Long-term colorectal cancer incidence and mortality after adenoma removal in women and men

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Funding information
Norwegian Research Council (Grants 231920, 250256), Norwegian Cancer Society (Grant 6741288).

Summary
Background: Women and men with colorectal adenomas are at increased risk of colorectal cancer and colonoscopic surveillance is recommended. However, the long-term cancer risk remains unknown.

Aims: To investigate colorectal cancer incidence and mortality after adenoma removal in women and men

Methods: We identified all individuals who had adenomas removed in Norway from 1993 to 2007, with follow-up through 2018. We calculated standardized incidence ratios (SIR) and incidence-based mortality ratios (SMR) with 95% confidence intervals (CI) for colorectal cancer in women and men using the female and male population for comparison. We defined high-risk adenomas as ≥2 adenomas, villous component, or high-grade dysplasia.

Results: The cohort comprised 40,293 individuals. During median follow-up of 13.0 years, 1079 women (5.5%) and 866 men (4.2%) developed colorectal cancer; 328 women (1.7%) and 275 men (1.3%) died of colorectal cancer. Colorectal cancer incidence was more increased in women (SIR 1.64, 95% CI 1.54-1.74) than in men (SIR 1.12, 95% CI 1.05-1.19). Colorectal cancer mortality was increased in women (SMR 1.13, 95% CI 1.02-1.26) and reduced in men (SMR 0.79, 95% CI 0.71-0.89). Women with high-risk adenomas had an increased risk of colorectal cancer death (SMR 1.37, 95% CI 1.19-1.57); women with low-risk adenomas (SMR 0.90, 95% CI 0.76-1.07) and men with high-risk adenomas had a similar risk (SMR 0.89, 95% CI 0.76-1.04), while men with low-risk adenomas had reduced risk (SMR 0.70, 95% CI 0.59-0.84).

Conclusions: After adenoma removal, women had an increased risk of colorectal cancer death, while men had reduced risk, compared to the general female and male populations. Sex-specific surveillance recommendations after adenoma removal should be considered.
1 | INTRODUCTION

Colorectal cancer is the third most common malignancy worldwide, and the second most common cause of cancer-related deaths. Screening programs with faecal occult blood tests (FOBT), sigmoidoscopy or colonoscopy have been introduced in many countries. The aim of screening is to reduce cancer incidence through the removal of adenomas, and reduce cancer mortality through incidence reduction and early detection of cancer.

Individuals who have had adenomas removed are considered at increased risk of developing new adenomas and colorectal cancer in the future and are therefore recommended endoscopic surveillance. As adenomas are found in more than 20% of women and 30% of men during screening, and screening activity is increasing, the number of individuals recommended for surveillance after adenoma removal is growing rapidly and might limit the availability of colonoscopy resources for diagnostic and therapeutic purposes.

We have previously shown that individuals who have had low-risk adenomas removed have a lower risk of colorectal cancer mortality than the general population, finding later confirmed by others. Although individuals who have had high-risk adenomas removed have a higher risk of colorectal cancer death in most studies, the magnitude and duration of excess risk is uncertain due to low precision and usually less than 10 years of follow-up. Nevertheless, individuals are currently recommended frequent surveillance colonoscopy after adenoma removal, typically every 3, 5, or 10 years depending on adenoma characteristics. These recommendations are based on scarce evidence.

There is emerging evidence that endoscopic screening may convey less benefit in women than in men. Thus, it is imminent to investigate if women and men have different risks for colorectal cancer incidence and mortality after adenoma removal, and consider sex-specific surveillance.

We here update our previous report on colorectal cancer incidence and mortality after removal of low- and high-risk adenomas in a large population-based cohort, now with 13.0 years of follow-up and sex-stratified analysis.

2 | MATERIALS AND METHODS

2.1 | Data sources

Norway has a public, single-payer healthcare system with universal coverage. All residents are assigned an individually unique national registration number linked to information on sex and date of birth, through which residents can be identified in national registries and hospital databases. All residents are assigned to a general practitioner, and all referrals to specialized healthcare go through the general practitioner. Both the general practitioner and a gastroenterologist evaluate the clinical need for an endoscopic procedure before it is performed.

