Colorectal cancer risk by genetic variants in populations with and without colonoscopy history

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Abstract

**Background:** Polygenic risk scores (PRS), which are derived from results of large genome-wide association studies (GWAS), are increasingly propagated for colorectal cancer (CRC) risk stratification. The majority of studies included in the large GWAS consortia were conducted in the United States and Germany, where colonoscopy with detection and removal of polyps has been widely practiced over the last decades. We aimed to assess if and to what extent the history of colonoscopy with polypectomy may alter metrics of the predictive ability of PRS for CRC risk.

**Methods:** A PRS based on 140 single nucleotide polymorphisms was compared between 4939 CRC cases and 3797 controls of the DACHS study, a population-based case-control study conducted in Germany. Risk discrimination was quantified according to the history of colonoscopy and polypectomy by areas under the curves (AUCs) and their 95% confidence intervals (CIs). All statistical tests were two-sided.

**Results:** AUCs (95% CIs) were higher among subjects without previous colonoscopy (0.622 [0.606-0.639]) than among those with previous colonoscopy and polypectomy (0.568 [0.536-0.601], difference [Δ AUC] = 0.054, p = 0.004). Such differences were consistently seen in sex-specific groups (women: Δ AUC = 0.073, p = 0.02; men: Δ AUC = 0.046, p = 0.048) and age-specific groups (<70 years: Δ AUC = 0.052, p = 0.07; ≥70 years: Δ AUC= 0.049, p = 0.045).

**Conclusions:** Predictive performance of PRS may be underestimated in populations with widespread use of colonoscopy. Future studies using PRS to develop CRC prediction models should carefully consider colonoscopy history in order to provide more accurate estimates.
In the past two decades, genome-wide association studies (GWASs) have identified a rapidly increasing number of single nucleotide polymorphisms (SNPs) that are independently associated with the risk of colorectal cancer (CRC).\textsuperscript{1-8} Recent studies have shown that polygenic risk scores (PRS) built from these SNPs may be useful for CRC risk prediction and risk stratification for personalized screening.\textsuperscript{9,10} Furthermore, a prior study suggested that people with high genetic risk are most likely to benefit from the targeted CRC screening strategies.\textsuperscript{11}

Evaluation of the predictive value of these PRS for CRC risk has to a large extent been based on studies from the United States and Germany, where colonoscopy has been widely used since the 1990s and 2000s, respectively,\textsuperscript{12} and where a substantial proportion of the older population from which the study populations were drawn has had prior colonoscopy.\textsuperscript{13} Much of the excess risk resulting from genetic predisposition is expected to lead to a more rapid progression of colorectal adenomas and higher CRC incidence.\textsuperscript{14} As adenomas are typically removed at colonoscopy, genetically determined variation in CRC risk is likely to be diluted among people with previous colonoscopy. This dilution may lead to underestimation of the predictive performance of PRS for CRC risk. Given that associations of PRS with CRC risk have mainly been derived from study populations in which a non-negligible proportion has had colonoscopy, estimates of the predictive value of PRS may have been underestimated for people without previous colonoscopy – that is the main target group for risk stratification in CRC screening.

In this study, we aimed to assess the relevance of including or excluding people with previous colonoscopy from estimates of the predictive value of PRS for CRC risk, and to derive undiluted estimates from people without previous colonoscopy in a large population-based case-control study.
Methods

Study design and study population

Our analysis is based on the DACHS (Darmkrebs: Chancen der Verhütung durch Screening) study, an ongoing large population-based case-control study on CRC conducted in southwestern Germany. Details on the DACHS study design and the study population have been reported elsewhere. Briefly, patients with a first diagnosis of CRC at age 30 or older (no upper age limit) are recruited in a population of approximately 2 million inhabitants in the Rhine-Neckar region of Germany since 2003. Patients are recruited in all of the 22 clinics providing first line therapy for CRC patients in the study region. Control persons who are frequency matched to the cases by age, sex, and county of residence are randomly drawn from population registries. The study was approved by the ethics committees of the Medical Faculty of the University of Heidelberg and of the state medical boards of Baden-Württemberg and Rhineland Palatinate. Written informed consent is obtained from each participant.

