Michael Hoffmeister
Dr. sc. hum.

Effects of drugs commonly prescribed to older adults on the risk of colorectal cancer: population-based case-control study from Germany

Geboren am 27.10.1973 in Bad Sobernheim
Diplom der Fachrichtung Ökotrophologie am 20.04.2001 an der Universität Gießen

Promotionsfach: DKFZ (Deutsches Krebsforschungszentrum)
Doktorvater: Prof. Dr. med. Hermann Brenner

Colorectal cancer (CRC) is the second most common cancer regarding incidence and mortality of all cancers in Germany. For the prevention of CRC, several risk factors and protective factors have been investigated. Among those, drugs and certain nutrients have the potential to act as chemoactive agents and might inhibit genetic alterations and other tumorigenetic processes. Recent research has drawn attention to risk reduction of CRC with the use of statins, and a number of epidemiological studies have suggested that nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin may reduce the risk of CRC. It has also been suggested that NSAIDs and statins in combination might provide stronger risk reduction of CRC than single drug treatment. In postmenopausal women, use of hormone replacement therapy (HRT) likely reduces the risk of CRC, while, for instance, the risks of breast and gynaecologic cancers seem to be increased. Previous studies found indication that the effect of HRT on CRC risk might be modified by (or interact with) other factors, such as body mass index (BMI) or age. Use of HRT in Germany is different from HRT use in other countries. To date, there is no large epidemiological study of low-dose aspirin, statins or HRT and the risk of CRC available from Germany, and there is only one study from the United States that investigated the joint effects of NSAIDs and statins on CRC risk. Thus, the influence of statins, low-dose aspirin (either and in combination) and HRT on the risk of CRC was investigated in the present research.

This population-based case-control study was conducted in the Rhine-Neckar-Odenwald region in the southwest of Germany. 540 patients with incident invasive CRC and 614 control subjects without CRC, who were frequency-matched to the cases by age, sex, and county of residence, were recruited from January 2003 until June 2004. The participants provided information on sociodemographic factors and a detailed medical and lifestyle history in a standardized questionnaire-based face-to-face interview with trained interviewers. Regular use of drugs was ascertained for a variety of indications, including blood dilution, cardiovascular disease prevention and lowering of blood lipids. Current use of low-dose

aspirin or statins at least 2 times per week for at least 1 year was regarded as current regular use. For the investigation of postmenopausal hormone use, details of menstruation history and removal of the uterus and ovaries, and duration and cause of HRT use were assessed. In addition, details of HRT were requested from the women's treating physicians.

Regular use of low-dose aspirin and statins in combination showed risk reduction of CRC by 37%, and risk reduction was particularly strong (62%) if both drugs were used for 5 years or more. Separate evaluation of both drugs showed a stronger risk reduction for statins than for low-dose aspirin, and the association of low-dose aspirin was further reduced after control for statin use, whereas control for low-dose aspirin use hardly affected risk reduction seen for statins. Ever use of HRT provided strong and statistically significant reduction of CRC risk of 59%. However, only current use or past use that ended up to 4 years previously was associated with reduced risk. Risk reduction was already apparent after less than 5 years use and did not seem to increase after 10-19 years or 20+ years. HRT use was associated with risk reduction of CRC among all women with BMI ≥23 kg/m^2. On the other hand, BMI was positively associated with increased risk of CRC among nonusers of HRT, but not among users of HRT.

In conclusion, this first large epidemiologic study from Germany provides further suggestion of a potential protective effect of statins from the risk of CRC. There was indication of a protective effect of low-dose aspirin already after 5 years of use, a result that might be associated with daily use which is typical for cardiovascular disease prevention. A combinational chemopreventive effect of low-dose aspirin and statins might provide stronger risk reduction than either of the single drugs. If confirmed, the single and combined effects found in the present study would imply major public health relevance given the large proportion of older adults who take statins and low-dose aspirin for cardiovascular disease prevention. The results for postmenopausal HRT and risk of CRC are compatible with existing evidence of a strong inverse relationship that was reported from other countries. Results were not consistent with previous studies regarding interaction with body mass: risk reduction with HRT appeared to be stronger in overweight and obese women. On the other hand, a positive association of BMI and CRC risk was found among nonusers of HRT, but not among users of HRT, which raises the question whether risk reduction of CRC associated with HRT use might neutralize the increase in risk of CRC associated with increasing BMI. The reasons for the inconsistency of results regarding the role of HRT in the association of BMI with CRC risk might include the different prescribing patterns of HRT between Germany and the USA, but this issue requires further study. Because risks seem to outweigh the benefits of hormone preparations studied in large randomized controlled trials, there seems to be no role for starting or continuing the prevention of CRC and other chronic diseases with HRT.