To what extent is male excess risk of advanced colorectal neoplasms explained by known risk factors? Results from a large German screening population

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Abstract
Colorectal cancer (CRC) incidence and prevalence of its precursors are substantially higher among males than among females in most countries but the reasons for the male excess risk are incompletely understood. We aimed to assess to what extent it is explained by known risk factors. Prevalence of advanced neoplasia (AN, ie, CRC or advanced adenoma) and CRC risk and preventive factors were ascertained among 15 985 participants of screening colonoscopy aged 55-79 years in Germany. Logistic regression was used to calculate odds ratios (ORs) for the association between male sex and AN with and without adjustment for known risk and preventive factors. In age-adjusted comparisons, men had 2-fold increased risk for AN compared to women (OR = 1.98, 95% confidence interval [CI] 1.79-2.19). After comprehensive adjustment for medical, lifestyle and dietary factors, the OR was reduced to 1.52 (95% CI 1.30-1.77), suggesting that these factors accounted for 47% of male excess risk. Male excess risk increased from proximal colon to distal colon and rectum, with age-adjusted ORs (95% CI) of 1.63 (1.38-1.91), 2.13 (1.85-2.45) and 2.36 (1.95-2.85), respectively, and with the proportion of excess risk explained by covariates being lower for AN in the rectum (26%) than for AN in the proximal (52%) or distal colon (46%). Male excess risk was somewhat lower (age-adjusted OR 1.87) and explained excess risk was smaller (36%) when men were compared to women who never used hormone replacement therapy. In conclusion, most of the male excess risk and the potential to overcome it remain to be explored by further research.

Abbreviations: AA, advanced adenoma; AN, advanced neoplasia; CI, confidence interval; CRC, colorectal cancer.
INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer globally, accounting for approximately 1.93 million new diagnoses in 2020. With age adjusted incidence rates (world standard) of 23.4 and 16.2 per 100 000 globally, incidence is substantially higher among men than among women. This also applies to Germany, where age adjusted incidence rates are even substantially higher than the global average (30.4 and 21.8 per 100 000, respectively). Even larger sex differences have been reported for prevalences of adenomas, the precursors of most CRCs. In contrast to other cancers for which major sex differences in incidence are being observed, such as lung cancer or other highly smoking-related cancers, which can be largely explained by smoking habits, the reasons for the large male excess risk of CRC are poorly understood. Protective effects of hormone replacement therapy (HRT) which have consistently been found in many studies point to a potential role of hormonal factors. Also, some of the known CRC risk factors, such as smoking or high consumption of processed and red meat are more common among men than among women in many societies. On the other hand, certain medications, such as aspirin for cardiovascular prevention, which also reduce the risk of CRC are more commonly used among men than among women.

In an earlier analysis of the KolosSal study, a study among almost 19,000 participants of screening colonoscopy in South-West Germany among whom CRC risk and protective factors were assessed, we found that a much larger proportion of colorectal neoplasia was statistically attributable to male sex than to family history or smoking. In this analysis of the KolosSal study, we aimed to assess to what extent the major sex differences in the prevalence of advanced colorectal neoplasms (AN, ie, CRC or advanced adenoma) can be explained by differences in a wide range of known or suspected CRC risk and preventive factors and to what extent their origin is yet to be explored. We considered the main established or suggested risk and protective factors for CRC: age, family history of CRC, diabetes, previous colonoscopy, aspirin and statins intake, smoking, alcohol consumption, body mass index (BMI), height, physical activity (PA), consumption of red and processed meat, fruit and vegetables, whole grain and finally use of HRT among women.

KEYWORDS
colorectal neoplasia, distal colon, male sex, prevalence, proximal colon

What’s new?
The prevalence of precursor lesions for colorectal cancer (CRC), advanced colorectal neoplasia (AN) is higher among males than females. Whether this difference is explained by variations in certain risk factors remains unclear. In this study, the authors found that male excess risk of AN was twice as high in men than women. About half of excess CRC risk among males could be attributed to medical, lifestyle, and dietary factors. Proportions of explained excess risk increased from the rectum to the distal and proximal colon. The findings warrant further investigation of factors contributing to AN and CRC risk in males.