The current analysis is based on 5129 CRC cases and 4149 CRC-free controls recruited from 2003 to 2017 for whom array-based genetic data were available (Figure 1). For this study, we excluded 15 participants without information on colonoscopy use. We furthermore excluded 244 participants who reported use of other types of lower gastrointestinal endoscopy (such as flexible sigmoidoscopy or rectoscopy) and 283 participants with colonoscopies less than one year ago. The latter exclusion was made in order to minimize the possibility of erroneous consideration of the diagnostic colonoscopy which was conducted as part of the diagnostic procedure leading to the cancer diagnosis.
Hence, a total of 8736 participants (4939 cases and 3797 controls) were included in our analyses.

**Data collection**

Patients were informed about the study by their physicians, usually during hospital stay a few days after surgery. Upon receipt of informed consent, interviews were scheduled either during hospital stay or shortly after discharge at patients’ homes. All CRCs were histologically confirmed, and pathology records and discharge letters were requested for all patients. Controls were contacted through mail and follow-up telephone calls, and interviews were scheduled at their homes. Standardized in-person interviews were conducted with both cases and controls by trained interviewers. In these interviews, blood or buccal samples were collected, and information on previous endoscopies of the large bowel, sociodemographic, and lifestyle factors, as well as a detailed family and medical history, were obtained.

During the interviews, participants were asked whether they had ever had an endoscopy of the large bowel, and if so, when the last one was performed, how often in total, and how often during the past five years. For each of up to four endoscopies per participant, we asked for the reason for conducting the endoscopy, the endoscopist or hospital where the examination was performed, the type of endoscopy applied (colonoscopy, sigmoidoscopy, or rectoscopy), and whether polyps had been removed during the procedure. In order to validate the information of self-reported endoscopies, we requested all available endoscopy and histology records from participants’ physicians. Data extracted from the endoscopy and histology records include type of endoscopy, reason for endoscopy use, completeness of colonoscopy (cecum reached), and most advanced finding (advanced adenoma, other adenomas, or no neoplasm). Prior studies have shown very high levels of overall sensitivity
(100%) and specificity (96%) of self-reported endoscopy as well as colonoscopy completion rate (94%) among DACHS study participants.\textsuperscript{16,17}

**Genotyping and derivation of the polygenic risk score**

Genotyping for the DACHS study population has been described in detail previously.\textsuperscript{18} In short, DNA was extracted from blood samples (in 99.1% of participants) or buccal cells (in 0.9% of participants) using conventional methods. Illumina HumanCytoSNP (for 35.8% of participants), Illumina HumanOmmiExpress (for 32.8% of participants), Illumina Infinium OncoArray (for 17.0% of participants), and the Illumina Infinium Global Screening Array (for 14.4% of participants) were used for genotyping (Supplementary Table 1). Imputation of missing genotypes was performed uniformly using the Haplotype Reference Consortium (version r1.1.2016) as reference panel. PLINK (version 1.9) was used to extract SNPs for the required regions of interest.

A validated set of 140 CRC-related SNPs that had been identified by GWASs among populations of European descent was used to construct the PRS (Supplementary Table 2).\textsuperscript{8} We calculated the PRS by summing the product of reported regression coefficients and number of risk alleles (0, 1, and 2) across the 140 SNPs for all study participants.

