

Energy balance and colorectal cancer risk

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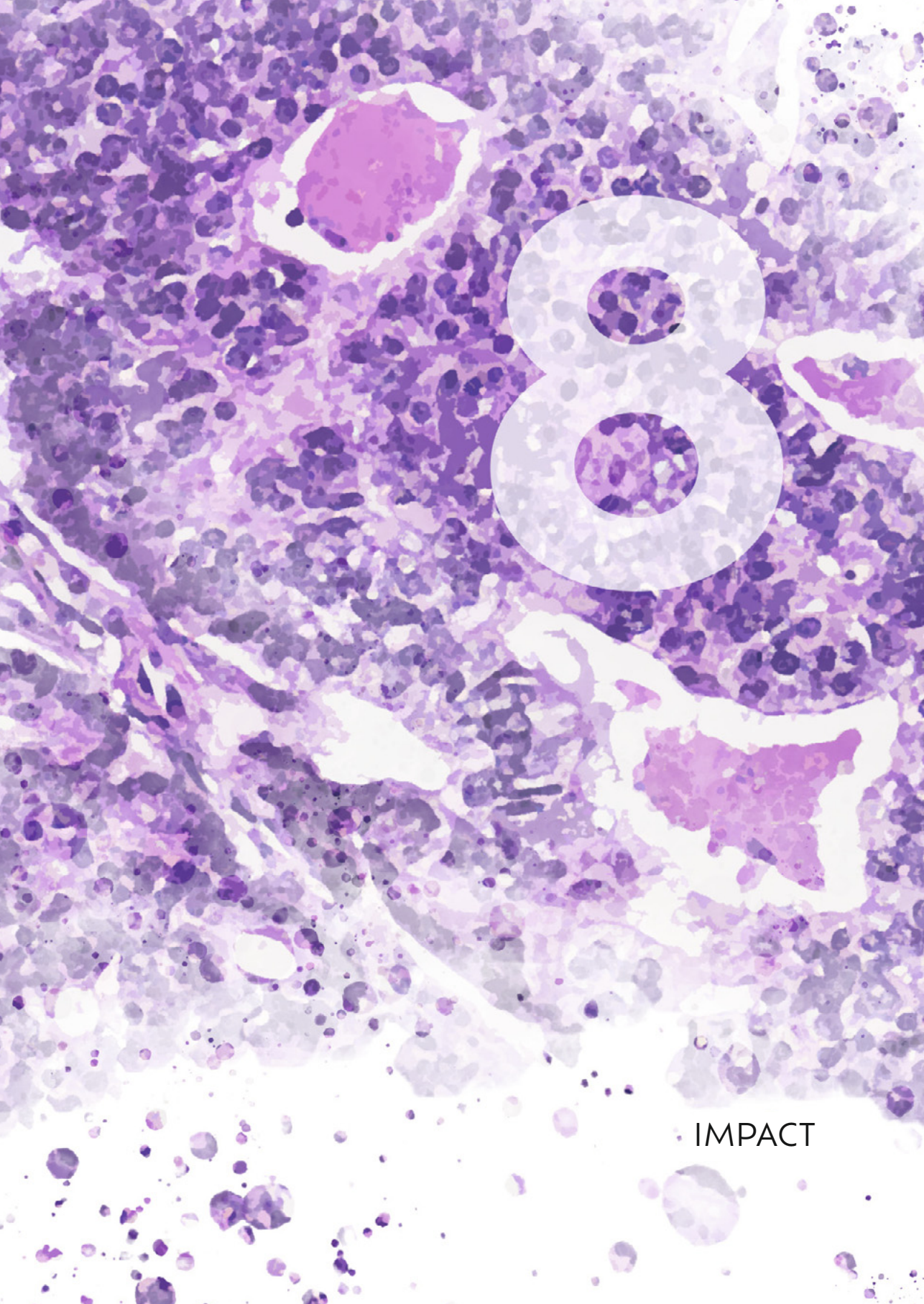
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· IMPACT

This section addresses the relevance and the potential scientific and social impact of the research presented in this thesis.