2 MATERIALS AND METHODS

2.1 Study design and population

Details of the design and setting of the KolosSal study have been described previously. Briefly, participants of screening colonoscopy were recruited in gastroenterology practices in Saarland, a small state in the South West of Germany, from May 18, 2005, through October 17, 2013. In Germany, screening colonoscopy has been offered as primary screening exam to men and women aged 55 or older since October 2002. Most screening colonoscopies in Germany are conducted in practices of gastroenterology or internal medicine. Endoscopists need to fulfill defined criteria to become eligible (≥200 colonoscopies and ≥50 polypectomies under supervision in the preceding two calendar years) or to maintain eligibility (≥200 colonoscopies per year and ≥10 polypectomies per year) for conducting screening colonoscopies. Histopathologic examination of removed polyps is performed decentrally; endoscopists send polyps to a certified pathological laboratory of their choice.

Nearly all practices conducting screening colonoscopies in Saarland participated in recruitment in this statewide study (n = 33). Distributions of age, sex and colonoscopy findings were very similar to those seen in the national registry of screening colonoscopies in Germany in the time period of study recruitment. The study was approved by ethics committees of the University of Heidelberg and of the Medical Association of Saarland. Each participant provided written informed consent.

Overall, 18,997 subjects were recruited between January 2, 2006, and October 22, 2013. For this analysis, the following exclusions were made (N = 3012) to ensure representativeness of our results for an average-risk screening population and to minimize the number of screening colonoscopies with missed neoplasms: age <55 or ≥80 years (N = 703), history of CRC or inflammatory bowel disease (N = 421); inadequate bowel preparation before colonoscopy (N = 1323), incomplete colonoscopy (cecum not reached; N = 179), or only undefined polyps found during colonoscopy (N = 386). Thus, 15,985 participants were retained for analysis (Figure 1).
Participants with colonoscopy results: 18,997

- N = 703
  - Age ≤55 or ≥80 years

- N = 421
  - History of CRC or IBD

- N = 1323
  - Inadequate bowel preparation

- N = 179
  - Incomplete colonoscopy

- N = 386
  - Only undefined polyps found

Included in analysis: 15,985

- N = 232
  - CRC

- N = 1627
  - AA

- N = 3317
  - NAA

- N = 10,809
  - No neoplasm

FIGURE 1 Flow diagram of participants excluded for various reasons and finally included participants. AA, advanced adenoma; CRC, colorectal cancer; IBD, inflammatory bowel disease; NAA, nonadvanced adenoma

2.2 Data collection

Participants, who were recruited in the practices before screening colonoscopy, filled out a standardized questionnaire in which they provided information on CRC risk and preventive factors, including medical factors (previous colonoscopies including their indication and findings, medication intake, family history of CRC, body height), lifestyle factors (smoking, alcohol intake, occupational and recreational PA) and dietary factors (short food frequency questionnaire including consumption frequencies of red and processed meat, whole grain, fruit and vegetables). Two trained investigators who were blinded with respect to the questionnaire data independently transferred results from screening colonoscopy and histology reports to a standardized form. Any discrepancy between the investigators was resolved by further review and discussion. Patients were classified according to the most advanced of the following findings at colonoscopy: CRC, advanced adenoma (defined as adenoma matching at least one of the following criteria: size >1 cm, tubulovillous or villous components, high-grade dysplasia), nonadvanced adenoma, no neoplasm.