**Statistical analysis**

We first described controls and cases with respect to the distribution of sex, age, and according to the history of colonoscopy. Next, the distribution of PRS among subgroups of cases and controls stratified according to history of colonoscopy with and without polypectomy was illustrated by boxplots, and differences in distribution between subgroups within cases and controls were evaluated for statistical significance using the t-test. Last, we assessed the risk of CRC according to levels of the PRS in groups of participants with and
without previous colonoscopy, where participants with colonoscopy were further categorized as with and without polypectomy. For these analyses, the PRS was categorized into 5 groups (each 20%) according to quintiles of their distribution in the respective control groups, and odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were derived by univariate logistic regression using the medium quintile (40-60%) as the reference group. ORs per standard deviation increase of the PRS were calculated from univariate logistic regression models as well as from models that were additionally adjusted for matching-factors age and sex. In addition, C-statistics, representing the area under the receiver operating characteristic curve (AUC) were derived for models containing continuous values of the PRS only. Besides analyses for the overall population, subgroup analyses were performed for women and men as well as for age groups <70 and ≥70 years. Furthermore, AUCs that were derived from participants without previous colonoscopy and participants with previous colonoscopy with and without polypectomy were compared using the method described by Gönen.19

Two-sided p-values <0.05 were considered statistically significant. Statistical analyses were carried out using the Statistical Analysis System (SAS) version 9.4 (SAS Institute, Cary, North Carolina, USA) and R version 3.3.4 (R Development Core Team 2010).

**Results**

Table 1 demonstrates the main characteristics of the study population. Approximately 60% of the study population were males and half of them were 70 years or older at the time of diagnosis, with little difference between cases and controls due to matching by sex and age. Cases much less often had a previous colonoscopy than controls (24.9% versus 58.0%).
The distribution of PRS among subgroups of cases and controls according to history of colonoscopy with and without polypectomy is shown in Figure 2. While the distributions were similar across subgroups among cases (Figure 2A), controls with previous colonoscopy and polypectomy had on average slightly higher PRS levels than those without colonoscopy and those with colonoscopy but without polypectomy (p-values <0.001, Figure 2B).

The PRS showed a clear gradient with CRC risk (Table 2). In the total study population, the ORs (95% CIs) for the lowest and highest quintile compared to the middle quintile were 0.55 (0.48-0.64) and 1.67 (1.47-1.90), respectively. In a model including the PRS as a continuous variable, the OR (95% CI) per increase in the PRS by one standard deviation (OR_{1SD}) was 1.49 (1.43-1.56). When stratifying participants according to history of colonoscopy, the associations were substantially stronger among subjects with no previous colonoscopy (OR_{1SD} = 1.57, 95% CI = 1.47-1.67) than among subjects with previous colonoscopy, in particular than those with previous colonoscopy and polypectomy (OR_{1SD} = 1.30, 95% CI = 1.16-1.46). These associations were essentially unchanged after controlling for age and sex. Predictive performance of PRS for CRC risk was likewise much higher among people without history of colonoscopy (AUC = 0.622, 95% CI = 0.606-0.639) compared to people with colonoscopy and polypectomy (AUC = 0.568, 95% CI = 0.536-0.601; Δ AUC = 0.054, p = 0.004).

In sex- and age-specific analyses, stronger associations of PRS with CRC were consistently seen among people without previous colonoscopy than those with previous colonoscopy and polypectomy (Figure 3A and 3B). Differences in AUC estimates were also consistently observed in women (Δ AUC = 0.073, p = 0.02) and men (Δ AUC = 0.046, p = 0.048), and in people aged <70 years (Δ AUC = 0.052, p = 0.07) and aged ≥70 years (Δ AUC = 0.049, p = 0.045).
Discussion

In this large case-control study from Germany, more than half of controls reported having had a previous colonoscopy, and one out of six reported to have had a previous colonoscopy with polypectomy. Although a PRS based on GWAS identified SNPs was predictive of CRC risk in those with and without history of colonoscopy, its predictive performance was higher among those with no history of colonoscopy than among those with colonoscopy, in particular than those with previous colonoscopy with polypectomy. Such differences were consistently seen in sex- and age-specific groups. Therefore, previous studies conducted in populations with widespread use of colonoscopies may have underestimated the predictive performance of PRS for CRC risk.

