Long-term risk of colorectal cancer after screen-detected adenoma

Experiences from a Danish gFOBT-positive screening cohort

Bjerrum, Andreas; Lindebjerg, Jan; Andersen, Ole; Fischer, Anders; Lynge, Elsebeth

Published in:
International Journal of Cancer

DOI:
10.1002/ijc.32850

Publication date:
2020

Document version
Peer reviewed version

Bjerrum Andreas (Orcid ID: 0000-0002-4967-0772)

Lynge Elsebeth (Orcid ID: 0000-0003-4785-5236)

Title: Long term risk of colorectal cancer after screen detected adenoma: Experiences from a Danish gFOBT positive screening cohort

Short title: Colorectal cancer risk after screen detected adenoma removal

Andreas Bjerrum[1], Jan Lindebjerg[3], Ole Andersen[4], Anders Fischer[2], Elsebeth Lynge[4]

[1] Department of Public Health, University of Copenhagen, Denmark
[2] Copenhagen University Hospital Herlev, Denmark
[3] Department of Pathology, Vejle Hospital, Denmark
[4] Nykøbing Falster Hospital, University of Copenhagen, Denmark

Correspondence to: Andreas Bjerrum, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, DK 1014 København K, Denmark
Tel: + 4530818474 E-mail: ab@medicinsk.dk

Key words: Colorectal cancer, screening, adenoma, FOBT

List of abbreviations:

aHR	Adjusted Hazard Ratio
CI	Confidence Interval
CRC	Colorectal Cancer
ESGE	European Society of Gastrointestinal Endoscopy
FOBT	Faecal Occult Blood Test
gFOBT	Guaiac-based Faecal Occult Blood Test
ICD	International Classification of Diseases
SNOMED	Systematized Nomenclature of Medicine

Novelty and Impact (79 words)?
In faecal occult blood test (FOBT) screening for colorectal cancer, approximately half of FOBT positive persons will have one or more adenomas. Adenoma surveillance is recommended to detect and remove new advanced adenomas and CRC, but evidence of surveillance effectiveness on CRC incidence is scarce. We found that persons with screen detected high-risk adenomas after a positive FOBT have twice the long-term risk of CRC compared to the general population, but this risk can be controlled by adenoma surveillance.

Word count: 3885

ABSTRACT :
Faecal occult blood test (FOBT) screening for colorectal cancer (CRC) is implemented in several countries. Approximately half of all FOBT positive persons have screen detected adenomas. Despite removal of these, patients with large/multiple adenomas have increased risk of later developing new advanced adenomas and CRC. International guidelines exist for colonoscopic surveillance following adenoma removal. These divide patients in to low-, intermediate and high-risk groups. We followed 711 FOBT positive patients with screening adenoma identified during population based CRC screening in two Danish counties in 2005-2006. As reference population, we included 1,240,348 persons in the same age group from the rest of Denmark not included in the screening. We estimated the long-term CRC risk stratified by adenoma findings during screening and compared with the reference group. After 12 years follow-up, the CRC incidence among all adenoma patients was 322 cases per 100,000 person-years (95% CI: 212-489) ranging from 251 (95% CI: 94-671) to 542 (95% CI: 300-978) cases per 100,000 person-years in the low-risk and high-risk groups, respectively. In the reference population, the CRC incidence was 244 (95% CI: 242-247) per 100,000. Patients with screen detected high-risk adenomas after a positive FOBT had an almost doubled risk of CRC compared to the reference population (aHR 1.95, 95% CI: 1.08-3.51), and the incidence in those with no follow-up visits was over 3.6 (aHR 3.64 ,95% CI: 1.82-7.29) times the incidence in the reference population. The increased CRC risk could be controlled if high-risk patients underwent follow-up colonoscopy (aHR 0.87, 95% CI: 0.28-2.69).

INTRODUCTION

In Denmark, colorectal cancer (CRC) is the second most frequent cancer for men and third most frequent cancer for women aged 50-74 years with age-standardised (Nordic Standard Population) incidences of 179 and 133 cases per 100,000 (Danish Population, 2007-2016)[1]. Randomised trials have shown that repeated guaiac faecal occult blood test (gFOBT) screening can detect early stages of the disease and reduce CRC mortality [2-5]. About 2.4% to 2.8% of participants in gFOBT screening will have a positive faecal test for occult blood [6, 7], and between 37% and 60% of gFOBT positive persons will have screening adenomas [4, 6, 8]. In a Danish CRC screening feasibility study, 2.4% had a positive FOBT and 38% with positive FOBT had one or more adenomas [9]. Removal of these cancer precursor lesions may prevent cancers and reduce mortality in this group [10]. Despite adenoma removal, patients with large and/or multiple colorectal adenomas have a higher risk of later developing new advanced adenomas and CRC compared to patients without adenomas [11-13].