During the study period, no colorectal cancer screening program existed in Norway. Thus, individuals who had adenomas removed were referred to endoscopy due to symptoms. However, between 1999 and 2001, 2208 individuals with adenoma were identified in a regional randomized sigmoidoscopy screening trial, and these individuals are not excluded from this adenoma cohort.

The Cancer Registry of Norway contains data on individuals with cancer. Because reporting of all cancer cases is mandatory in Norway, registration is close to 100% complete. Adenomas were similarly registered in the Cancer Registry between 1993 and 2007. The Registry classifies all cancers and adenomas according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3). All adenomas reported to the Cancer Registry more than four months apart are recorded as separate occurrences. As in our previous report, we pooled all adenomas within the same occurrence and classified the individual according to the most severe characteristic. The number of adenomas removed is recorded as single or multiple, and the size of the adenomas is not registered in the Cancer Registry.

Before 2013, Norwegian guidelines recommended colonoscopy surveillance 10 years after adenoma removal for patients younger than 75 years with advanced adenomas (defined as high-grade dysplasia, villous growth pattern, or diameter ≥ 10 mm) and after 5 years for those with three or more adenomas. Surveillance was not recommended for patients with low-risk adenomas nor for patients older than 74 years of age. In 2013, European Society of Gastrointestinal Endoscopy (ESGE) guidelines were implemented.

2.2 | Study design

From the Cancer Registry, we retrieved information on all individuals aged 40 years and older who had adenomas removed between 1993 and 2007, including dates of adenoma removal, colorectal cancer diagnosis, emigration, and death, until the end of follow-up on 31 December 2018, and cause of death if cancer related. We excluded individuals with previous colorectal cancer, and individuals with familial adenomatous polyposis (through linkage with the Norwegian Polyposis Registry). Individuals were identified by topographical ICD-O-3 codes 180, 182 through 189, 199, or 209, combined with morphological ICD-O-3 codes 8140, 8210, 8211, 8261, or 8263. Adenoma location was defined as distal (rectum or sigmoid colon) or proximal (proximal to the sigmoid colon), multiple (distal and proximal), or unspecified (not registered). We lacked information about polyp size and exact number of adenomas, as polyp number is only registered as one or more than one in the registry. Therefore, we classified high-risk adenomas as adenomas with high-grade dysplasia, and/or a (tubulo-)villous growth pattern, and/or multiple adenomas (modified high-risk criteria), as previously reported. This slightly differs from the established ESGE high-risk criteria (high-grade dysplasia, and/or (tubulo-)villous growth pattern, and/or ≥3 adenomas, and/or size ≥10 mm).
We retrieved information on colorectal cancer cases and deaths in the general population from the Cancer Registry, and information on the population from Statistics Norway. The general population was stratified by age, sex and calendar year of diagnosis. The matched general population was colorectal cancer-free until the year of first adenoma removal, similar to the study population who was excluded if they had a previous colorectal cancer. We compared observed colorectal cancer incidence and mortality in the adenoma cohort with rates in the general population.

Colorectal cancer mortality was our primary endpoint, and colorectal cancer incidence was our secondary endpoint.

2.3 | Medical chart review

To validate the accuracy of adenoma information and classification, we performed a manual medical chart review including original pathology and endoscopy reports. A random subcohort of 1100 individuals were selected from the adenoma cohort,7 of which 948 patient charts were obtained (Figure S1). Detailed information of the individuals’ lower endoscopies, colectomies and pathology reports was registered in a structured database.

2.4 | Ethics and approvals

The study was approved by the Regional Committees for Medical and Health Research Ethics South East (2014/2352), which waived informed consent for patients included in the study due to its registry-based design. All living individuals sampled for the manual chart review were provided with written information about the study and could opt out.

