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Risk factors for advanced colorectal neoplasia and colorectal cancer detected at surveillance: a nationwide study in the modern era

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Risk factors for advanced colorectal neoplasia and colorectal cancer detected at surveillance: a nationwide study in the modern era

Aim: Recommendations for surveillance after colonoscopy are based on risk factors for metachronous advanced colorectal neoplasia (AN) and colorectal cancer (CRC). The value of these risk factors remains unclear in populations enriched by individuals with a positive faecal immunochemical test and were investigated in a modern setting.

Methods and Results: This population-based cohort study included all individuals in the Netherlands of ≥55 years old with a first adenoma diagnosis in 2015. A total of 22,471 patients were included. Data were retrieved from the Dutch Nationwide Pathology Databank (Palga). Primary outcomes were metachronous AN and CRC. Patient and polyp characteristics were evaluated by multivariable Cox regression analyses. During follow-up, 2416 (10.8%) patients were diagnosed with AN, of which 557 (2.5% from the total population) were CRC. Adenomas with high-grade dysplasia (hazard ratio [HR] 1.60, 95% confidence interval [CI] 1.40–1.83), villous histology (HR 1.91, 95% CI 1.59–2.28), size ≥10 mm (HR 1.12, 95% CI 1.02–1.23), proximal location (HR 1.12, 95% CI 1.02–1.23), two or more adenomas (HR 1.28, 95% CI 1.16–1.41), and serrated polyps ≥10 mm (HR 1.67, 95% CI 1.42–1.97) were independent risk factors for metachronous AN. In contrast, only adenomas with high-grade dysplasia (HR 2.49, 95% CI 1.92–3.24) were an independent risk factor for metachronous CRC.

Conclusions: Risk factors for metachronous AN and CRC were identified for populations with access to a

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Abbreviations: AN, advanced colorectal neoplasia; CI, confidence interval; CRC, colorectal cancer; ESGE, European Society of Gastrointestinal Endoscopy; FIT, faecal immunochemical test; HR, hazard ratio; IQR, interquartile range; Palga, Dutch Natuinwide Pathology databank; SD, standard deviation.

faecal immunochemical test (FIT)-based screening programme. If only risk factors for metachronous CRC are considered, a reduction in criteria for surveillance seems reasonable.

Keywords: advanced colorectal neoplasia, bowel cancer screening programmes, colorectal cancer, histopathological risk factors

Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related morbidity and death worldwide.[1] Colonoscopy for both symptomatic patients as well as patients participating in CRC screening programmes aims to detect CRC at an early stage or, ideally, at a precursor stage and to resect these lesions, if feasible.[2–5] These procedures have been shown to reduce the risk of CRC development and subsequent mortality.[2,3 6,7]

Based on the presence of individual risk factors upon examination of removed precursor lesions, patients are recommended for endoscopic surveillance.[4,5,8] However, the definition of high-risk precursors varies between guidelines.[4,5,8,9] The European Society of Gastrointestinal Endoscopy (ESGE) guideline is based primarily on risk factors for CRC. Currently, only individuals with detection and removal of ≥5 adenomas, adenomas ≥10 mm, adenomas with high-grade dysplasia, or any serrated polyp ≥10 mm or with dysplasia are considered high-risk and are recommended surveillance colonoscopy after 3 years.[5] In contrast to the ESGE guideline, the US Multi-Society Task Force incorporates metachronous advanced colorectal neoplasia (AN), and therefore includes villous and tubulovillous adenomas in addition.[4] Until recently, other guidelines identified proximal adenomas as a risk factor, but did not include high-grade dysplasia as a risk factor.[9]

Recent clinical studies predominantly focused on CRC as an outcome, in contrast to earlier studies that assessed the risk of metachronous AN.[10–18] However, few studies investigating risk factors for adverse outcome have solely included patients after the introduction of a CRC screening programme.[17] Therefore, the goal of the current study was to identify histopathological risk factors for metachronous AN and CRC during follow-up in both the general and screening population, after the implementation of a faecal immunochemical test (FIT)-based screening programme.

Material and Methods

STUDY DESIGN

Data were retrieved from the Dutch Nationwide Pathology Databank (Palga, reference number LZV2021-2).[19] Patients with an index colonoscopy in 2015 and histopathological examination of at least one lesion and at least one colonoscopy or colorectal resection with histopathological examination in the following 5 years were selected. Colonoscopies without histopathological examinations are not present in the pathology databank. Index colonoscopy was defined as the first procedure that resulted in histological examination of biopsies or polypectomies of colorectal origin. The study included patients at the national CRC screening age or older. The follow-up of surveillance colonoscopies ended on April 22, 2021, to ensure inclusion of all patients with a 5-year surveillance interval. Index colonoscopies were performed either in symptomatic patients or after a positive FIT as part of the national CRC screening programme. Most surveillance colonoscopies would have been performed based on the national surveillance guidelines, but were not restricted to these criteria.[9] Exclusion criteria were: age of 54 years or younger at index colonoscopy, the presence of hereditary CRC syndromes, the presence of inflammatory bowel disease, and diagnosis of CRC at index colonoscopy or within 6 months of the index colonoscopy. The primary outcome of this study was metachronous AN or CRC separately. Advanced colorectal neoplasia was defined as either advanced adenoma (i.e. adenoma ≥10 mm, high-grade dysplasia, tubulovillous histology, or villous histology), advanced serrated polyp (i.e. serrated polyp ≥10 mm) or CRC (i.e. adenocarcinoma with at least submucosal invasion of colorectal origin). Serrated polyps were defined as sessile serrated lesions, traditional serrated adenomas, and hyperplastic polyps.[5] Traditional serrated adenomas were not included as a sole risk factor, but were included in the serrated polyps with dysplasia category. Adenomas with a villous component of >25%

were defined as tubulovillous adenomas and adenomas with a villous component of >75% as villous adenomas. High-grade dysplasia was defined according to the prevailing WHO classification of digestive system tumours.[20,21] Adenoma size was based on the histology reports.[22] The study was approved by the Scientific and Privacy Committee of Palga and the Investigational Research Board of the Amsterdam UMC, location VUmc (2021.0146).