2.3 Statistical analysis

We first conducted age adjusted and multivariate adjusted logistic regression models to assess the association between sex and prevalence of advanced colorectal neoplasia. Next, to assess the potential of covariates for explaining sex differences in AN prevalence, we assessed associations between covariates and both, sex and AN. We focused on established and suspected CRC risk and preventive factors, including medical, lifestyle and dietary factors. As medical factors, we considered family history of CRC, “diabetes-years” (continuous, years since diagnosis of diabetes), previous colonoscopy (yes/no), regular aspirin intake (yes/no), regular intake of statins (yes/no). We investigated the following lifestyle factors (all as continuous variables): smoking pack-years, alcohol consumption (drinks per week; 1 drink = 0.33 L of beer, 0.25 L of wine, or 0.02 L of liquor, reflecting the standard portion sizes in the study population), BMI based on self-reported height and weight, PA. Finally, the following dietary factors were considered (continuous variables): red and processed meat consumption, intake of fruit, vegetable and whole grain. Information on other potentially relevant dietary factors such as dairy product intake, fish and vitamin D were not available. We also estimated separate models comparing AN risk among men to women who never used HRT because HRT has been associated with a significantly lower CRC risk. Overall PA was assessed by metabolic equivalent-hours (MET-h) comprising light recreational PA, light and hard physical work and moderate to intense PA. We also created a score for red and processed meat intake, and a “healthy food score” for fruit, vegetable and whole grain intake (see Table S1 for details). Due to the presence of missing data in adjustment variables, we used multiple imputation with 10 imputed data sets.

Covariate adjustment was done first for age only, followed by age plus medical factors, age plus lifestyle factors, age plus dietary factors, and finally all factors combined. The following outcomes were assessed: any AN, proximal colon AN, distal colon AN and rectal AN. In addition, for any AN only, analyses stratified by the median age of all participants were performed, to investigate if changes in associations between sex and AN by covariate adjustment were age-dependent.

For selected models we estimated the share of the excess risk among men compared to women that can be explained by the investigated risk and protective factors. This “explained share of excess risk,” estimated from odds ratios (ORs), was calculated as (age-adjusted OR – fully adjusted OR)/age-adjusted OR – 1). All analyses were done in R version 4.0.5. Multiple imputation was done using the “mice” package. Analyses were performed on imputed data sets and results were pooled using mice’s “pool” function. ORs and corresponding 95% confidence intervals were calculated from the results of logistic regression models. Statistical significance was assessed at an α level of .05 in two-sided testing.