2.5 | Statistical analyses

Analyses were performed for women and men separately. We calculated person-years at risk from the date of adenoma removal until colorectal cancer diagnosis and until colorectal cancer death. All time-to-event data were censored at the time of emigration, death or end of follow-up (31 December 2018). For individuals who had adenomas removed on more than one occasion, person-years at risk were calculated separately following each adenoma removal. Person-years at risk were stratified according to sex, 5-year age group, calendar year and year of first adenoma removal. We calculated person-years at risk until colorectal cancer death for the general population in Norway. The number of events and person-years was used to calculate overall and adenoma location-specific incidence-based colorectal cancer mortality, as in our previous report.5

We calculated standardized incidence ratios (SIR) and standardized incidence-based mortality ratios (SMR) by dividing observed colorectal cancer cases and deaths among women and men in the cohort by the expected number of colorectal cancer cases and deaths that would have occurred if the cohort had had the same rate as the female and male background population. The rates of colorectal cancer diagnosis and death were derived as the number of colorectal cancer cases and deaths per 100 000 person-years at risk over the years of follow-up. We calculated 95% confidence intervals (CI) under the assumption that the occurrence of events followed a Poisson distribution. We calculated SIR and SMR stratified by sex, age group, calendar period, and adenoma location and characteristics. We constructed cumulative curves for colorectal cancer mortality among women and men considered at low-risk and high-risk after the initial adenoma removal, and we treated death from other causes as a competing risk. Cumulative curves were compared using Gray’s test.26

We used Cox proportional hazard models stratified by sex, to estimate hazard ratios (HR) with 95% CI in order to separate out the effects of age, number of adenoma occurrences, adenoma location, number of adenomas, grade of dysplasia, growth pattern, and period of adenoma removal. We fitted multivariable models using stepwise regression with forward selection for inclusion of variables. The same model was used for women and for men.

Due to a higher proportion of women compared to men aged 80 years or older at first adenoma removal, we performed sensitivity analyses excluding these individuals. We also performed sensitivity analysis stratified on period of first adenoma removal (1993-1999 and 2000-2007), as clinical practice has evolved during the period of the study. As current guidelines recommend surveillance at the latest 10 years after adenoma removal,16,18,27 we performed sensitivity analyses restricting to 10 years of follow-up. Further, we censored our follow-up at the next adenoma removal, to account for adenoma removal performed for surveillance or clinical indications, which may alter the future risk of colorectal cancer incidence and mortality. All tests were two-sided, and P values less than 0.05 were considered statistically significant. Stata software version 16.1 (StataCorp) was used for analyses.

3 | RESULTS

3.1 | Characteristics of the adenoma cohort

The adenoma cohort comprised 40 293 individuals, where 2208 (5.5%) were identified at screening,26 and the rest due to symptoms. Of these, 19 725 were women (49.0%) and 20 568 men (51.0%) (Table 1). A total of 45 340 adenoma removals were recorded, 22 017 in women (48.6%) and 23 323 in men (51.4%). The total follow-up time was 492 736 person-years (median 13.0 years, inter-quartile range (IQR) 7.3-17.0 years). A total of 26 461 individuals were alive and followed for 10 years or more. Median age at first adenoma, colorectal cancer diagnosis and colorectal cancer death were, respectively, 67.0, 79.9 and 80.2 years for women, and 65.4, 77.5 and 77.8 years for men. Table 1 displays individual characteristics and characteristics of removed adenomas in women and men.
3.2 | Chart review study

Among the 948 individuals in the sample, 488 were women (51.5%) and 460 men (48.5%) (Table S1). Among the women, 230 (78.8%) out of 292 low-risk adenomas (sensitivity 84%, positive predictive value (PPV) 79%) and 208 (82.2%) out of 253 high-risk adenomas (sensitivity 77%, PPV 82%) were similarly classified using the modified high-risk criteria based on Cancer Registry data, where information on adenoma size and number was missing, compared to the ESGE criteria (Table S2). Among the men, 225 (79.2%) out of 284 low-risk adenomas (sensitivity 83% and PPV 79%) and 188 (80.3%) out of 234 high-risk adenomas (sensitivity 76% and PPV 80%) were similarly classified in the Cancer Registry (Table S2). Thus, the accuracy of the modified criteria was 80% for both women and men.