DATA COLLECTION

Patient and lesion characteristics were collected for index- and follow-up colonoscopies. Patient characteristics included: age at index colonoscopy, sex, and whether the index colonoscopy was part of the CRC screening programme. The number of registered follow-up colonoscopies were categorized into 1, 2, or ≥3 and the time to the first follow-up colonoscopy was classified in years. Potential risk factors were primarily based on the prevailing Dutch guideline in 2021 and included the following characteristics: age, sex, adenoma with high-grade dysplasia, adenoma with villous histology, adenoma size ≥10 mm, serrated polyp size ≥10 mm, serrated polyp with dysplasia, number of adenomas (≥2), and proximally located adenomas.[9] Proximally located adenomas were defined as adenomas located in the cecum, ascending colon, hepatic flexure, transverse colon, and splenic flexure. If multiple lesions were present, patients were categorized according to the presence of the most advanced feature for each specific characteristic (e.g. if a patient had two lesions, one adenoma >10 mm with low-grade dysplasia and one adenoma <10 mm with high-grade dysplasia, the patient was categorized as having the following potential risk-factors: adenoma >10 mm and high-grade dysplasia).

STATISTICAL ANALYSES

Descriptive statistics were used to evaluate patient and polyp characteristics. Normality was assumed based on the number of patients included in the study and data are presented accordingly. The cumulative incidence of AN and CRC was depicted by one minus Kaplan–Meier estimates. To identify risk factors for AN and CRC, both patient and polyp characteristics were entered into univariable and multivariable Cox regression analyses. The proportional hazards assumption was evaluated by Schoenfeld residuals.[23] In multivariable Cox regression models, all potentially clinically relevant variables were included. The end of follow-up was determined by the date of the last colonoscopy, the occurrence of AN or CRC, and was censored after 72 months of follow-up. Since the data provided an overview of daily practice, and therefore included a broad variety of patients, several sensitivity analyses were carried out. First, analyses were performed of patients divided into the general population on the one hand, and in the CRC screening population after a positive FIT on the other hand. Second, a sensitivity analysis that included the number of surveillance colonoscopies and time to the first follow-up colonoscopy was performed to correct for potential bias caused by these variables. Third, an analysis was performed that excluded patients with the first surveillance colonoscopy within 1 year, because a surveillance interval of less than 1 year is indicative of a low-quality or incomplete index colonoscopy, or a piecemeal resection.[9] In addition, the outcomes of the first follow-up colonoscopy were analysed for this group. Last, an analysis including risk factors determined by the updated postpolypectomy surveillance guideline of the ESGE was performed: adenoma size ≥10 mm; serrated polyp size ≥10 mm; serrated polyp with dysplasia (including traditional serrated adenoma); five or more adenomas, and adenoma with high-grade dysplasia.[5] In this analysis the number of adenomas and dysplasia in serrated polyps differ from the risk factors determined in other analyses. *P*-values of <0.05 were considered statistically significant. Statistical analyses were carried out using SPSS v. 26 (IBM, Armonk, NY, USA).

Results

In the Netherlands a total of 91,735 patients of 55 years or older underwent a colonoscopy followed by a histopathological examination registered in Palga in 2015. After excluding patients with preceding histopathology reports of the colon or rectum (n = 25,403), patients without surveillance colonoscopies or without histopathological examination at surveillance colonoscopy (n = 34,107), patients with synchronous CRC (n = 5,693), and patients with other types of cancer (e.g. squamous cell carcinomas, neuroendocrine tumours) during follow-up (n = 61), 22,471 patients were available for analyses (Figure 1). Included patients were more often referred for a positive FIT and had more advanced characteristics at baseline (Table S1). Baseline characteristics of the index colonoscopy and histopathological findings are presented in Table 1. Mean age at index colonoscopy