RELEVANCE

Colorectal cancer has been amongst the five most common cancers worldwide for decades¹⁻⁴, with an estimated 1.9 million new cases in 2020⁴. It has been estimated that more than 50% of colorectal cancers are attributable to modifiable risk factors and thus potentially preventable⁵. Organizations like the World Cancer Research Fund (WCRF) and the International Agency for Research on Cancer (IARC) regularly publish updated reports on scientific evidence for cancer prevention^{6,7}. Both reports indicate convincing evidence for associations of adiposity, height, and physical activity with colorectal cancer risk. However, while many studies reported associations between these energy balance-related factors and colorectal cancer, associations often appear to be weak and are not always consistent between studies⁸. This might be caused by disease heterogeneity, i.e. when exposure factors are differentially associated with subgroups of a disease⁹. This issue is being addressed by using a molecular pathological epidemiology (MPE) approach, as was done in the current thesis.

MPE is an emerging transdisciplinary field incorporating molecular pathology into epidemiological research¹⁰. Classification of (colorectal) cancers into subgroups based on specific molecular characteristics addresses disease heterogeneity, whereby weak or masked associations can be revealed. In addition, MPE research can strengthen the evidence for causal relationships by providing further insights into etiology and pathogenesis of a disease. In the current thesis, we investigated whether energy balance-related factors (i.e. adiposity, physical activity, height, and energy restriction) are differentially associated with risk of colorectal cancer subgroups based on estimated presence of the Warburg-effect.

After the discovery of the Warburg-effect (i.e. increased glycolysis under aerobic conditions) in the 1920s¹¹, a long period passed with lack of interest in this phenomenon. In recent decades, however, the Warburg-effect regained interest in the scientific community. We were the first to investigate whether the Warburg-effect might be involved in the etiological pathway between energy balance-related factors and colorectal cancer. The results presented in this thesis indicate involvement of the Warburg-effect in the etiological pathway of adiposity with colon cancer. The etiological pathway of physical activity and adult-attained height are probably explained by mechanisms other than the Warburg-effect. No clear patterns were observed for the three energy restriction proxies. Since we were the first to investigate these associations, confirmation in additional large prospective MPE studies is required. Nevertheless, the suggested involvement of the Warburg-effect in the association between adiposity and colon cancer contributes additional insights

into the underlying mechanisms of this etiological pathway. A better understanding of how exposures (such as energy balance-related factors) affect disease initiation may ultimately improve preventive strategies. In addition, in a study that was not included in the current thesis, we observed that colorectal cancer cases with estimated presence of the Warburg-effect had a worse survival compared to cases without¹². Therefore, this new way of colorectal cancer subtyping based on estimated presence of the Warburg-effect seems to have both etiological as prognostic significance.

More generally, the results presented in this thesis support the evidence that energy balance-related factors like adiposity, height, and physical activity are associated with colorectal cancer risk. In addition, our results revealed stronger associations for specific subgroups of colorectal cancer, further demonstrating how important these factors are in the prevention of colorectal cancer. Over the past decades, overweight and obesity has been rising amongst adults as well as children and adolescents. Among Dutch adults (age ≥ 20 years), overweight has increased from 35.3% in 2001 to 36.8% in 2020, and obesity from 9.6% to 14.2%¹³. In Dutch children and adolescents (age 4-19 years), overweight has increased from 9.2% in 2001 to 12.5% in 2020, whereas the percentage of obese children and adolescents remained the same (2.5%)¹³. These numbers are alarming and highlight the need of prevention with a focus on a healthy energy balance throughout life.

KNOWLEDGE TRANSFER

The scientific knowledge presented in this thesis has been shared with fellow researchers through publication in several international scientific journals. In addition, our results have been presented at various conferences and symposia for different audiences. Our results have been presented online at the Virtual Annual Meeting (2021) of the American Association for Cancer Research (AACR), which is a large international conference with a broad audience of cancer researchers. Furthermore, our results have been presented online at the 13th Joint Meeting of the British Division of the International Academy of Pathology and the Pathological Society of Great Britain & Ireland (Manchester Pathology 2021) and online at the Dutch Epidemiological conference (WEON 2021). The audience of these conferences mainly consists of pathologists and epidemiologists, respectively. Lastly, our results were presented live at the Science Day of the Maastricht University Medical Centre+, of which the audience consisted of a broad audience of researchers and clinicians.

CONCLUSION

In this thesis, we investigated associations between energy balance-related factors and colorectal cancer risk in relation to subtypes based on the estimated presence of the Warburg-effect in the tumor. Our results underline the importance of preventive strategies aimed at reaching and/or maintaining a healthy energy balance throughout life. Since we were the first to investigate these associations in relation to the Warburg-effect, confirmation of the results presented in this thesis is necessary. Nevertheless, these results provide additional insights into underlying mechanisms of the etiological pathway between energy balance-related factors and colorectal cancer risk, which may ultimately improve preventive strategies.

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