Excluding the misclassified adenomas from the sample did not significantly change the distribution of individual and adenoma characteristics in the sample.

In the sample, 80% had a colonoscopy at their first adenoma removal, and there was no difference between women and men. The remaining 20% had a sigmoidoscopy, rectoscopy or colectomy.

3.3 | Colorectal cancer incidence

A total of 1945 individuals in the adenoma cohort (4.8%, 402 per 100 000 person-years) developed colorectal cancer during follow-up; 1079 women (5.5%, 440 per 100 000 person-years) and 866 men (4.2%, 364 per 100 000 person-years) (Figure 1 and Table S3).
The absolute risk of developing colorectal cancer in the general population was 269 per 100 000 person-years for women, and 325 per 100 000 person-years for men. Colorectal cancer incidence was more increased in women who had adenomas removed (SIR 1.64, 95% CI 1.54-1.74, 171 more cases per 100 000 person-years) than in men (SIR 1.12, 95% CI 1.05-1.19, 39 more cases per 100 000 person-years), as compared to women and men in the general population.

Women had a two-fold increased colorectal cancer incidence after high-risk adenoma removal (SIR 1.99, 95% CI 1.84-2.15, 282 more cases per 100 000 person-years) compared to the female population, while the increase was less among women with low-risk adenomas (SIR 1.32, 95% CI 1.20-1.45, 81 more cases per 100 000 person-years).

Men also had increased colorectal cancer incidence after high-risk adenoma removal (SIR 1.36, 95% CI 1.25-1.49, 128 more cases per 100 000 person-years) compared to the male population, but reduced incidence after removal of low-risk adenomas (SIR 0.88, 95% CI 0.79-0.98, 36 fewer cases per 100 000 person-years).

Cumulative colorectal cancer incidence was significantly different between individuals after removal of low-risk compared to high-risk adenomas for both women and men (Gray's test P value < 0.001) (Figure S2).

During follow-up, 603 individuals (1.5%, 122 per 100 000 person-years) died from colorectal cancer; 328 women (1.7%, 131 per 100 000 person-years) and 275 men (1.3%, 113 per 100 000 person-years) (Figures 1, 2, Table S4). The absolute risk of colorectal cancer death in the general population was 116 per 100 000 person-years for women, and 143 per 100 000 person-years for men. Compared to the general population, colorectal cancer mortality was increased for women after adenoma removal (SMR 1.13, 95% CI 1.02-1.26, 15 more deaths per 100 000 person-years), and reduced for men (SMR 0.79, 95% CI 0.71-0.89, 29 fewer deaths per 100 000 person-years).

Women had higher colorectal cancer mortality than the female population after removal of high-risk adenomas (SMR 1.37, 95% CI 1.19-1.57, 47 more deaths per 100 000 person-years) (Figure 1, Table S4), while there was no difference after removal of low-risk adenomas (SMR 0.90, 95% CI 0.76-0.84, 39 fewer deaths per 100 000 person-years).

Men had similar colorectal cancer mortality to the male population after removal of high-risk adenomas (SMR 0.89, 95% CI 0.76-1.04, 18 fewer deaths per 100 000 person-years) (Figure 1, Table S4), while the mortality was reduced after removal of low-risk adenomas (SMR 0.70, 95% CI 0.59-0.84, 39 fewer deaths per 100 000 person-years).

**FIGURE 1** Standardized incidence ratios (SIR) (A) and incidence-based mortality ratios (SMR) (B) with 95% confidence intervals for colorectal cancer among women and men who had undergone adenoma removal compared to the general female and male population. The vertical grey lines indicate SIR and SMR = 1.0. Details are given in Tables S3 and S4.
Cumulative colorectal cancer mortality was significantly different between individuals after removal of low-risk and high-risk adenomas for both women and men (Gray's test $P$ value < 0.001) (Figure 3).