3 RESULTS

3.1 Study population characteristics

Characteristics of the study population are presented in Table 1. Age distribution was similar among males and females. CRCs and AAs were more commonly found among men. Prevalence of several CRC
| Characteristic                      | Total (N = 15 985) | Men (N = 7822) | Women (N = 8163) | P value | Missing (N, %) |
|------------------------------------|--------------------|----------------|------------------|---------|----------------|
| **Most advanced finding at colonoscopy** |                    |                |                  |         |                |
| Colorectal cancer                  | 219 (1.3)          | 141 (1.8)      | 78 (1.0)         | <.001   | 0 (0%)         |
| Proximal colon                     | 48 (21.9)          | 22 (15.6)      | 26 (33.3)        | .01     |                |
| Distal colon                       | 83 (37.9)          | 58 (41.1)      | 25 (32.1)        |         |                |
| Rectum                             | 88 (40.2)          | 61 (43.3)      | 27 (34.6)        |         |                |
| Advanced adenoma                   | 1640 (10.1)        | 1049 (13.4)    | 591 (7.2)        | <.001   |                |
| Any AN                             | 1859 (11.4)        | 1190 (15.2)    | 669 (8.2)        | <.001   |                |
| Nonadvanced adenoma                | 3317 (20.4)        | 1926 (24.6)    | 1391 (17.0)      | <.001   |                |
| No neoplasm                        | 10 809 (66.5)      | 4706 (60.2)    | 6103 (74.8)      | <.001   |                |
| **Age (years)**                    |                    |                |                  |         |                |
| 55-59                              | 5976 (37.4)        | 2814 (36.0)    | 3162 (38.7)      | <.001   | 0 (0%)         |
| 60-64                              | 3463 (21.7)        | 1686 (21.6)    | 1777 (21.8)      |         |                |
| 65-69                              | 3305 (20.7)        | 1650 (21.1)    | 1655 (20.3)      |         |                |
| 70-74                              | 2253 (14.1)        | 1152 (14.7)    | 1101 (13.5)      |         |                |
| 75-79                              | 988 (6.2)          | 520 (6.6)      | 468 (5.7)        |         |                |
| **Family history (CRC)**           |                    |                |                  |         |                |
| No known FDR                       | 13 836 (86.6)      | 6825 (87.3)    | 7011 (85.9)      | <.001   | 0 (0%)         |
| ≥1 FDR                             | 2149 (13.4)        | 997 (12.7)     | 1152 (14.1)      |         |                |
| **Diabetes**                       |                    |                |                  |         |                |
| Yes                                | 1887 (11.8)        | 1092 (14.0)    | 795 (9.8)        | <.001   | 48 (0.3%)      |
| No                                 | 14 050 (88.2)      | 6707 (86.0)    | 7343 (90.2)      |         |                |
| **Previous colonoscopy**           |                    |                |                  |         |                |
| Yes                                | 4624 (29.6)        | 2220 (29.6)    | 2404 (30.2)      | .06     | 341 (2.1%)     |
| No                                 | 11 020 (70.4)      | 5474 (70.4)    | 5546 (69.8)      |         |                |
| **Aspirin (ASA) (regular intake)** |                    |                |                  |         |                |
| Yes                                | 1167 (92.5)        | 733 (9.7)      | 434 (5.5)        | <.001   | 475 (3.0%)     |
| No                                 | 14 343 (7.5)       | 6835 (90.3)    | 7508 (94.5)      |         |                |
| **Statins (regular intake)**       |                    |                |                  |         |                |
| Yes                                | 2532 (16.3)        | 1425 (18.8)    | 1107 (13.9)      | <.001   | 475 (3.0%)     |
| No                                 | 12 978 (83.7)      | 6143 (81.2)    | 6835 (86.1)      |         |                |
| **Smoking**                        |                    |                |                  |         |                |
| Ever                               | 8142 (54.5)        | 4964 (65.5)    | 3178 (56.9)      | <.001   | 1043 (6.5%)    |
| Never                              | 6800 (45.5)        | 2612 (34.5)    | 4188 (43.1)      |         |                |
| **Pack-years**                     |                    |                |                  |         |                |
| 0 to <2                            | 7189 (51.7)        | 2779 (40.6)    | 4410 (62.5)      | <.001   | 2071 (13.0%)   |
| 2 to <10                           | 1707 (12.3)        | 839 (12.2)     | 868 (12.3)       |         |                |
| 10 to <20                          | 1790 (12.9)        | 1056 (15.4)    | 734 (10.4)       |         |                |
| 20 to <30                          | 1203 (8.6)         | 754 (11.0)     | 449 (6.4)        |         |                |
| 30 to <40                          | 911 (6.5)          | 565 (8.2)      | 346 (4.9)        |         |                |
| ≥40                                | 1114 (8.0)         | 860 (12.5)     | 254 (3.6)        |         |                |
| **Alcohol consumption (standard beverages per week)** | | | | | |
| 0 to <2.4                          | 4726 (32.5)        | 1421 (19.1)    | 3305 (46.6)      | <.001   | 1443 (9.0%)    |
| 2.4 to <6                          | 4846 (33.3)        | 2372 (31.9)    | 2474 (34.9)      |         |                |
| ≥6                                 | 4970 (34.2)        | 3653 (49.1)    | 1317 (18.6)      |         |                |
risk and protective factors differed significantly between men and women. For example, men were more likely to have been diagnosed with diabetes (14% vs 10%), to have ever smoked (66% vs 57%), to consume ≥6 standard alcoholic drinks per week (49% vs 19%), and to be overweight or obese (76% vs 62%). Women were more physically active than men, consumed higher amounts of fruit and vegetables and whole grain. Almost half of the women (45.4%) had ever used HRT.

