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LETTER TO THE JOURNAL

Nine-fold variation of risk of advanced colorectal neoplasms according to smoking and polygenic risk score: Results from a cross-sectional study in a large screening colonoscopy cohort

Colorectal cancer (CRC) is the third most common cancer and the second most common cause of cancer-related death globally [1]. The slow progression through the adenoma-carcinoma sequence provides great opportunities for prevention by lifestyle intervention and screening [2]. Smoking has been demonstrated to be associated with an increased risk of CRC and an even much stronger increased risk of CRC precursors in a dose-response manner [3, 4]. Gene-environment interaction studies might help unravel the underlying complex mechanisms through which lifestyle risk factors induce colorectal carcinogenesis, and they may disclose the potential for targeted prevention [5]. Although evidence on interactions between smoking and specific single CRC susceptibility locus on the risk of CRC or its precursors is limited [6, 7], polygenic risk score (PRS), aggregating information from a set of CRC-related risk variants identified in genome-wide association studies (GWASs), may help to increase statistical power in gene-environment interaction studies in which interactions may often be missed due to the weak main effects of individual loci and the harsh penalty of multiple comparisons [5]. PRSs have been shown to enhance CRC risk stratification models that already included established lifestyle risk factors of CRC [8, 9]. PRSs also have been shown to be associated with the prevalence of CRC precursors [10]. However, how and to what extent the impact of smoking on the risk of colorectal neoplasms differs by PRS levels is undetermined. We aimed to evaluate the independent and joint impact of smoking and PRS on the risk of colorectal neoplasms in a large colonoscopy screening study. Furthermore, we employed the recently developed "genetic risk equivalent (GRE)" metric [9] to quantify the effect of smoking in terms of equivalent differences in background genetic risk.

Data for this analysis was drawn from the Begleitende Evaluierung innovativer Testverfahren zur Darmkrebsfrüherkennung (BliTz) study (Supplementary Methods). Participants were classified according to the most advanced finding at colonoscopy as follows: any neoplasm (including advanced neoplasm and non-advanced adenoma) and no finding. Smoking status was classified as never, former, and current smoking. Pack-years of smoking were calculated as a measure of lifetime exposure from the average daily cigarette consumption divided by 20 and multiplied by the duration of smoking in years. The PRS, based on 140 CRC-related single nucleotide polymorphisms (SNPs) identified in a recent large international GWAS [10], was calculated as the weighted sum of the number of risk alleles of the respective variants (Supplementary Table S1). PRS was categorized according to the distribution of PRS by quartiles among participants without colorectal neoplasms.

Using logistic regression models, we assessed the associations of smoking and PRS with the presence of colorectal neoplasms. Adjusted odds ratios (aORs) of smoking were translated to GREs, calculated as the ratios of regression coefficients obtained from the models with the respective colorectal neoplasms as endpoint and smoking and PRS percentiles as independent variables, estimating by how much the genetic risk (expressed in terms of PRS percentiles) may be "compensated for" by avoiding the smoking.

Among 4,809 eligible participants, the proportion of male participants was 62.4% among 2,234 participants with any neoplasm [including 871 participants with advanced neoplasm (814 with advanced precancerous lesion and 57 with CRC)], compared to 43.4% among 2,575 participants with no findings of neoplasms at screening colonoscopy (Supplementary Table S2, Supplementary

Abbreviations: CRC, colorectal cancer; CI, confidence interval; GRE, genetic risk equivalent; GWAS, genome-wide association study; OR, odds ratio; PRS, polygenic risk score; SNP, single nucleotide polymorphism..

