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## **Lifestyle factors and their association with overall, recurrence-free and colorectal cancer-specific survival in a population-based study of colorectal cancer patients in Germany**

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Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the fourth most common cause of cancer related death worldwide. In 2012, CRC accounted for almost 1.4 million incident cases and over 650,000 deaths. These numbers underline the need for new possibilities to enhance prognosis of CRC patients after diagnosis. Past studies have shown that smoking, alcohol consumption, physical inactivity and excess BMI can be associated with increased CRC incidence and mortality. However, evidence has been rather inconclusive on the association between these lifestyle factors and prognosis after diagnosis. Lifestyle changes, if found relevant to prognosis could represent an ideal complement to established forms of therapy.

Previous evidence on smoking behavior and CRC prognosis was evaluated in a systematic review and meta-analysis and survival analyses were conducted using data from the DACHS-study to evaluate smoking behavior, alcohol consumption, physical activity and BMI in association with overall, CRC-specific, recurrence-free and disease-free survival.

For the systematic review a literature search was performed systematically in both MEDLINE and ISI Web of Science, including studies that analyzed overall, CRC-specific, recurrence-free and disease-free survival according to smoking status and/or intensity.

Survival analyses were conducted based on data from originally 3,146 individuals, aged 30 years or older, with a first, histologically confirmed diagnosis of CRC recruited in 2003-2010 within the DACHS-study. The DACHS-study is an ongoing population-based case-control study carried out in the southwest of Germany. Comprehensive and cancer stage specific assessments of the impact of smoking behavior on overall, CRC-specific, non-CRC specific, recurrence-free and disease-free survival were performed, including smoking status and intensity assessments. Furthermore the impact of recent and lifetime alcohol consumption, latest and lifetime physical activity, and BMI at diagnosis and prediagnostic BMI changes on overall, CRC-specific, recurrence-free and disease-free survival was evaluated. Smoking behavior and BMI variables were evaluated in a sample of 3,130 newly diagnosed CRC patients, based on DACHS data from 2014, while alcohol consumption and physical activity were evaluated in a sample of 3,121 CRC patients, based on the same DACHS data but in an updated version from 2015.

In the 16 studies, included in the systematic review current and former smoking were associated with a poorer prognosis compared with never smokers. When compared with never smokers, pooled random effects hazard ratios (95%-confidence intervals) for overall survival, based on 6 and 4 studies were 1.26 (1.15-1.37) and 1.11 (0.93-1.33) for current and former smokers, respectively.

In the survival analysis involving DACHS-data continued smoking at diagnosis and high-dose smoking were associated with lower recurrence-free and disease-free survival among non-metastatic CRC patients. Detrimental effects of smoking were seen in stage I-III colon cancer cases and men, whereas no associations were seen among women, stage IV or rectal cancer patients. Lifetime alcohol abstaining was associated with poorer overall and CRC-specific survival than lifetime light drinking. Lifetime heavy drinkers showed poorer overall and disease-free survival. Recent alcohol abstaining was associated with poorer overall, CRC-specific, and disease-free survival. Lifetime abstainers with non-metastatic disease showed poorer CRC-specific and recurrence-free survival. Wine abstaining but not beer or liquor abstaining was associated with poorer survival. Associations between alcohol consumption and prognosis varied according to presence of diabetes and age. Associations between lifetime physical activity and improved survival were found when adjusted for age and sex, only, but associations might be restricted to walking and/or metastatic CRC patients. Lifetime activity was differentially associated with survival depending on age at diagnosis. Latest activity was associated with improved survival supposedly restricted to non-metastatic CRC patients and associations were most prominent for walking. Compared with normal weight patients, overweight (BMI: 25-<30 kg/m<sup>2</sup>) and obesity (BMI: ≥30 kg/m<sup>2</sup>) were associated with improved overall and CRC-specific survival, with associations being more pronounced in nonmetastatic CRC patients. Compared with stable BMI, a strong prediagnostic BMI decrease of >5 kg/m<sup>2</sup> was associated with poorer prognosis for all survival outcomes, and associations were particularly pronounced in men.

Taking into account strengths and limitations of present evaluations, results support the existence of detrimental effects of smoking on CRC prognosis after CRC diagnosis. They point to the potential of enhancing perspectives of cancer survival by enhanced efforts of smoking prevention and promotion of smoking cessation and abstinence, both in general and among CRC patients in particular. Alcohol abstaining and heavy drinking behavior were associated with poorer survival after CRC diagnosis. Protective effects of lighter alcohol consumption might be restricted to wine consumption and associations might differ according to age and presence of diabetes mellitus. Increased prediagnostic physical activity was associated with improved survival of CRC patients after diagnosis, although associations could be restricted to certain activity types and/or depend on (non)metastatic disease state. Current evidence suggests that increased physical activity has beneficial effects on many health outcomes, which seems to include also activity among patients already diagnosed with cancer. Results suggest an association of prediagnostic overweight with an improved prognosis, particularly in nonmetastatic CRC patients. Furthermore, results showed a BMI decrease before diagnosis to be an independent predictor of poor prognosis.

Further research is needed on the interaction of lifestyle factors with other factors that vary between patients, such as therapy. The potential to enhance prognosis of CRC patients by smoking prevention or cessation, moderated alcohol consumption, increased physical activity and proper weight maintenance, including exact dose-response assessments needs to be evaluated in future research, as do factors relevant to patient adherence to lifestyle interventions.