Furthermore, when looking at the distribution of PRS among subgroups of cases and controls stratified according to history of colonoscopy and polypectomy, we found that the distributions were similar across subgroups among cases; however, controls with previous colonoscopy and polypectomy had on-average higher PRS levels than those without colonoscopy and those with colonoscopy but without polypectomy. This finding further supports the hypothesis that CRC risk driven by the genetic variants would be attenuated after colonoscopy and polypectomy.

The largest GWAS consortia of studies on CRC risk from Western populations are the GECCO and CORECT consortia. Several studies from these consortia have investigated the ability of the PRS together with family history for the prediction of CRC risk. Jeon et al. assessed the predictive performance of a PRS (based on 63 CRC susceptibility SNPs) in combination with family history and obtained an AUC estimate of 0.59 for both women and
Furthermore, Archambault et al. reported the AUC estimates for a 95-SNPs PRS ranging from 0.54 to 0.65 across groups jointly defined by age and family history.\textsuperscript{21} In the latter study, the largest AUC estimates were particularly seen for those aged below 50 years and without family history of CRC, who are usually not offered screening exams and therefore are less likely to have undergone screening colonoscopy. The estimates of these two publications were derived from pooled analyses of 14 and 42 studies, of which 11 and 23 (including the DACHS study) were from the United States or Germany, respectively, where a majority of older adults have had prior colonoscopy.\textsuperscript{22,23} Given that our results suggested a diluted predictive performance of PRS in participants who have undergone colonoscopy and polypectomy, the actual AUC estimates may be higher than those suggested by previous studies.

The PRS has been proposed to improve risk prediction models for risk-adapted, personalized starting ages for CRC screening, which is an application among people with no history of colonoscopy.\textsuperscript{13,19} For these people, the predictive performance of PRS derived from populations without previous colonoscopy would be most relevant. To our knowledge, no previous study has explicitly reported such results. Based on our findings we suggest that such results should be routinely reported besides overall predictive performance in order to enable more valid analyses of the merits of risk stratification among people without previous colonoscopy.

Thus far, only a fraction of all CRC risk loci has been identified, so it is expected that the predictive power of the PRS will further improve as more genetic risk variants are discovered and machine learning approaches are applied to the enlarged sample size in the consortia. Although differences in AUC between people without and with previous colonoscopy and polypectomy may seem to be modest in our sample, they are larger than the
gains in AUCs typically reported in new rounds of GWAS consortia results after discovery of additional SNPs.

Although the predictive performance of PRS was found to be higher among those without previous colonoscopy in our study, the PRS also clearly discriminated CRC risk among those with previous colonoscopy and may also be useful for risk stratification in these groups, e.g. for defining risk adapted screening or surveillance intervals. For instance, a recent study based on data from the DACHS population suggested that the recommended 10-year screening interval for colonoscopy may not need to be shortened among people with high PRS, but could potentially be prolonged for people with low and medium PRS.²⁴ Such tailored screening intervals may enable offering screening colonoscopy in countries with limited resources and make screening colonoscopy even more cost-effective or cost-saving in countries with sufficient resources.²⁵

In addition, the possibility should be kept in mind that the role of specific genetic variants may differ between the first manifestation of colorectal neoplasms and their recurrence after colonoscopy with polypectomy in which case PRS derived from a mix of people with and without previous colonoscopy might be suboptimal for both groups of people. Further research should aim for deriving best performing PRS for each of these groups, e.g. by groups specific GWAS. To our knowledge, no such group specific PRS have previously been derived by GWAS.