### 3.2 Prevalence of AN according to sex and covariates

Prevalence of CRC was 1.8% (141/7822) and 1.0% (78/8163) in men and women, respectively (P < .001). Men also had a higher prevalence of advanced and nonadvanced adenomas (13.4% vs 7.2% and 24.6% vs 17.0%, respectively) (Table 1). The almost 2-fold higher prevalence of CRC and AA among men than among women translated into a
**TABLE 2** Odds ratios for having advanced neoplasia among males compared to females, according to adjustment for selected covariates

| Odds ratio (95% confidence interval) | Established or likely CRC risk and protective factors | Lifestyle factors | Diet factors |
|-------------------------------------|--------------------------------------------------------|------------------|--------------|
|                                     | Established or likely CRC risk and protective factors | Lifestyle factors | Diet factors |
|                                     | Medical factors |                          |                           |
|                                     | Age\(^b\) | Family history\(^ab\) | Diabetes years\(^b\) | Previous colonoscopy\(^b\) | Aspirin (regular use)\(^b\) | Statins (regular use) | Body height | Pack-years\(^b\) | Alcohol consumption\(^b\) | BMI\(^b\) | Physical activity\(^b\) | Red and processed meat\(^b\) | Fruit and vegetables | Whole grain | EER |
| Outcome: any AN (N = 1859, thereof 1190 among men and 669 among women) | 1.98 (1.79-2.19) | x | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
|                                     | 1.84 (1.59-2.12) | x | x | x | x | x | x | x | - | - | - | - | - | - | - | 14% |
|                                     | 1.71 (1.54-1.91) | x | - | - | - | - | - | x | x | x | x | x | - | - | - | 28% |
|                                     | 1.84 (1.65-2.04) | x | - | - | - | - | - | - | - | - | x | x | x | 14% |
|                                     | 1.52 (1.30-1.77) | x | x | x | x | x | x | x | x | x | x | 47% |
| Outcome: proximal colon AN (N = 638, thereof 389 among men and 249 among women) | 1.63 (1.38-1.91) | x | - | - | - | - | - | - | - | - | - | - | - | - | - |
|                                     | 1.54 (1.23-1.93) | x | x | x | x | x | x | - | - | - | - | - | - | - | 14% |
|                                     | 1.44 (1.21-1.72) | x | - | - | - | - | - | x | x | x | x | - | - | - | 30% |
|                                     | 1.53 (1.29-1.81) | x | - | - | - | - | - | - | - | - | x | x | x | 16% |
|                                     | 1.30 (1.02-1.65) | x | x | x | x | x | x | x | x | x | x | x | x | x | 52% |
| Outcome: distal colon AN (N = 917, thereof 609 among men and 308 among women) | 2.13 (1.85-2.45) | x | - | - | - | - | - | - | - | - | - | - | - | - | - |
|                                     | 1.97 (1.61-2.40) | x | x | x | x | x | x | - | - | - | - | - | - | - | 14% |
|                                     | 1.84 (1.58-2.14) | x | - | - | - | - | - | x | x | x | x | - | - | - | 26% |
|                                     | 1.95 (1.69-2.26) | x | - | - | - | - | - | x | x | x | x | - | - | - | 16% |
|                                     | 1.61 (1.30-1.98) | x | x | x | x | x | x | x | x | x | x | x | x | x | 46% |
| Outcome: rectal AN (N = 504, thereof 348 among men and 156 among women) | 2.36 (1.95-2.85) | x | - | - | - | - | - | - | - | - | - | - | - | - | - |
|                                     | 2.25 (1.73-2.92) | x | x | x | x | x | x | - | - | - | - | - | - | - | 8% |
|                                     | 2.06 (1.68-2.52) | x | - | - | - | - | - | x | x | x | x | - | - | - | 22% |
|                                     | 2.29 (1.88-2.80) | x | - | - | - | - | - | - | - | x | x | x | 5% |
|                                     | 2.00 (1.52-2.64) | x | x | x | x | x | x | x | x | x | x | x | x | x | 26% |