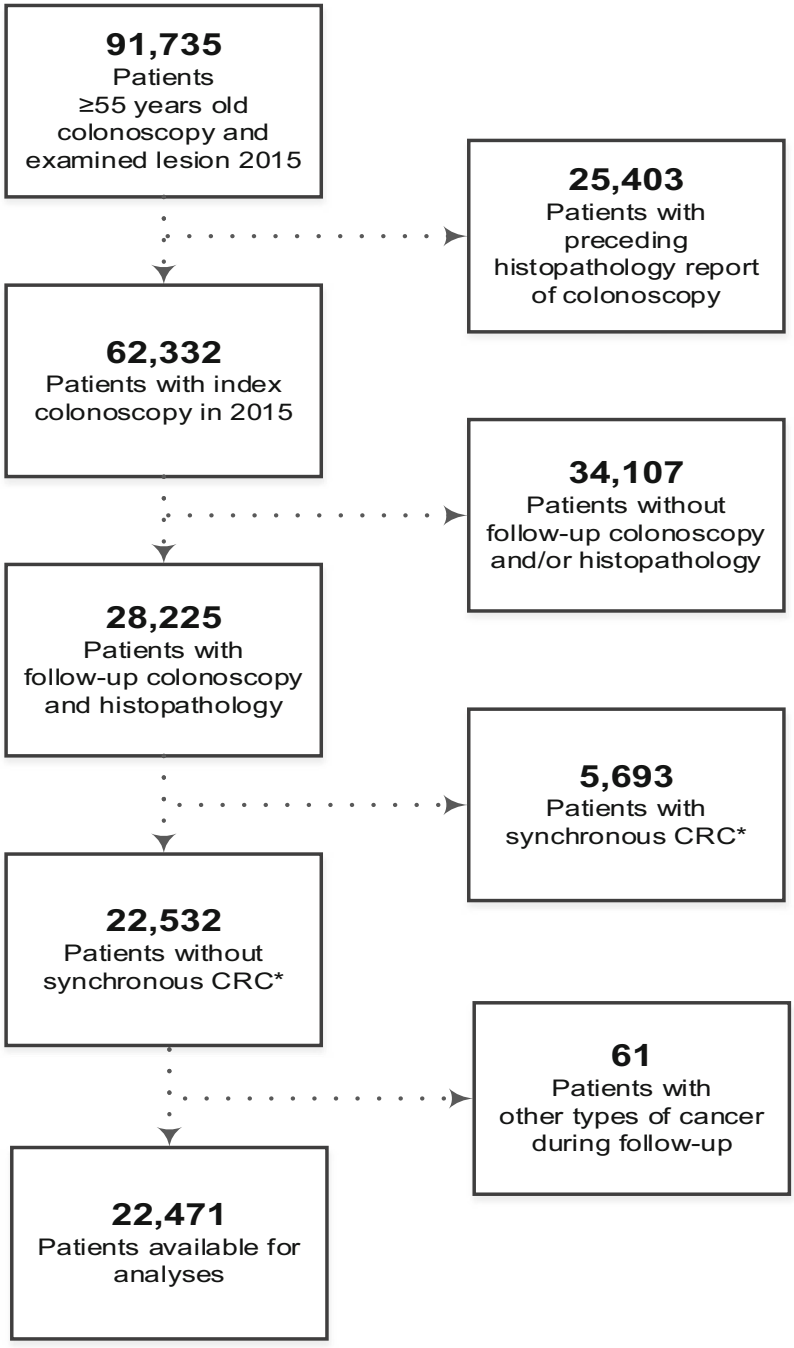


Figure 1. Flow-chart of included patients. *Diagnosed colorectal cancer within 182 days of index colonoscopy. CRC, colorectal cancer.

was 66.3 ± 5.4 years and 62.2% (n = 13,974) of the patients were male. In 28.1% (n = 6,322) of the patients, no potential histopathological risk factors were identified at index colonoscopy. During follow-up, metachronous AN was detected in 10.8% (n = 2,416) of the patients and CRC in 2.5% (n = 557). The cumulative incidence of AN and CRC during follow-up is depicted in Figure 2. Of the patients with metachronous AN or CRC, the median time to detection was 37.6 and 34.6 months, respectively. Univariable analyses are presented in Table S2.

Table 1. Baseline characteristics

Characteristics index colonoscopy 2015 (n = 22,471)	
Male	13,974 (62.2%)
Age at index colonoscopy (mean ± SD)	66.3 ± 5.4
FIT based CRC screening program	11,206 (49.9%)
Number of adenomas (median, IQR)	2 (1–3)
Number of colonoscopies including index (median, IQR)	2 (2–3)
High-grade dysplasia	2,050 (9.1%)
High-grade dysplasia only risk factor	281 (1.3%)
Villous adenoma	868 (3.9%)
Adenoma size ≥10 mm	7,398 (32.9%)
Serrated polyp size ≥10 mm	1,009 (4.5%)
Proximal adenoma	9,482 (42.2%)
Two or more adenomas	11,798 (52.5%)
No potential risk factors present	6,322 (28.1%)
Surveillance colonoscopies	
Metachronous advanced neoplasia*	2,416 (10.8%)
First neoplasia is colorectal cancer	514 (2.3%)
Colorectal cancer	557 (2.5%)

FIT, faecal immunochemical test; CRC, colorectal cancer; SD, standard deviation; IQR, interquartile range.
*Advanced neoplasia: advanced adenoma (i.e. adenoma ≥10 mm, high-grade dysplasia, tubulovillous histology, or villous histology) or advanced serrated polyp (i.e. serrated adenoma ≥10 mm) or colorectal cancer (i.e. adenocarcinoma of colorectal origin).

VILLOUS ADENOMA

Villous adenomas were present in 3.9% (n = 868) of the patients at index colonoscopies (Table 1). The presence of villous adenomas at index colonoscopies was associated with a higher incidence of metachronous AN in multivariable analysis (hazard ratio [HR] 1.91 95% confidence interval [CI] 1.59–2.28), as well as in all sensitivity analyses (Figures 3 and 4, Tables S3–S8). In multivariable analysis, villous adenomas were not associated with CRC during follow-up (HR 1.27; 95% CI 0.85–1.90; Figures 3 and 4, Tables S3–S8).

ADENOMA SIZE

The histopathological finding of adenomas with a diameter of ≥10 mm at index colonoscopy was a risk factor for AN during follow-up colonoscopies in multivariable analysis (HR 1.12; 95% CI 1.02–1.23; Figure 3, Table S3). Similar outcomes were observed in the sensitivity analyses, except for the analysis of patients in the screening population (Figure 4, Table S4). Remarkably, adenoma size of ≥10 mm during histopathological examination at index colonoscopy was associated with a lower risk of metachronous CRC (HR 0.66; 95% CI 0.53–0.83), which persisted in several sensitivity analyses, such as the screening population (Figures 3 and 4, Tables S3, S4, S7). In the analysis that excluded potential incomplete or low-quality index colonoscopies a similar trend was observed; however, this trend did not reach statistical significance (Tables S5 and S6).