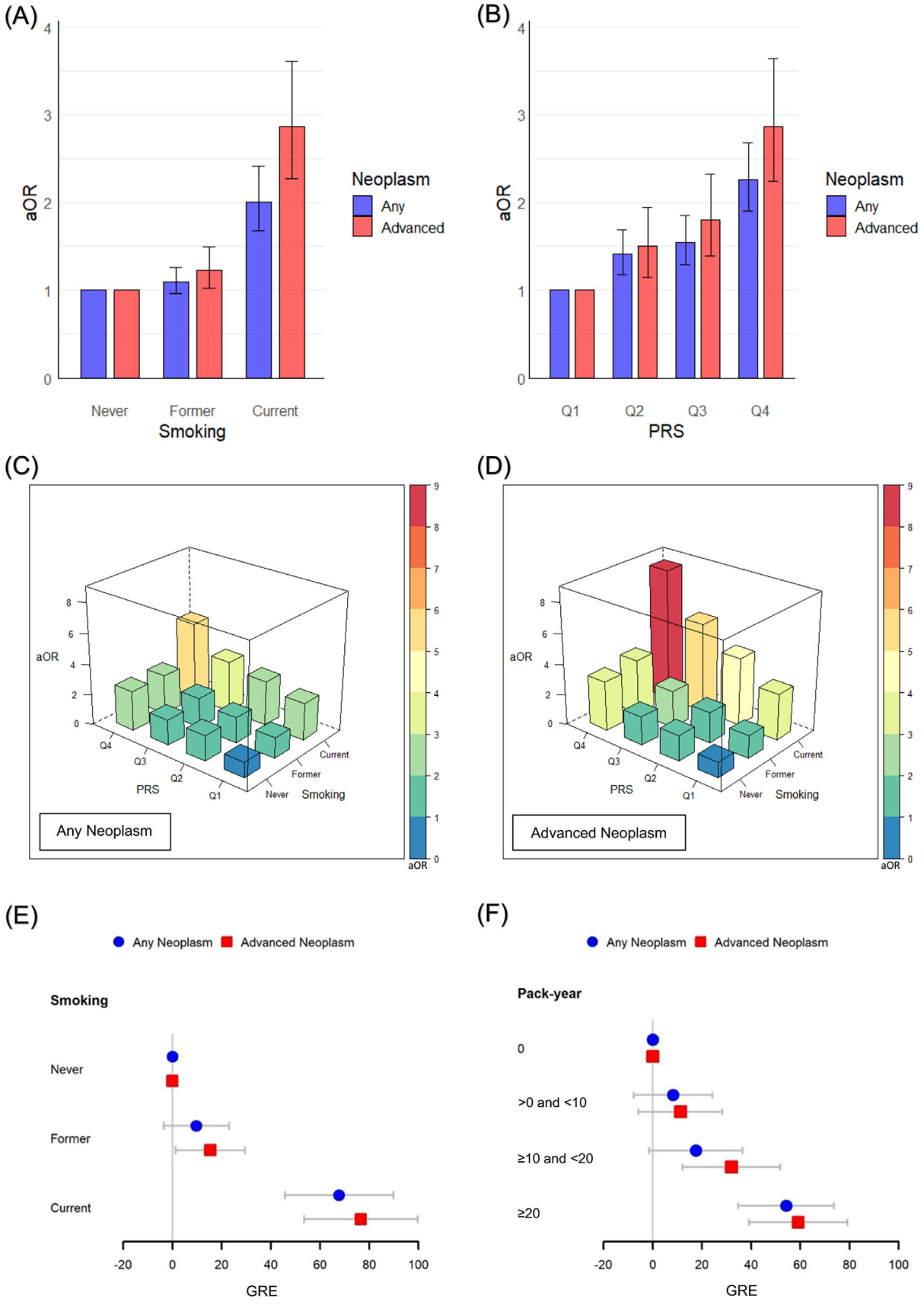

FIGURE 1 Associations of smoking and polygenic risk score with the risk of colorectal neoplasms and the relevant genetic risk equivalents: a cross-sectional analysis based on 4,809 screening colonoscopy participants. (A-B) Individual associations of smoking status (A) and PRS (B) with colorectal neoplasm risk. Adjustment variables in models included age, sex, education, body mass index, physical activity,

Figure S1). Median age was also slightly higher among participants with neoplasms (62 years) than among those without neoplasms (60 years). Current smoking and PRS were strongly associated with an increased risk of colorectal neoplasms, with aORs [95% confidence intervals (CI)] of 2.01 (1.68-2.41) for current versus never smokers and 2.26 (1.90-2.68) for the highest versus lowest quartile of PRSs. Even stronger associations were observed with the presence of advanced neoplasms, with aORs (95% CI) of 2.86 (2.27-3.61) and 2.86 (2.24-3.64), respectively (Figure 1A-B, Supplementary Table S3). In general, the associations between PRS and the risk of colorectal neoplasm seemed to be somewhat more pronounced among never smokers than among former or current smokers, but interactions between smoking status and PRS were not statistically significant (Supplementary Table S4). Joint classification by smoking status and PRS showed very strong variation in risk, with aOR (95% CI) for any neoplasm reaching levels as high as 5.11 (3.59-7.28) and for advanced neoplasm reaching levels as high as 8.66 (5.45-13.76) for current smokers in the highest PRS quartile compared to never smokers in the lowest PRS quartile (Figure 1C-D, Supplementary Table S5).