Abbreviations: AN, advanced neoplasia (colorectal cancer or advanced adenoma); BMI, body-mass index; EER, explained excess risk (share of excess risk among males statistically explained by covariate adjustment); x, adjusted for the respective covariate; -, not adjusted for that covariate. Proximal colon: coecum until transverse colon. Distal colon: left flexure until sigmoid colon.

\(^ab\)Any known first-degree relative with CRC.

\(^b\)Established risk or protective factors.
crude OR of 2.01 (95% CI 1.82-2.22) for any AN, with a stronger association for rectal AN (OR = 2.39) than for AN in the distal colon (OR = 2.15) and the proximal colon (OR = 1.66) (Table S2). Among the covariates, age, family history, diabetes, alcohol intake, BMI, being tall, and red and processed meat intake were also associated with significantly increased odds of AN, whereas ever having had a colonoscopy, fruit, vegetable, whole grain intake, and among women current use of HRT were associated with significantly lower odds of AN.

3.3 Impact of covariate adjustment

Adjustment for medical factors in addition to age had a small but relevant impact on the association between sex and prevalence of AN (OR = 1.84 compared to 1.98) (Table 2). Individual adjustment for either lifestyle or dietary factors resulted in similarly reduced ORs of 1.71 and 1.84, respectively. Comprehensive simultaneous adjustment for medical, lifestyle and dietary factors resulted in an OR of 1.52, which suggests that in total 47% ([1.98-1.52]/[1.98-1] = 0.46/0.98 = 0.47) of the excess risk of men is statistically explained by these factors. All associations of male sex with AN risk remained statistically significant.

With age adjusted ORs (95% CI) of 1.63 (1.38-1.91), 2.13 (1.85-2.45) and 2.36 (1.95-2.85), respectively, male excess risk increased from proximal colon to distal colon and rectum. Adjustment for medical, lifestyle or diet factors all diminished the associations between male sex and risk of proximal, distal or rectal AN to some extent. The degree of attenuation, and hence the proportion of explained excess risk by all factors combined was similar for AN in the proximal colon (52%) and distal colon (46%), but lower for AN in the rectum (26%). Figure 2 illustrates observed attenuations in OR with covariate adjustment.

The excess risk for AN of men was slightly lower in comparisons with women who never used HRT (age-adjusted OR: 1.87, 95% CI 1.65-2.12) (Table S3). ORs again decreased with more comprehensive adjustment to 1.56 (95% CI 1.31-1.86) in the fully adjusted model.
although attenuations were more modest than for the comparisons of men with all women, and only 36% of the excess risk of men was explained by the covariates. For rectal AN, even smaller difference was seen between age adjusted and fully adjusted ORs (25% explained excess risk).

3.4 | Age-specific results

ORs of male vs female sex with the same adjustment variables were very similar among younger (55-64 years) and older participants (65-79 years), suggesting no modifying effect of age on the association between sex and risk of any AN. In the younger participants (Table S4), ORs for any AN gradually decreased from 2.02 to 1.58 with more comprehensive adjustment, and similar decreases were observed for location-specific outcomes (proximal colon AN: from 1.59 to 1.22, distal colon AN: 2.10 to 1.51, rectal AN: 2.50 to 2.44). In older participants (Table S5), somewhat smaller decreases of ORs for proximal and distal colon AN were observed, from 1.65 to 1.37 and from 2.17 to 1.71, respectively. Changes in OR any AN were similar compared to younger participants (from 1.94 to 1.45), whereas they were stronger for rectal AN (from 2.20 to 1.63).