Our study has specific strengths and limitations. Strengths include the large sample size and use of the latest GWAS results for deriving the PRS. Nevertheless, despite the large overall sample size, power was insufficient to assess differences in dose-response patterns between PRS and CRC risk according to history of colonoscopy and their potential interactions by sex and age in more detail. Furthermore, the PRS constructed by our study
was primarily based on SNPs that were identified and validated from people of European descent. Thus, results for the PRS used in this study may not be generalized to other ethnic groups. Nevertheless, we hypothesize that a similar difference in PRS performance according to history of colonoscopy might also apply to PRS derived from other ethnic groups. Our results are based on data from Germany where prevalence of having had a screening colonoscopy is higher than in most other countries except the US. Although similar differences in predictive ability of PRS between people with and without previous colonoscopy would be expected in other countries, the attenuation of the overall predictive ability of PRS (i.e., in the entire population regardless of history of colonoscopy) by previous colonoscopy would be expected to be less pronounced in countries with lower colonoscopy uptake rates. Also, variations in prevalence of colonoscopy may lead to different magnitude of underestimation of CRC risk explained by genetic variants between subgroups of the population, such as between sexes and across age groups.

Despite its limitations, our study demonstrates that a PRS, derived from common genetic variants, is expected to yield better predictive performance among people without previous colonoscopy – that is the main target group for defining risk adapted screening strategies, than among people with history of colonoscopy and polypectomy. Thus, the predictive performance of PRS may have been underestimated by previous studies that were based on populations with widespread use of colonoscopy. Future studies using the PRS alone or along with lifestyle and environmental risk profiling to categorize risk subgroups should carefully take history of colonoscopy into account. The most accurate possible risk stratification should be aimed to optimize the efficacy of individualized screening approaches.
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Author contributions: FG, JCC, MH and HB contributed to the conception and design of the study. JCC, MH, and HB contributed to the acquisition of data. FG and HB contributed to the analysis and interpretation of data. FG and HB contributed to the draft of the article. XC, JCC and MH contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

Data Availability

The data underlying this article are available upon reasonable request to the corresponding author.

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### Table 1. Main characteristics of the study population

| Characteristic                  | Cases No. (%) | Controls No. (%) |
|--------------------------------|---------------|------------------|
| **Sex**                        |               |                  |
| Women                          | 1965 (39.8)   | 1447 (38.1)      |
| Men                            | 2974 (60.2)   | 2350 (61.9)      |
| **Age, years**                 |               |                  |
| <60                            | 1016 (20.6)   | 725 (19.1)       |
| 60-69                          | 1470 (29.8)   | 1153 (30.4)      |
| ≥70                            | 2453 (49.7)   | 1919 (50.5)      |
| Mean (SD)                      | 68.8 (10.6)   | 68.5 (10.9)      |
| **History of colonoscopy**     |               |                  |
| No                             | 3713 (75.2)   | 1595 (42.0)      |
| Yes                            |               |                  |
| Without polypectomy            | 690 (14.0)    | 1503 (39.6)      |
| With polypectomy               | 536 (10.9)    | 699 (18.4)       |
Table 2. Association between PRS and CRC risk among participants with and without previous colonoscopy