SERRATED POLYP SIZE

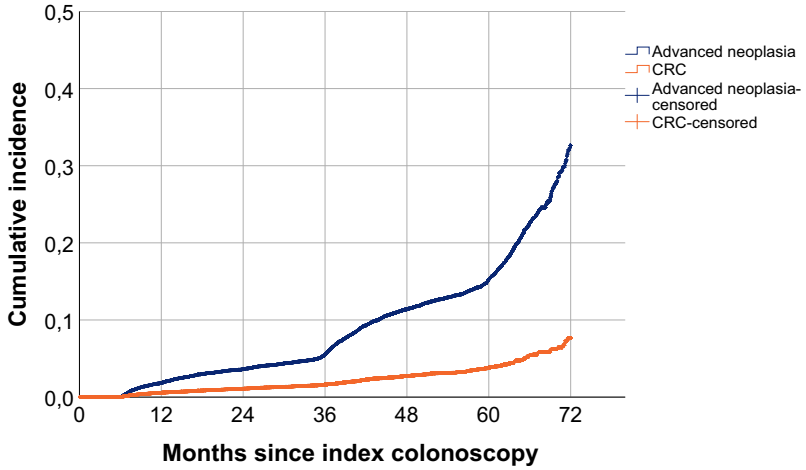
Serrated polyps with a diameter ≥10 mm were observed in 4.5% (n = 1,009) of the patients at index colonoscopies (Table 1). The presence of serrated polyps ≥10 mm at index colonoscopy was a risk factor for metachronous AN in all analyses (Figures 3 and 4, Tables S3–S8). However, serrated polyps ≥10 mm were not associated with metachronous CRC. Furthermore, in the analysis that corrected for the number of surveillance colonoscopies and the time to the first surveillance colonoscopy, the finding of serrated polyps ≥10 mm at index was associated with a lower risk of metachronous CRC (HR 0.57; 95% CI 0.35–0.93; Table S7).

LOCATION

At index colonoscopy, proximally located adenomas were a predictor of AN in the overall study population (HR 1.12; 95% CI 1.02–1.23) and in the screening population (HR 1.34; 95% CI 1.18–1.52; Figures 3 and 4). This association could not be observed in the other subgroup analyses. Also, the location of adenomas was not associated with metachronous CRC (Figures 3 and 4, Tables S3–S8).

NUMBER OF ADENOMAS

The examination of two or more adenomas after index colonoscopy was a risk factor for AN during follow-up in multivariable and several sensitivity analyses (Figures 3 and 4, Tables S3–S6, Table S8). Only when corrected for the number of colonoscopies and the timing of the first surveillance colonoscopy, the number of adenomas examined was not associated with metachronous AN (Table S7). The examination of two or more adenomas after index colonoscopy



Advanced neoplasia

Months	0	12	24	36	48	60	72
Cumulative events	0	358	685	1010	1728	2030	2404
Number at risk	22,471	18,692	17,146	14,853	8,385	5,422	213

CRC

Months	0	12	24	36	48	60	72
Cumulative events	0	110	204	291	420	490	553
Number at risk	22,471	18,696	17,152	14,861	8,132	5,424	212

Figure 2. Estimated cumulative incidence of metachronous advanced colorectal neoplasia* and colorectal cancer (n = 22,471). *Advanced colorectal neoplasia: advanced adenoma (i.e. adenoma ≥10 mm, high-grade dysplasia, tubulovillous histology, or villous histology) or advanced serrated polyp (i.e. serrated adenoma ≥10 mm) or colorectal cancer (i.e. adenocarcinoma of colorectal origin). CRC = colorectal cancer.

was either not associated with metachronous CRC (Figures 3 and 4, Tables S3–S5, Table S8), or associated with a lower risk of CRC, depending on the analysed (sub)group (Tables S6 and S7).

HIGH-GRADE DYSPLASIA

High-grade dysplasia was observed in 9.1% (n = 2,050) of index colonoscopies, and high-grade dysplasia as the only potential risk factor was observed in 1.3% (n = 281) of the patients (Table 1). High-grade dysplasia at index colonoscopy was a risk factor for metachronous AN (Figures 3 and 4, Tables S3–S6, Table S8). Only after correction for the number of colonoscopies and timing of the first surveillance colonoscopy this association could not be confirmed (Table S7). The presence of high-grade dysplasia at index colonoscopy was shown to be a risk factor for CRC in all analyses, with hazard ratios varying from 1.61 to 2.98 (Figures 3 and 4, Tables S3–S8).

FIT-BASED CRC SCREENING PROGRAMME

Approximately half of the index colonoscopies were performed for FIT-positive participants in the national FIT-based CRC screening programme (n = 11,206, 49.9%; Table 1). The overall multivariable analysis showed that participation in screening was associated with a lower incidence of AN during follow-up (HR 0.85; 95% CI 0.78–0.93; Figure 3, Material S3). Sensitivity analyses that excluded potential incomplete or low-quality index colonoscopies resulted in similar outcomes (Tables S5 and S6). Nevertheless, this association was not observed in an analysis that corrected for the number of colonoscopies and the timing of the first surveillance colonoscopy (Table S7). Participation in the FIT-based CRC screening programme was not associated with a lower incidence of CRC during surveillance (HR 0.82; 95% CI 0.68–1.00; Figure 3, Table S3, Tables S5–S7). Sensitivity analysis of patients in the screening programme is provided in Figure 4 and Table S4.