The strong associations between current smoking and risk of colorectal neoplasms translated into very high GREs (Figure 1E-F, Supplementary Table S6). For example, GREs (95% CI) of 67.7 (45.7-89.8) and 76.6 (53.5-99.7) for current smokers compared to never smokers suggest that smoking had an equivalent effect on the risk of carrying any neoplasm or advanced neoplasm, as having a 68 or 77 percentiles higher PRS, respectively. For example, the risk of smokers in the 10th percentile of PRS would be as high as the risk of never smokers in percentiles 78 and 87 of PRS. Corresponding GREs (95% CI) for 20 or more pack-years of smoking were 54.2 (34.7-73.7) and 59.1 (39.1-79.1), respectively. For non-advanced adenomas, aORs and GREs were smaller (Supplementary Tables S7-S11).

In this large CRC screening study, we observed that current smoking and higher PRS levels were strongly and independently associated with an increased risk of carrying colorectal neoplasms. Our findings may have important clinical and public health implications. In clinical individual consultation, high GREs may help to communicate the large benefits of smoking abstinence and smoking cessation for cancer prevention. The joint risk estimates by smoking and PRS may also help to identify people who would benefit most from screening colonoscopy or from earlier starting of CRC screening. From a public health perspective, high GREs may help to quantify and communicate smoking-related adverse effects on colorectal carcinogenesis and may help to support efforts of smoking prevention on the population level.

Our study has several limitations. First, assessment of lifestyle factors including smoking through a standardized questionnaire is not perfect. However, these factors were ascertained before screening colonoscopy, and their ascertainment could not be affected by colonoscopy results. Although multivariable statistical analysis adjusted for established CRC risk factors, residual confounding attributable to imperfect recall or unaccounted risk factors cannot be completely excluded. Although, to the best of our knowledge, no previous study has calculated GREs for smoking and colorectal neoplasms, our risk estimates for smoking and PRS are consistent with those from other studies and countries, supporting external validity of our results. However, the study population was mainly consisted of white individuals, thereby limiting the generalizability of the results to other populations.

Our study provides comprehensive evidence on the relationships between smoking, PRSs, and the risk of colorectal neoplasms. The strong association of smoking with the presence of advanced neoplasms and the high GRE of smoking underline the large potential of abstaining from smoking in reducing the risk of colorectal cancer. Although the relative risk of smoking was similar across various levels of PRS, the absence of interaction of PRS and smoking on the multiplicative scale suggests that, in terms of absolute risk reduction, abstaining from smoking is particularly beneficial for those with high genetic risk. We hope that our finding, that abstaining from smoking can "compensate" for a large proportion of genetically increased risk, may help to support efforts to promote smoking cessation which has beneficial effects far beyond CRC prevention, both within and beyond the context of CRC screening.

alcohol consumption, red and processed meat consumption, history of hormone replacement therapy, history of diabetes, use of non-steroidal anti-inflammatory drugs, family history of CRC in a first-degree relative, history of colonoscopy, and PRS (A) or smoking status (B). (C-D) Joint associations of smoking status and PRS with any colorectal neoplasm risk (C) or advanced colorectal neoplasm risk (D). Never smokers in the lowest PRS quartile were used as the reference group; adjustment variables in models included age, sex, education, body mass index, physical activity, alcohol consumption, red and processed meat consumption, history of hormone replacement therapy, history of diabetes, use of non-steroidal anti-inflammatory drugs, family history of CRC in a first-degree relative and history of colonoscopy. (E-F) Genetic risk equivalents for comparisons between different smoking statuses (E) or between different pack-years of active smoking categories (F). PRS was categorized according to the distribution of PRS among participants without neoplasms. Abbreviations: CRC, colorectal cancer; aOR, adjusted odds ratio; GRE, genetic risk equivalents; PRS, polygenic risk score; Q, quartile.

AUTHOR CONTRIBUTIONS

HB designed the study. RF and XC analyzed the data. RF, XC, TN, TS, MH and HB interpreted the data. RF, XC, TN and HB drafted the manuscript. All authors provided comments, revised the draft and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

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DATA AVAILABILITY STATEMENT

The raw data underlying this article cannot be shared due to privacy reasons.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The BliTz study was approved by the Ethics Committees of the Medical Faculty Heidelberg (178/2005) and Ethics Committees of the responsible state physicians' chambers (Baden-Wuerttemberg, M118-05-f; Rhineland-Palatinate, 837.047.06(5145); Saarland, 217/13; Hesse, MC 254/2007). Informed consent was obtained from each participant.

CLINICAL TRIAL REGISTRATION

The BliTz study is registered at the German Clinical Trials Register (DRKS-ID: DRKS00008737).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.