4 | DISCUSSION

Age adjusted incidence rates of CRC are approximately 1.5-fold higher among men than among women in Germany.1 Sex-specific differences are estimated to be even higher regarding prevalence of adenomas, as suggested by a large study of >4.4 million screening colonoscopies in Germany.2 Male sex has been identified as risk factor for AN very consistently,11,20,21 for example, with an RR of 1.83 (95% CI 1.69-1.97) estimated in a meta-analysis of 18 cohorts including >920 000 participants of screening colonoscopy.22 Only one study included in that meta-analysis23 adjusted for smoking and alcohol consumption but no other factors potentially contributing to this sex difference. A number of modifiable risk factors for CRC have been identified many of which are likely to be differentially distributed among men and women.24 However, to our knowledge, it has not been studied previously to what extent sex differences in AN risk can be explained by differences in risk factor distributions. In this study of almost 16 000 participants of screening colonoscopy in Germany, we compared ORs of male vs female sex for having advanced colorectal neoplasia, without and with adjustment for established CRC risk and protective factors.

We found that, in models adjusted for age only, men had an approximately 2-fold higher risk of AN than women (OR 1.98). Comprehensive covariate adjustment reduced the OR to 1.52. This would imply that approximately half of the excess risk among men could be explained by the considered covariates. Similar explained proportions were estimated for AN in the proximal and distal colon compared to a smaller proportion of rectal AN (26%). ORs for male sex and overall AN risk were consistently slightly lower in comparisons to women who had never used HRT (age-only and fully-adjusted ORs: 1.87 and 1.56, respectively).

Our results suggest that a relevant fraction of the male excess risk remains that cannot be attributed to the known established risk/protective factors assessed in this study. However, the proportion of male excess risk explained may have been underestimated to some extent by residual confounding resulting from imperfect measurement or reporting of those factors.

Substantially lower CRC risk among women who ever took oral contraceptives or HRT compared to women who did not25,26 point to a major role of hormonal factors in CRC risk which may explain the remaining male excess risk to some extent. Estrogen has been suggested to potentially lower CRC risk by inhibiting inflammatory cytokines such as interleukin-627 and by increasing apoptosis in cell lines28 which may explain a relevant part of sex differences in CRC risk. In our study, the proportion of male excess risk explained by known risk factors was smaller (36%) when men were compared to women who had never used HRT. Unfortunately, we did not have information on oral contraceptive use, nor other potential indicators of lifetime hormone levels, such as age at menarche and menopause, parity or breastfeeding in our study. Further research is required to more fully disclose the sources of the lower AN and CRC risk of women compared to men.

Apart from observed AN risk among those who participate in screening colonoscopy, sex-specific differences are also expected with respect to socioeconomic status (SES) and use of screening colonoscopy, with stronger associations between SES and colonoscopy screening participation among males than females.29 If consideration of SES may increase the explainable proportion of male excess risk should be investigated in further studies.

Adjustment for body height notably reduced the association between male sex and AN risk. The mechanisms behind this observation are unclear. In the UK Biobank prospective cohort study, no association between height and CRC risk and no interaction with sex was observed, and the conceivable link with insulin-like growth factor I (IGF-I) could not be confirmed for CRC.30

Our results have several strengths, including the large size of the cohort and inclusion of average risk participants of screening colonoscopy rather than preselected participants who had colonoscopy for clarification of symptoms. To our knowledge, this is the first study to systematically quantify the impact of covariate adjustment in estimating the association between sex and risk of AN, overall and stratified by location. To avoid data-driven variable selection and thus spurious associations, we focused on established CRC risk and protective factors. We used quantitative information on covariates (eg, smoking pack-years) wherever possible. Multiple imputation was used to ensure equal numbers of observations in different regression models, avoiding bias that could have been introduced in complete cases analysis. The potential impact of HRT on CRC risk was considered by complementary analyses focusing on the comparison of men with women who never used HRT.