| Study population and PRS | Cases | Controls | OR (95% CI)$^a$ |
|--------------------------|-------|----------|-----------------|
| **Total**                |       |          |                 |
| Quintile, No. (%)        |       |          |                 |
| Quintile 1 (6.21 – 7.81) | 522 (10.6) | 760 (20.0) | 0.55 (0.48-0.64) |
| Quintile 2 (7.82 – 8.09) | 742 (15.0) | 759 (20.0) | 0.78 (0.68-0.90) |
| Quintile 3 (8.10 – 8.32) | 946 (19.2) | 759 (20.0) | Reference |
| Quintile 4 (8.33 – 8.58) | 1143 (23.1) | 759 (20.0) | 1.21 (1.06-1.38) |
| Quintile 5 (8.59 – 10.4) | 1586 (32.1) | 760 (20.0) | 1.67 (1.47-1.90) |
| Mean (SD)                | 8.28 (0.45) | 8.10 (0.46) | 1.49 (1.43-1.56)$^b$ |
| AUC (95% CI)$^c$         | 0.609 (0.597-0.621) | -- |
| **No colonoscopy**      |       |          |                 |
| Quintile, No. (%)        |       |          |                 |
| Quintile 1 (6.34 – 7.82) | 401 (10.8) | 343 (21.5) | 0.55 (0.45-0.68) |
| Quintile 2 (7.83 – 8.11) | 536 (14.4) | 327 (20.5) | 0.79 (0.65-0.95) |
| Quintile 3 (8.12 – 8.35) | 705 (19.0) | 317 (19.9) | Reference |
| Quintile 4 (8.36 – 8.61) | 871 (23.5) | 295 (18.5) | 1.42 (1.18-1.71) |
| Quintile 5 (8.62 – 9.84) | 1200 (32.3) | 313 (19.6) | 1.85 (1.54-2.22) |
| Mean (SD)                | 8.28 (0.45) | 8.08 (0.47) | 1.57 (1.47-1.67)$^b$ |
| AUC (95% CI)$^c$         | 0.622 (0.606-0.639) | -- |
| **Colonoscopy without polypectomy** |       |          |                 |
| Quintile, No. (%)        |       |          |                 |
| Quintile 1 (6.21 – 7.76) | 62 (9.0) | 301 (20.0) | 0.46 (0.32-0.64) |
| Quintile 2 (7.77 – 8.02) | 131 (19.0) | 300 (20.0) | 0.97 (0.72-1.29) |
| Quintile 3 (8.03 – 8.24) | 136 (19.7) | 301 (20.0) | Reference |
| Quintile 4 (8.25 – 8.52) | 143 (20.7) | 300 (20.0) | 1.05 (0.79-1.40) |
| Quintile 5 (8.53 – 10.4) | 218 (31.6) | 301 (20.0) | 1.60 (1.23-2.10) |
| Mean (SD)                | 8.25 (0.44) | 8.09 (0.45) | 1.44 (1.31-1.58)$^b$ |
| AUC (95% CI)$^c$         | 0.600 (0.575-0.625) | -- |
| **Colonoscopy with polypectomy** |       |          |                 |
| Quintile, No. (%)        |       |          |                 |
| Quintile 1 (6.77 – 7.84) | 70 (13.1) | 140 (20.0) | 0.75 (0.51-1.10) |
| Quintile 2 (7.85 – 8.11) | 103 (19.2) | 140 (20.0) | 1.10 (0.76-1.59) |
| Quintile 3 (8.12 – 8.34) | 93 (17.4) | 139 (19.9) | Reference |
| Quintile 4 (8.35 – 8.58) | 112 (20.9) | 140 (20.0) | 1.20 (0.83-1.72) |
| Quintile 5 (8.59 – 9.73) | 158 (29.5) | 140 (20.0) | 1.69 (1.19-2.39) |
| Mean (SD)                | 8.29 (0.46) | 8.17 (0.45) | 1.30 (1.16-1.46)$^b$ |
| AUC (95% CI)$^c$         | 0.568 (0.536-0.601) | -- |

$^a$ Odds ratios were derived from univariate logistic models. Abbreviation: CI, confidence interval; OR, odds ratio; PRS, polygenic risk score.
Odds ratio for per standard deviation of PRS increase. Odds ratios (95% CI) remained almost unchanged after additionally adjustment for age and sex, which were 1.49 (1.43-1.56), 1.57 (1.48-1.67), 1.44 (1.31-1.58), and 1.30 (1.16-1.46) for the total population, people without colonoscopy, people with colonoscopy but without polypectomy, and people with colonoscopy and polypectomy, respectively.

AUC estimates were derived from univariate logistic models. P-value for the difference of AUCs in the population without colonoscopy versus with colonoscopy but without polypectomy was 0.15, while p-value for the difference of AUCs in the population without colonoscopy versus with colonoscopy and with polypectomy was 0.004.
Figures legends

Figure 1. Flow diagram of cases and controls included in the analyses. Abbreviation: CRC, colorectal cancer.