The risk of proximal colon cancer mortality was increased after a proximal adenoma removal for women (SMR 1.51, 95% CI 1.10-1.81), but not for men (SMR 1.29, 95% CI 0.89-1.89) (Table S5).

Results from univariable and multivariable analyses of colorectal cancer mortality comparing women and men in the adenoma cohort are shown in Table 2. In multivariable analysis, colorectal cancer mortality after adenoma removal increased with age at first adenoma removal, multiple or unspecified adenoma locations (women: HR 1.51, 95% CI 1.10-1.81; men: HR 1.58, 95% CI 1.22-2.06), multiple simultaneous adenomas (women: HR 1.41, 95% CI 1.10-1.81; men: HR 0.87, 95% CI 0.66-1.15), villous or tubulovillous growth pattern (women: HR 1.52, 95% CI 1.21-1.91; men: HR 1.55, 95% CI 1.20-2.00), and high-grade dysplasia (women: HR 1.58, 95% CI 1.10-2.25; men: HR 1.62, 95% CI 1.10-2.41) (Table 2).
men: HR 1.38, 95% CI 0.92-2.08). Colorectal cancer mortality was lower among those who had their first adenoma removed in years 2000-2007 (women: HR 0.77, 95% CI 0.61-0.97; men: HR 0.70, 95% CI 0.55-0.90), than those who had their first adenoma removed in 1993-1999.

3.5 | Sensitivity analysis

In sensitivity analyses where we excluded individuals aged 80 years or older at first adenoma, or stratified by the period of first adenoma removal (1993-1999 or 2000-2007), the results did not change (data not shown). When we restricted the analyses to 10 years of follow-up, results were similar (Table S6). Censoring follow-up at the next adenoma removal did not affect the results (data not shown).

4 | DISCUSSION

Our study revealed that compared to the general female and male population, both women and men have increased colorectal cancer incidence after adenoma removal, while colorectal cancer mortality

| Variable | Women | | | | | | Men | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | Univariable (95% CI) | P Value | Multivariable (95% CI) | P Value | | | Univariable (95% CI) | P Value | Multivariable (95% CI) | P Value | | | | | | | |
| Age at first adenoma removal | | | | | | | | | | | | | | | | | |
| 40-49 years | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 50-59 years | 3.72 (1.59-8.72) | <0.001 | 3.65 (1.56-8.54) | <0.001 | 1.29 (0.72-2.31) | 0.39 | 1.27 (0.71-2.28) | 0.42 |
| 60-69 years | 6.16 (2.69-14.14) | <0.001 | 5.73 (2.50-13.15) | <0.001 | 2.56 (1.48-4.43) | 0.001 | 2.39 (1.38-4.15) | 0.002 |
| 70-79 years | 14.91 (6.54-33.98) | <0.001 | 13.36 (5.86-30.47) | <0.001 | 5.22 (3.00-9.06) | <0.001 | 4.77 (2.74-8.31) | <0.001 |
| ≥80 years | 30.65 (13.20-71.18) | <0.001 | 28.41 (12.21-66.10) | <0.001 | 10.49 (5.66-19.42) | <0.001 | 9.91 (5.33-18.42) | <0.001 |
| Period of first adenoma removal | | | | | | | | | | | | | | | | | |
| 1993-1999 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 2000-2007 | 0.75 (0.59-0.94) | 0.012 | 0.77 (0.61-0.97) | 0.024 | 0.68 (0.53-0.87) | 0.003 | 0.70 (0.55-0.90) | 0.01 |
| No of adenoma occurrences | | | | | | | | | | | | | | | | | |
| 1 | 1.00 | | | | | | | | | | | | | | | | |
| ≥2 | 1.07 (0.77-1.48) | 0.69 | | | | | | | | | | | | | | | |
| Adenoma location | | | | | | | | | | | | | | | | | |
| Distal | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Proximal | 1.04 (0.73-1.47) | 0.84 | 1.04 (0.73-1.47) | 0.84 | 1.05 (0.72-1.54) | (0.80) | 1.07 (0.73-1.57) | 0.73 |
| Multiple or unspecified | 1.54 (1.22-1.95) | <0.001 | 1.51 (1.18-1.93) | 0.001 | 1.49 (1.16-1.92) | 0.002 | 1.58 (1.22-2.06) | 0.001 |
| No of adenomas per occurrence | | | | | | | | | | | | | | | | | |
| 1 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| ≥2 | 1.81 (1.43-2.29) | <0.001 | 1.41 (1.10-1.81) | 0.007 | 1.15 (0.88-1.49) | 0.31 | 0.87 (0.66-1.15) | 0.33 |
| Growth pattern | | | | | | | | | | | | | | | | | |
| Tubulous | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Villous or tubulovillous | 1.79 (1.44-2.24) | <0.001 | 1.52 (1.21-1.91) | <0.001 | 1.76 (1.37-2.26) | <0.001 | 1.55 (1.20-2.00) | 0.001 |
| Grade of dysplasia | | | | | | | | | | | | | | | | | |
| Low | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| High | 1.63 (1.15-2.30) | 0.006 | 1.58 (1.10-2.25) | 0.012 | 1.44 (0.97-2.15) | 0.07 | 1.38 (0.92-2.08) | 0.12 |
is increased for women, but reduced for men. Women had 37% increased colorectal cancer mortality after removal of high-risk adenomas (47 more per 100 000 person-years) compared to the female population. Women who had low-risk adenomas removed, and men who had high-risk adenomas removed, had similar mortality as the female and male population, respectively. Men had 30% reduced colorectal cancer mortality after removal of low-risk adenomas (39 fewer per 100 000 person-years) compared to the male population.