ESGE GUIDELINE

In addition, an analysis was performed that included risk factors as determined by the ESGE postpolypectomy colonoscopy surveillance guideline (Figure 5, Table S9). The finding of serrated polyps ≥10 mm (HR 1.44; 95% CI 1.20–1.73); serrated polyps with

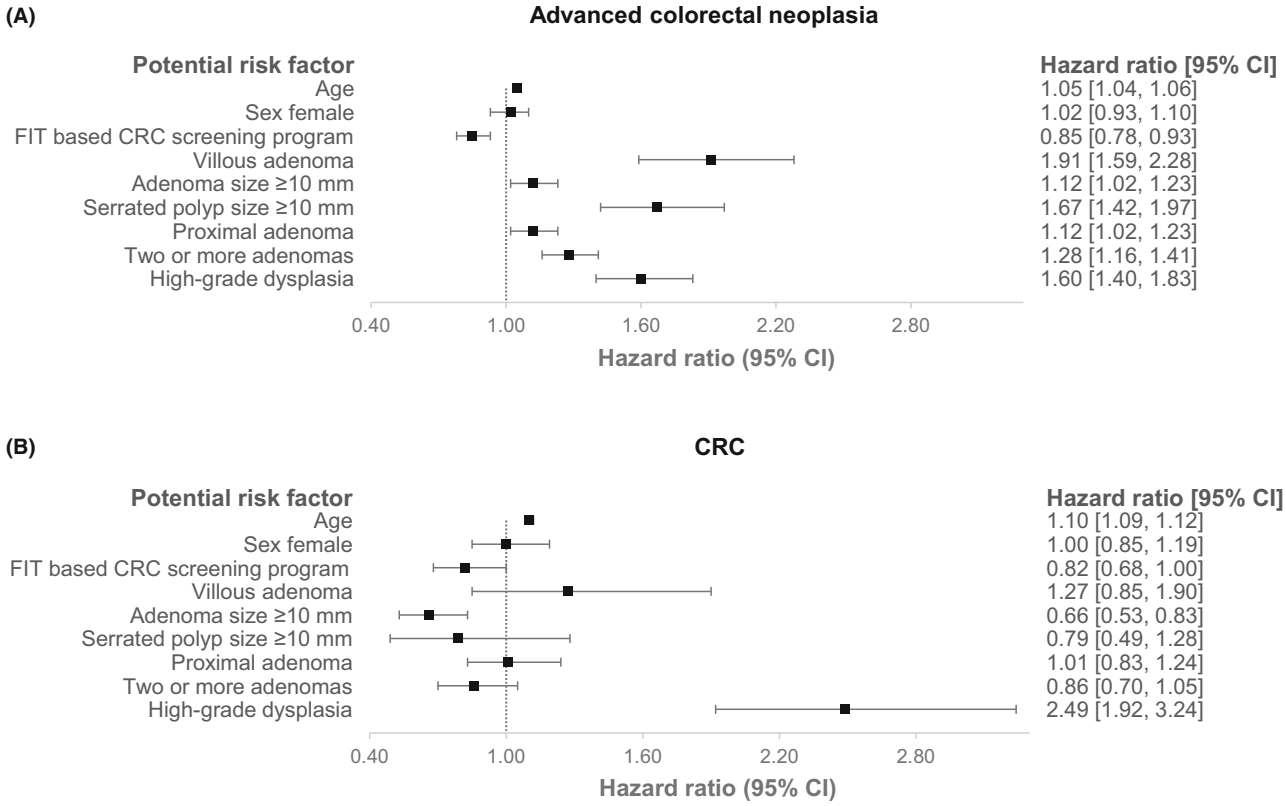


Figure 3. Forest plots of multivariable Cox regression model (n = 22,471) for (A) metachronous advanced neoplasia* and (B) metachronous colorectal cancer. *Advanced colorectal neoplasia: advanced adenoma (i.e. adenoma ≥10 mm, high-grade dysplasia, tubulovillous histology, or villous histology) or advanced serrated polyp (i.e. serrated adenoma ≥10 mm) or colorectal cancer (i.e. adenocarcinoma of colorectal origin). CRC, colorectal cancer.

dysplasia (HR 1.54; 95% CI 1.25–1.90); five or more adenomas (HR 1.56; 95% CI 1.38–1.75); and adenomas with high-grade dysplasia (HR 1.72; 95% CI 1.50–1.96) at index colonoscopy were associated with AN during follow-up. However, the presence of an adenoma with a diameter of ≥10 mm (HR 1.00; 95% CI 0.92–1.10) was not a predictor of metachronous AN. Adenomas with high-grade dysplasia (HR 2.69; 95% CI 2.08–3.47) were a risk factor for CRC, whereas adenomas with a diameter of ≥10 mm (HR 0.53; 95% CI 0.43–0.65) were associated with a lower risk of metachronous CRC.

Discussion

This population-based study identified independent risk factors for metachronous AN and CRC after the implementation of a FIT-based screening programme. A substantial difference in risk factors for detection of metachronous AN and CRC was observed. Overall, the current study showed that characteristics such as villous histology, high-grade dysplasia, polyp size, and the number of adenomas are predictors of metachronous AN. However, it also indicated high-grade dysplasia as the only independent risk factor for CRC at follow-up, and suggested that histological (sub)type of the lesion, polyp size, and the number of adenomas at index colonoscopy may not be associated with metachronous CRC.

In line with these findings, high-grade dysplasia has been shown to be a risk factor for both CRC and CRC related mortality in several studies.[10,13,17,18,24,25] Hence, high-grade dysplasia is included in most guidelines.[4,5] A previous Dutch population study by Van Heijningen *et al.* showed no association between high-grade dysplasia and metachronous AN.[16] However, at the time of that study considerable interobserver variation in grading of dysplasia was present.[16,26] Since then, efforts have been made to standardize the diagnosis of high-grade dysplasia, by providing special targeted education to pathologists.[27] These efforts may have contributed to the predictive value of high-grade dysplasia in the current study.