Our study also has limitations. Measurements of some covariates may have lacked precision due to imperfect reporting and assessment which may have resulted in imperfect control of the impact of those
From potential imprecision of reported data, also social desirability bias is conceivable. For example, if answers of women were more influenced by social desirability than answers of men, this could have led to overestimation of the gradient in unhealthy behavior between men and women. In that case, the proportion of excess male risk explained by unhealthy behavior could have been overestimated in our study. Even though investigations of CRCs (rather than ANs, the combination of CRCs and AAs) including location-specific subgroups as individual outcome would be clinically relevant, case numbers were insufficient for analyses of CRC and its subtypes. Thus, further research on this question is warranted. Recruitment for the KolosSal study took place in 2005-2013, and sex differences for some of the risk factors may have changed since then. In particular, there has been an assimilation of smoking prevalences in recent years which may have led to a slight attenuation of sex differences since the years of recruitment. Finally, the study region might not be entirely representative for the rest of Germany or even other parts of the world with different risk/protective factor profiles.

Few other studies assessed similar covariates (“healthy lifestyle”) like ours. However, they focused on associations of those covariates on CRC risk directly, rather than their contribution to CRC risk that would otherwise be attributed to male sex as a risk factor. For example, Carr et al. found in a large population-based case-control study from Germany that their healthy lifestyle score (including smoking, alcohol, diet, PA and body fatness) was strongly associated with CRC risk, with an OR of 0.33 when the healthiest group was compared to the least healthy reference group. Aleksandrova et al. considering the same five factors as Carr et al, found an OR of 0.63 for five “healthy lifestyle” factors compared to 0 or 1 in the EPIC cohort comprising almost 350,000 participants.

Some potentially relevant aspects could not be covered in this article. Those include validating self-reported risk factor exposure and analyses stratified by ethnic group (which is also associated with CRC risk). In addition, future studies would ideally assess all exposure analyses stratified by ethnic group (which is also associated with CRC risk).35 In particular, there has been an assimilation of smoking prevalences in recent years which may have led to a slight attenuation of sex differences since the years of recruitment. Finally, the study region might not be entirely representative for the rest of Germany or even other parts of the world with different risk/protective factor profiles.

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Some potentially relevant aspects could not be covered in this article. Those include validating self-reported risk factor exposure and analyses stratified by ethnic group (which is also associated with CRC risk). In addition, future studies would ideally assess all exposure analyses prospectively over time rather than using self-reported cross-sectional data which may be affected by recall bias, that is, differential recall of past risk factor exposure between men and women. Detailed information on exposure over time would also allow for estimations of associations between AN risk and “aspirin-years,” the time-course of weight gain etc. in addition to smoking pack-years and “diabetes-years” and might further improve covariate adjustment. Furthermore, we did not have data on genetic risk for CRC although information on first-degree relatives with CRC was considered. It has been shown that polygenic risk scores provide important risk information beyond family history. However, given their similar distribution among men and women, their consideration would unlikely have changed our results to any relevant extent. Also, additional modifiable risk and protective factors are likely to exist.

In summary, our study suggests that the known, mostly modifiable and protective factors assessed in this study explain almost half of the excess risk of AN among males compared to females. However, it also implies that a similarly large proportion of sex-specific differences cannot (yet) be explained by a range of established or suspected CRC risk and protective factors. This underlines the need for further research to this end. In particular, a better understanding of the role of hormonal factors throughout the course of life might help to provide clues for explaining the remaining “sex gap.” Notwithstanding the remaining gaps of knowledge, both men and women can and should considerably reduce their CRC risk by adhering to a healthy lifestyle and using effective CRC screening offers, such as colonoscopy or fecal immunochemical test.

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CONFLICT OF INTEREST
All authors have completed the ICMJE uniform disclosure form and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, no other relationships or activities that could appear to have influenced the submitted work.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT
The KolosSal study was approved by ethics committees of the University of Heidelberg (057/2005) and of the Medical Association of Saarland (54/05). Informed consent was obtained from each participant.

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

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