The European guidelines for quality assurance in colorectal cancer screening and diagnosis (EU guidelines) from 2010 provide guidance for colonoscopic surveillance following adenoma removal. The EU guidelines provide a basic algorithm to divide adenoma patients into low, intermediate and high-risk groups of developing advanced adenomas and cancer based on the size and number of adenomas detected at index colonoscopy [14]. High risk patients are recommended an extra colonoscopy within 12 months to check for missed synchronous lesions, followed by 3-yearly surveillance. Patients with intermediate risk should be offered surveillance at 3-yearly intervals, while low-risk patients return to the screening programme[14]. In addition, the guidelines propose optional criteria to classify small adenomas (<10 mm) as intermediate risk if they present high grade neoplasia or villous characteristics (optional EU guidelines). In 2013, the European Society of Gastrointestinal Endoscopy (ESGE) developed guidelines for post-polypectomy colonoscopy surveillance[15]. These guidelines recommend surveillance colonoscopy 3 years after the index colonoscopy in persons with high risk adenoma while persons with low risk adenoma are re-invited to screening 10 years

after the index colonoscopy[15]. Like the optional EU guideline, the ESGE guidelines are based on size, number and histological/morphological characteristics.

The unique Danish population and health registers allowed us to assess the long-term incidence of CRC in patients with screen detected adenomas during a single round gFOBT screening feasibility study in two Danish counties in 2005-2006. After a follow-up of 12-years we examine whether FOBT positive persons with high risk adenomas according to the EU or ESGE guidelines have increased long-term risk of CRC compared to other Danes and whether adenoma surveillance is associated with a decreased risk.

MATERIAL AND METHODS

Study design and study population

This population-based cohort-study was based on data from 183,238 persons from two Danish counties invited to participate in a single-round gFOBT screening feasibility study between August 2005 and August 2006. The purpose of the feasibility study was to assess participation level before a possible national scale-up. The feasibility study population was deliberately drawn from two parts of Denmark, to make the results representative for the total population. Among the persons invited, a total of 80,563 persons participated in screening. Of these, 1,924 persons had a positive gFOBT and were included in the study. For half of the study population (those from Vejle County) all colonoscopies were performed in a hospital, and this was also the case for the majority of coloscopies from the other half (those from Copenhagen County). Remaining coloscopies were undertaken by private specialists in gastroenterology. Nationwide roll out of FOBT screening started in Denmark in April 2014.

As reference population, we included 1,240,348 persons in the same age group on 2 August 2005 from the rest of Denmark not included in the screening feasibility study. We used the invitation scheme from the feasibility study to assign pseudo-invitation dates to persons in the reference group.

Based on the unique Danish personal identification, we linked each person with the Danish Population Register to obtain dates of death and emigration; with the Danish Cancer Register to obtain information about history of CRC; with the National Patient Register for diagnoses of colorectal disease and hospital colonoscopies, polypectomies and surgical interventions; with the Health Service Register for private sector colonoscopies and polypectomies; with the Pathology Register for incident CRC, advanced adenomas and pathology reports of colorectal specimens; and with the screening pilot database for invitation date, participation status, gFOBT result and date for screening colonoscopy. For each person, data were collected from the (pseudo-)invitation date to date of CRC, death, emigration or December 31st, 2017, whichever came first.

We excluded persons who died, emigrated or were diagnosed with inflammatory bowel disease (ICD8: 563.01/563.02/563.09/563.19 and ICD10: K50/K51) prior to invitation. We excluded persons with colorectal cancer (ICD10: C18/C19/C20/C21) diagnosed before date of invitation. Furthermore, we excluded persons who underwent colonoscopy, sigmoidoscopy or any invasive colon or anorectal procedure in the period from 2 years before the feasibility study started, i.e. 2nd August 2003, until the invitation date. Data linkage identified a number of persons from the two screening counties, who were excluded from the feasibility study for unknown reasons. This last group was excluded from the screening group in our analyses since we had no information related to screening participation.

Screening participants with a positive gFOBT were linked to the Pathology Register to search for reports on colorectal polyps using the Systematized Nomenclature of Medicine (SNOMED) and exclude patients with screening CRC (see supl. annex for SNOMED codes). An experienced pathologist (author JL) manually searched the Pathology Register and all polyps were evaluated for grade of dysplasia, number, size of largest removed polyp, and polyp characteristics (villous, tubular, serrated). Patients with serrated polyps without dysplasia were excluded. Only patients having dysplastic polyp(s) removed during index colonoscopy were included as screening adenoma patients.