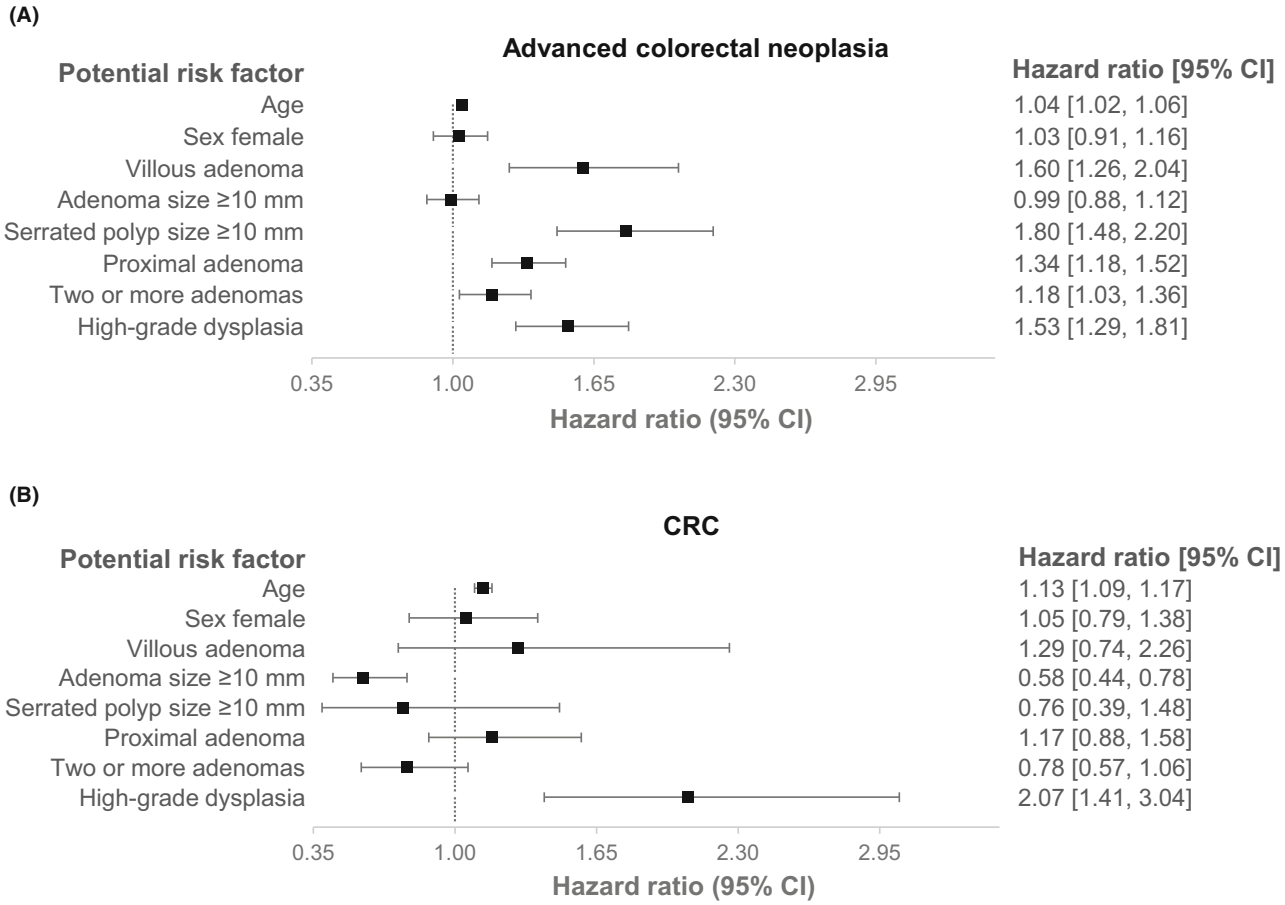


Figure 4. Forest plots of subgroup analysis of patients in the FIT-based CRC screening programme (n = 11,206), multivariable Cox regression model for (A) metachronous advanced neoplasia* and (B) metachronous colorectal cancer. *Advanced colorectal neoplasia: advanced adenoma (i.e. adenoma ≥10 mm, high-grade dysplasia, tubulovillous histology, or villous histology) or advanced serrated polyp (i.e. serrated adenoma ≥10 mm) or colorectal cancer (i.e. adenocarcinoma of colorectal origin). CRC = colorectal cancer.

In addition, several recent studies analysing CRC incidence after removal of adenomas have shown that the number of adenomas may not be related to the development of CRC.[10,11,17] A potential explanation might be that patients with large or a high number of adenomas undergo surveillance more frequently, which could result in the prevention of CRC. Still, the subgroup analysis of the current study that corrected for the number of follow-up colonoscopies showed that the finding of large or two or more adenomas was associated with a lower risk of CRC.

Polyp size is a risk factor that has been incorporated in leading guidelines.[4,5,8] Even though polyp size was associated with metachronous AN in most analyses of this study, it was not a risk factor for metachronous CRC. Even more, our results suggested that the presence of larger adenomas might be associated with a lower risk of metachronous CRC. A recent Polish study in a population screened by colonoscopies suggested that for an increased risk of CRC the 10 mm cutoff should be changed to 20 mm.[17] Based on these outcomes, the ESGE guideline states that in a health system with limited capacity solely surveillance for adenomas ≥20 mm or with high-grade dysplasia should be considered.[5] In more detailed Cox regression analyses of the current study data, we tested all potential cutoff sizes (from 10 mm to 50 mm in steps of 5 mm); however, these analyses did not show a statistically significant association between polyp size and metachronous CRC (data not shown). In addition to the frequency of follow-up as described above, the suggestion of a lower risk of metachronous CRC after removal of large or multiple polyps could potentially be a reflection of biological predisposition. Endogenic factors, including genetic constitution or immune response and exogenous factors such as lifestyle factors and diet may influence the development from adenoma to CRC. Potentially,

