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Use of family history and genetic risk scores for colorectal cancer risk stratification

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Colorectal cancer (CRC) remains a major health problem, being one of the most common cancers and the fourth most common cancer related cause of death worldwide. Due to the mainly slow progression of CRCs via the adenoma-carcinoma sequence, CRC lends itself to screening, more than other cancer entities do. Risk stratification might help to increase screening efficacy, and identification of people at high and low risk might raise awareness to those in most need and hence increase compliance with current screening guidelines. One of the most important risk factors that have been found to date is having a family history (FH) of CRC, which is considered in most screening guidelines. In recent years, many common genetic variants have been found to be associated with a higher risk for CRC. Their combination into genetic risk scores (GRS) might also offer the possibility to conduct meaningful risk stratification.

The analyses presented in this dissertation are based on three different studies. Data from the ongoing DACHS study, one of the largest population-based case-control studies on CRC in the world, was used to assess associations between FH and the risk for CRC. For this, a total of 4,334 cases with a confirmed diagnosis of CRC and 4,232 controls, all aged 30 years or older were analyzed. Analyses regarding the associations between the GRS and CRC risk and between GRS and FH were also based on the detailed data from the DACHS study. These analyses were based on 2,363 cases and 2,198 controls, for whom genotyping data were available. Analyses concerning the associations between GRS and the risk for advanced neoplasms (i.e. the combination of CRC and its precursors) were conducted within the BLITZ study, an ongoing study which includes individuals of every age at average risk undergoing screening colonoscopy in southern Germany. For a total of 1,043 participants of the BLITZ study, genomic data was available. Comprehensive analyses of family history in Germany were done within the RAPS study, a multicenter cross sectional study conducted in Munich, Stuttgart and Dresden, and for which information of 28,706 participants could be used.

Data from the RAPS study indicated that the prevalence of having a FH of CRC in Germany is around 9.4% at ages 40-54 and mainly attributable to affected parents. The prevalence of having a FH increased with increasing age of participants. Participants with a FH were more likely to already have undergone previous colonoscopies, a finding also observed in the DACHS study. Having a FH of CRC in a first-degree relative was associated with an odds ratio (OR) of 1.73 (95% confidence interval (CI) 1.48-2.03), with increasing ORs for an increasing number of affected relatives. Joint risk stratification of FH and previous colonoscopies revealed that individuals who had undergone colonoscopies have a reduced risk for CRC, irrespective of

having a FH (e.g. OR of 0.45, 95% CI 0.36-0.56 for participants with a FH in FDR and previous colonoscopy vs. individuals without FH and no colonoscopy).

Risk stratification with a GRS based on previously published single nucleotide polymorphisms found to be associated with a higher risk of CRC confirmed existing promising results and added new insights: Compared to people with the lowest genetic risk, individuals with a higher number of common genetic variants had a higher risk for CRC, with steadily increasing ORs for increasing genetic risk categories (e.g. OR of 2.96, 95% CI 2.20-3.97 for people in the highest vs. people in the lowest GRS decile). A higher GRS also was associated with a higher risk for advanced adenomas (ORs 2.08, 95% CI 1.39-3.12 and 2.71, 95% CI 1.80-4.10, for medium and high GRS vs. low GRS, respectively), but not with a higher risk for non-advanced adenomas (OR 1.05, 95% 0.70-1.55 for highest vs. lowest GRS). Individuals with a high GRS reached the same risk for advanced neoplasms as people in the lowest GRS category approximately 18 years earlier (risk advancement period 17.5, 95% CI 7.8-27.3). Joint association between FH, GRS and the risk for CRC showed that a significant proportion of individuals without FH but in the highest GRS categories have a higher or equally increased risk for CRC compared to half the people with a FH (ORs 1.18, 95% 0.84-1.67 and 1.02, 95% 0.72-1.45 for individuals without FH in the two highest GRS deciles compared to participants with FH and GRS equal or below median).

Considering all strengths and limitations of both existing studies and the analyses presented in this dissertation, risk stratification for CRC and its precursors based on family history and genetic risk scores is meaningful, feasible and technically possible. While family history can identify individuals at increased risk, equally good risk stratification can be achieved with employing a genetic risk score. The latter furthermore provides more refined risk stratification possibilities as it covers a range of values rather than being a binary variable. Considering both information at the same time provided even better risk stratification, although it is often thought that FH merely serves as a proxy for yet undetected genetic alterations. The results presented here indicate that this might not be the case, that both family history and genetic risk represent largely independent sources of risk, and that risk stratification can be improved by considering both pieces of information simultaneously. This is especially interesting in the case of CRC precursors, as genetic risk scores were associated with a higher risk for advanced adenoma, but not with non-advanced adenoma, a highly relevant finding which might help improving more personalized, risk-adapted prevention strategies. With the increasing number of GWAS, associated fine-mapping studies and the subsequent discovery of more common genetic variants in the years to come, it can be expected that risk stratification with GRS will enhance in the near future. At the same time, although feasible and meaningful, risk stratification as of today is still too expensive, time-consuming and impractical from a physician's point of view. With decreasing genotyping costs and more accurate GRS due to larger number of common genetic variants, risk stratification with GRS could however indeed complement existing criteria for risk stratification strategies such as FH and help identify those in biggest need for prevention.