Colorectal cancer incidence and mortality is higher in the general male population than in the female. After adenoma removal, colorectal cancer mortality was 131 per 100 000 person-years (95% CI 118-147 per 100 000 person-years) in women and 113 per 100 000 person-years (95% CI 101-128 per 100 000 person-years) in men. As previously suggested, this might indicate that colorectal adenomas are the most robust cancer risk predictors, and that adenoma removal can reduce the risk to a certain level, irrespective of other risk factors, but not below that level. In a Swedish study, the incidence and mortality of colorectal cancer after adenoma removal was similar to what is observed here, while the risk in the general population was much lower, in line with national cancer statistics between Norway and Sweden. Consequently, a larger excess risk was seen in the Swedish cohort than in our study. This observation is in line with our observed difference between women and men, and the ability of adenomas to predict risk irrespective of background risk in the population.

We found that both women and men who had low-risk adenomas removed had lower colorectal cancer mortality than the general population, a choice of comparison group endorsed by the World Endoscopy Organization. This is different from previous studies, where colorectal cancer mortality was similar after removal of low-risk adenomas, compared to individuals who are adenoma-free at screening. The difference in comparison group likely explain the differing results: the comparison group of the general population resembles the control group in a screening trial, that is a mixture of individuals with and without adenomas, while the comparison group of the adenoma-free resembles screening compliers without findings at screening colonoscopy, a group recognized to have a minimal risk of colorectal cancer.

Strengths of our study include the large size, population-based design, and complete long-term follow-up. A limitation is the lack of detailed information about the number and size of removed adenomas. However, we performed a chart review of a random sample of the adenoma cohort which showed adequate consistency of the registry data applied. The gross majority of those who changed risk group after chart review, did so because of adenoma size larger than 10 mm. These individuals, whose adenomas harbour only a single high-risk characteristic, probably increase the observed risk after removal of low-risk adenomas. Had they correctly been included among those who had high-risk adenomas removed, the risk after high-risk adenoma removal would expectedly drop. This is comparable to stage migration or the Will Rogers phenomenon: The risk of colorectal cancer incidence among the individuals with adenoma size larger than 10 mm, who changed risk group after chart review, was above average for the low-risk group. Thus, reclassifying these would have decreased the average risk of the remaining low-risk group. The same individuals, however, likely had a risk of colorectal cancer incidence lower than those already in the high-risk group into which they are moved. Thus, reclassifying these would also decrease the average risk of colorectal cancer incidence in the high-risk group. As in our previous report, the observed misclassification of some individuals may thus have led to overestimation of the true risk for individuals both after removal of low- and high-risk adenomas.