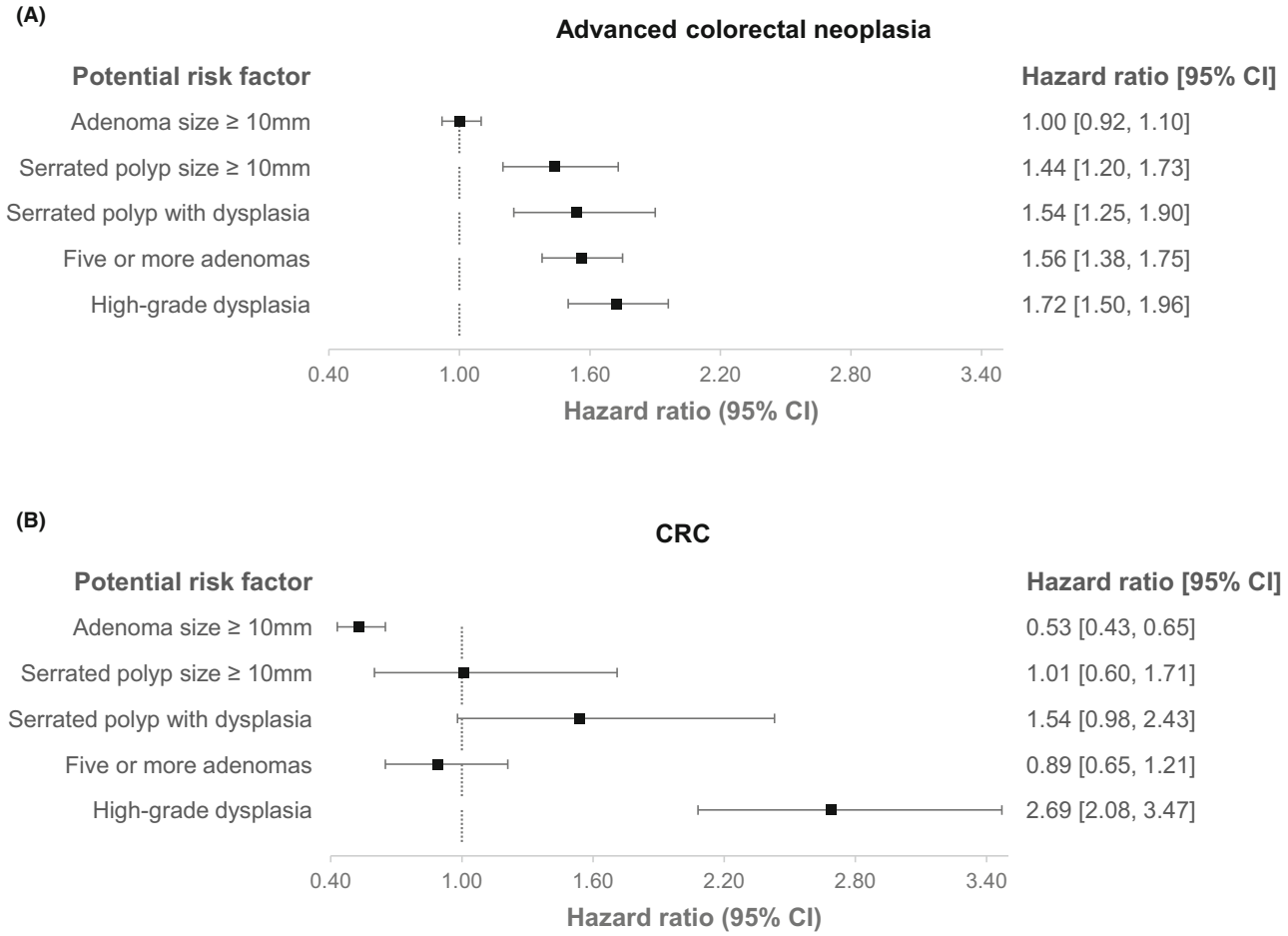


Figure 5. Forest plots of multivariable Cox regression model according to ESGE guidelines (n = 22,471) for (A) metachronous advanced neoplasia* and (B) metachronous colorectal cancer. *Advanced colorectal neoplasia: advanced adenoma (i.e. adenoma ≥10 mm, high-grade dysplasia, tubulovillous histology, or villous histology) or advanced serrated polyp (i.e. serrated adenoma ≥10 mm) or colorectal cancer (i.e. adenocarcinoma of colorectal origin). CRC = colorectal cancer.

some patients might lack the predisposition for adenomas to progress to CRC and therefore gain the chance to develop large or multiple adenomas over the years prior to their first colonoscopy. This may be underlined by the finding that the lower risk of metachronous CRC was mainly present in the group of patients diagnosed within the FIT-based screening programme and not in the symptomatic patients, suggesting a different and probably more inert biological behaviour of these larger polyps (lead time bias of population screening). Last, the diagnosis of advanced adenoma may have influenced patients' behaviour. It seems plausible that upon receiving a diagnosis of advanced adenomas, patients may have adopted healthier lifestyles. Changes such as quitting smoking or drinking, losing weight, and adopting a healthier diet could have potentially influenced the development of metachronous CRC in at-risk patients. Future studies, however, should reveal whether such theories may be supported.

Part of the changes in the spectrum of high-risk features may be directly related to the shift from AN to CRC as an outcome measure. The introduction of CRC screening programmes is another major factor, which was accompanied by profound changes in the involved fields of medicine. For example, the obligatory e-learnings regarding the pathological assessment of high-grade dysplasia prior to the start of the screening programme did result in less diagnostic variability.[27] On top of that, according to the European guidelines, a quality measure of a maximum of 10% of high-grade dysplasia was installed for the annual audits of CRC screening laboratories.[28] Both the e-learnings and the audits have significantly reduced the proportion of high-grade dysplasia.[27,29] Next to these improvements in histopathology, there

have been developments in the field of gastroenterology as well. Quality indicators for all colonoscopies are prospectively registered and quality assurance has been established for screening colonoscopies through the implementation of accreditation and audits in the CRC screening programme.[30,31] The high accreditation rate of 65.7% of Dutch gastroenterologists may have led to improved quality of colonoscopies both inside and outside of the screening programme.[30] The lower risk of metachronous AN after screening colonoscopies might underline improved colonoscopy quality (e.g. higher detection rate) in a population that presumably has a higher risk of an adverse outcome.

