risk and particularly estrogen and progesterone receptor-positive subtypes. In analogy with these findings, early life energy restriction before and or during the pubertal growth spurt both reduce adult-attained height and decrease the risk of estrogen and progesterone receptor-positive subtypes of postmenopausal breast cancer. Furthermore, the identified pathways using genetic variation derived from the novel selection method for genetic variants supported the involvement of, among others, hormonal mechanisms linking adult-attained

height to both postmenopausal breast cancer risk and colorectal cancer risk. Therefore, the findings from this thesis point to: a) a possible common underlying mechanism that involves hormonal growth factors that may link adult-attained height to postmenopausal breast and colorectal cancer risk; and b) critical exposure periods in early life (before and during the pubertal growth spurt) when exposures may have their prime effect on postmenopausal breast cancer risk. As indicated by this thesis and the literature, specific tumour subtypes and tumours occurring in different anatomical subsites are often characterized by different risk factor profiles. In addition, the effects of early life exposures on adult-attained height and cancer risk may be lasting, even though early life exposures may be transient in nature, such as energy restriction. Therefore, studying early life modifiable exposures that influence adult-attained height and taking into account their timing in early life, could provide us with a better insight into when cancer prevention strategies are most effective. This may lead to new future cancer prevention strategies aimed at early life in contrast to the conventional prevention strategies that are generally focused on adults.