Figure 2. The distribution of PRS among subgroups of cases and controls stratified according to history of colonoscopy.

Panel A shows distribution among cases; Panel B shows distribution among controls. Differences in distribution between subgroups within cases and controls were evaluated for statistical significance using the t-test. All statistical tests were two-sided. Abbreviation: PRS, polygenic risk score.

Figure 3. Association between PRS and CRC risk according to sex and age among participants with and without previous colonoscopy.

Panel A shows odds ratio per standard deviation increase in PRS; Panel B shows area under the curve. AUCs were compared using the method described by Gönen. All statistical tests were two-sided. Abbreviation: CI, confidence interval; OR, odds ratio; PRS, polygenic risk score. \(^a\)P-value refers to the difference of AUCs in the population without colonoscopy versus with colonoscopy but without polypectomy. \(^b\)P-value refers to the difference of AUCs in the population without colonoscopy versus with colonoscopy and with polypectomy.
Figure 1.

Study participants with genetic data available

- CRC cases (n=5129); controls (n=4149)
  - Missing information on endoscopy use
    - Cases (n=8); Controls (n=7)
    - Sigmoidoscopy or rectoscopy
      - Cases (n=122); Controls (n=122)
    - Colonoscopy use <1 year ago
      - Cases (n=60); Controls (n=223)

Included in the analyses

- CRC cases (n=4939); controls (n=3797)
Figure 3.

A

| Category   | OR (95% CI) | p-value |
|------------|-------------|---------|
| Women      |             |         |
|            | 1.50 (1.40-1.61) |         |
|            | 1.63 (1.48-1.81) |         |
|            | 1.34 (1.17-1.55) |         |
|            | 1.20 (0.99-1.46) |         |
| Men        |             |         |
|            | 1.49 (1.40-1.57) |         |
|            | 1.53 (1.42-1.66) |         |
|            | 1.53 (1.35-1.75) |         |
|            | 1.34 (1.17-1.55) |         |
| <70 yrs    |             |         |
|            | 1.57 (1.47-1.67) |         |
|            | 1.64 (1.51-1.79) |         |
|            | 1.58 (1.37-1.83) |         |
|            | 1.32 (1.10-1.60) |         |
| 70 yrs+    |             |         |
|            | 1.42 (1.34-1.51) |         |
|            | 1.49 (1.36-1.64) |         |
|            | 1.33 (1.18-1.51) |         |
|            | 1.28 (1.11-1.49) |         |

B

| Category   | AUC (95% CI) | p-valuea | p-valueb |
|------------|-------------|----------|----------|
| Women      |             |          |          |
|            | 0.610 (0.591-0.629) |         |         |
|            | 0.629 (0.603-0.655) |         |         |
|            | 0.585 (0.548-0.623) |         |         |
|            | 0.556 (0.501-0.611) | 0.06     | 0.02     |
| Men        |             |          |          |
|            | 0.608 (0.593-0.623) |         |         |
|            | 0.618 (0.596-0.639) |         |         |
|            | 0.614 (0.580-0.648) |         |         |
|            | 0.572 (0.532-0.612) | 0.85     | 0.048    |
| <70 yrs    |             |          |          |
|            | 0.622 (0.605-0.639) |         |         |
|            | 0.632 (0.611-0.654) |         |         |
|            | 0.628 (0.591-0.665) |         |         |
|            | 0.580 (0.528-0.632) | 0.85     | 0.07     |
| 70 yrs+    |             |          |          |
|            | 0.595 (0.578-0.612) |         |         |
|            | 0.610 (0.585-0.635) |         |         |
|            | 0.577 (0.543-0.611) |         |         |
|            | 0.561 (0.520-0.602) | 0.13     | 0.045    |

Population: Total, No colonoscopy, Colonoscopy without polypectomy, Colonoscopy with polypectomy.