A strength of the current study is that data were based on a large population-based cohort, which allowed multivariable Cox regression analyses on specific risk factors. Other studies frequently compared advanced adenomas to nonadvanced adenomas, which presumes a certain incontrovertibility of the included risk factors. Furthermore, this has been one of the first studies that is based on population data of patients who are solely included after the implementation of a CRC screening programme. The outcomes of our study might be a first indication that there has been a shift in risk profile, which could potentially be related to the implementation of screening and subsequent changes in practice. One of the limitations of this study is that by using the Dutch Nationwide Pathology Databank we were unable to correlate histopathological outcomes with colonoscopy data. For this reason, resection techniques and quality indicators, such as bowel preparation and completeness of the endoscopy, could not be evaluated. Previous studies, however, showed that poor-quality endoscopies were associated with adverse outcomes.[10,16,24] In addition, lesions for which only a biopsy or piecemeal resection was performed may have been included. To try to overcome these obstacles, sensitivity analyses were performed that excluded patients who underwent a second colonoscopy within 1 year (Tables S3 and S4). Another limitation might be that AN was defined as advanced adenoma (i.e. adenoma ≥10 mm, high-grade dysplasia, tubulovillous histology, or villous histology), advanced serrated polyp (i.e. serrated adenoma ≥10 mm) or CRC (i.e. adenocarcinoma of colorectal origin). Inclusion of villous and tubulovillous morphology in advanced neoplasia is not in line with the ESGE guideline. However, removal of these features would not have led to changes in the outcome (Table S10). Moreover, this cohort does not include patients who underwent a surveillance colonoscopy without any biopsies or polypectomies. This may have increased the absolute risk for AN and/or CRC, but the relative risk among variables is most likely not affected. In addition, polyp size was based on histopathological reports and could therefore only be determined in *en bloc* resections. In a limited number of cases, the size of the polyps could not be determined due to fragmentation. Measurements during endoscopic and histopathological evaluation are hampered by bias, and guideline recommendations are conflicting.[5,8] Endoscopic measurements are known for terminal digit preferences, whereas after removal the specimen shrinks prior to histopathological evaluation.[32–35] Moreover, the proportional hazard assumption of the Cox regression analyses was not met for the variables: participation in the CRC screening programme, adenoma size, and two or more adenomas.[23,36] This deviation is caused by the colonoscopy surveillance guideline implemented prior to this study. The guideline recommends surveillance after either 3 or 5 years of follow-up; consequently, an adverse outcome will be diagnosed more frequently around these timepoints. In addition to this, adherence to the national guideline might have influenced the outcomes. For example, high-grade dysplasia was not considered a risk factor according to the national guideline. For this reason, these patients did not require surveillance, whereas patients with other risk factors did undergo surveillance that may have led to prevention of metachronous CRC. Still, in only 1.3% of the patients was high-grade dysplasia present as a sole risk factor. Furthermore, the current study did not include data regarding CRC-related mortality and only identified adverse outcomes within 6 years, which implies that progression from AN to CRC was relatively fast.

In conclusion, this nationwide study in both the general and screening population one year after the introduction of the national CRC screening programme identified independent risk factors for metachronous advanced neoplasia and CRC in the modern era. Moreover, a substantial difference in risk factors was observed between metachronous AN and CRC. Considerably fewer risk factors were identified for metachronous CRC, as high-grade dysplasia was the only consistent independent risk factor for CRC throughout the study. At present, guidelines show a trend in narrowing the indications for surveillance colonoscopies by focusing on metachronous CRC. If other studies in populations with access to CRC screening endorse the outcomes of this study, it might seem feasible to further reduce the criteria for surveillance in future guidelines.

Author contributions

L.S.: data curation, formal analysis, investigation, project administration, visualization, writing original draft. A.S.: data curation, investigation, writing review & editing. B.L.: formal analysis, methodology, writing review & editing. I.L.: conceptualization, methodology, writing review & editing. M.K: conceptualization, methodology, writing review & editing. J.T.: conceptualization, methodology, supervision, writing original draft, writing review & editing. N.v.G.: conceptualization, methodology, supervision, writing original draft, writing review & editing. I.N.: conceptualization, methodology, supervision, writing original draft, writing review & editing. All authors read and approved the final article.

Conflict of interest

The authors declare no conflicts of interest.

Data availability statement

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

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Comparison of included patients and excluded patients without follow-up examinations.

Table S2. Univariable Cox regression for metachronous advanced neoplasia* and colorectal cancer (n = 22,471).

Table S3. Multivariable Cox regression model for metachronous advanced neoplasia* and metachronous colorectal cancer (n = 22,471).

Table S4. Analysis of patients in the FIT based CRC screening programme only, multivariable Cox regression model for metachronous advanced neoplasia* and colorectal cancer n = 11,206.

Table S5. Multivariable Cox regression model for metachronous advanced neoplasia* and colorectal cancer in patients with first follow-up colonoscopy ≥1 year after index colonoscopy n = 15,249.

Table S6. Multivariable Cox regression model, analysis of outcomes of first follow-up colonoscopy in patients with first follow-up colonoscopy ≥1 year after index colonoscopy n = 15,249.

Table S7. Multivariable Cox regression model for metachronous advanced neoplasia* and colorectal cancer including number of colonoscopies and time to colonoscopy (n = 22,471).

Table S8. Analysis of patients not in the FIT based CRC screening programme, multivariable Cox regression model for metachronous advanced neoplasia* and colorectal cancer n = 11.265.

Table S9. Multivariable Cox regression model for metachronous advanced neoplasia* and colorectal cancer according to ESGE guidelines (n = 22,471).

Table S10. Multivariable Cox regression model for metachronous advanced neoplasia without tubulovillous morphology and villous morphology (n = 22,471).