We did not have information on quality indicators of colonoscopy, for example, adenoma detection rate, bowel cleansing or caecum intubation rates. Colonoscopy have been reported to be more painful and caecal intubation rate lower in women than men, suggesting an average lower quality examination in women. We do, however, have a comparable distribution of proximal adenomas between women and men in the cohort, and it is therefore unlikely that quality and completeness of examination is different for women and men. A more painful experience of colonoscopy might affect surveillance adherence among women, and we did not have data on surveillance. However, we performed a sensitivity analysis censoring our follow-up at next adenoma removal, which did not affect our results. Surveillance without adenoma removal cannot change the outcome as no risk-modifying intervention was performed.

Recent evidence on sigmoidoscopy screening shows a lower benefit in women than in men. For colonoscopy screening, potential differences between women and men are still unclear since none of the studies have sufficiently long follow-up to evaluate the effect on incidence and mortality. However, like FOBT and colonoscopy, sigmoidoscopy is considered a screening tool for the whole colorectum, and a positive test leads to follow-up by colonoscopy. Biologically, there is no reason to believe that the development of adenomas diagnosed due to symptoms are different to those diagnosed at screening. Our finding, that women who had an adenoma removed have increased colorectal cancer incidence and mortality after adenoma removal, are in line with these previous findings on sigmoidoscopy screening.

The observed difference in risk for women and men of colorectal cancer incidence and mortality after adenoma removal is probably explained by factors related to both biology and identification. First, the pathogenesis might be different; if more cancers occurring in women are developed through the serrated pathway rather than the adenoma-carcinoma sequence, then the effect of adenoma removal might be less in women than in men. Previously, it has been shown that individuals with both adenomas and sessile serrated lesions have particularly high cancer risk. There is conflicting evidence whether serrated polyps are more common in women than in men. Since this study is based on an adenoma registry, we did not have information about serrated polyps. Future studies on the cancer risk after adenoma removal should also take serrated lesions into consideration.

Second, the age-standardized risk of colorectal cancer is less in the female general population than in males. Thereby, the reference level used in the comparisons is also different. This means that even...
if the cancer risk had been identical for women and men who had had adenomas removed, then the comparison relative to the general female and male population would still show a higher risk for women than for men.

Our observed sex-specific differences in risk of colorectal cancer incidence and mortality after adenoma removal, with an increased risk in women, challenge current surveillance recommendations, which do not consider patient’s sex.17,18 Our findings should prompt discussions about sex-specific surveillance recommendations after adenoma removal.

ACKNOWLEDGEMENTS
A sincere thanks to the dedicated medical chart review team; Sofia E. Olsen, MNSc, Emilia Teresa Kabat, MD, and Conor Farrell, MD.

Declaration of personal interests: None.

AUTHORSHIP
Guarantor of the article: Henriette C. Jodal.

Author contributions: MB, HOA, MK and ML designed the study, with contribution from all authors. HCJ, DK, MH, IB, and PT reviewed medical records. HCJ and ML analysed the data. HCJ wrote the first draft of the manuscript, and all authors revised the manuscript and approved the final version.

DATA AVAILABILITY STATEMENT
Deidentified data will be available upon request.

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**SUPPORTING INFORMATION**
Additional supporting information will be found online in the Supporting Information section.

**How to cite this article:** Jodal HC, Klotz D, Herfindal M, et al. Long-term colorectal cancer incidence and mortality after adenoma removal in women and men. *Aliment Pharmacol Ther.* 2022;55:412-421. doi:10.1111/apt.16686