We used information about the number, size and adenoma characteristics (dysplasia and villous components) from the index colonoscopy to categorize patients according to the EU guidelines and the ESGE guidelines (Table 1).

The National Patient Register and Health Service Register were searched for follow-up visits (using the procedure codes for colonoscopy, sigmoidoscopy and endoscopic polypectomy) and the findings were matched with corresponding pathology records. We did not classify an endoscopy as a follow-up visit if CRC was diagnosed, as the procedure did not offer any protection against CRC.

Since patients may undergo several colonoscopies in succession, we grouped colonoscopies with the preceding investigation(s) if they were performed within a period of 1 year. Consequently, colorectal cancer or adenomas diagnosed within 1 year of the screening colonoscopy were assumed to be screen detected cancers and adenomas, respectively. The first colonoscopy performed more than 12 months after the screening colonoscopy was considered as the first follow-up visit and any colonoscopies within the following year were included as part of this visit. This was repeated for all subsequent colonoscopies until all were grouped into follow-up visits. The adenoma risk stratification for screening and follow-up visits was based on the cumulated number of adenomas for the grouped procedures, the size of the largest adenoma removed, the highest grade of dysplasia and detection of villous features. Pathology reports were reviewed for possible multi session polyp removal. In case the reports held information that an adenoma was removed in a multi session procedure, the date of the initial biopsy was recorded as the date of diagnosis, and the size, type and degree of dysplasia of the adenoma was recorded based on the combined samples.

CRC incidence

For patients with screen detected adenoma, the time at risk started 1 year after the index colonoscopy. Likewise, for the reference population, time at risk started 1 year after the pseudo-invitation date. We searched the Pathology Register for relevant SNOMED codes to identify incident CRC cases (Supl. annex for SNOMED codes).

Statistical analysis

Summary statistics were used to describe mean distribution of sex, age and number of endoscopies in the group of adenoma patients and the reference population as well as median time to first follow-up visit for adenoma patients. Differences in variables were tested using the t-test, Wilcoxon rank-sum test and chi-square test to compare means, medians and proportions as appropriate. We calculated the incidence of CRC per 100,000 person-years along with 95% confidence intervals, assuming Poisson distribution and used log-rank to test for inequality across adenoma risk groups. We used Cox regression with time at risk, as defined above, as the underlying time scale to calculate hazard ratios for CRC in screening adenoma patients from the different risk groups, with or without follow-up visits, relative to the reference population. We treated follow-up visits as a time varying covariate in the incidence and Cox regression analyses. The hazard ratios were adjusted for sex and age (aHR). We used Kaplan–Meier survival statistics to display differences in CRC incidence between patients with and without a follow-up visit compared and the reference population. All statistical analyses were conducted with Stata version 15.1.

Ethics

The Danish Data Protection Agency approved the linkage between the registers in this study (J.-no. 2015-41-4012). The study was not subject to approval by the Ethics Committee since data collection did not involve patient contact or access to patients' medical records.

Data Availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

RESULTS

Among 1,924 screening participants with a positive gFOBT, we identified 711 patients with one or more screening adenoma in the Pathology Register. A total of 897 had no pathological

findings, 170 were diagnosed with screening CRC, and 146 patients had other pathology (including patients with serrated polyps without dysplasia). Among the 711 adenoma patients, 7 were censored within 1 years after screening colonoscopy due to other reasons than CRC. As reference population we identified 1,341,021 persons aged 50-74 years on 2nd August 2005 and living in the Danish counties that did not take part in the screening feasibility study. A total of 110,673 persons were excluded from the reference population based on the predefined criteria, and another 18,629 persons were censored within the grace period of 1 year from the date of pseudo invitation. Consequently, this follow-up analysis included 1,222,430 persons divided into the screening adenoma group of 704 persons, and a reference group of 1,221,726 persons.

In the group of screening adenoma patients, there was an overrepresentation of men compared to the reference population (66% vs. 49%; $p < 0.001$), the adenoma patients were older on the invitation date (mean age 63.4 years vs. 61.2 years; $p < 0.001$) and had more endoscopies in the follow up period (2.6 vs. 1.6; $p < 0.001$) compared to the reference population. The mean age at time of screening was 63.4 years for patients without follow-up visits and 63.1 years to those with follow-up. Two thirds (307/468, 66%) of male adenoma patients and 62% (147/236) of female adenoma patients went for a follow-up visit. Since follow-up visits were treated as a time varying covariate, the same person would first contribute time to the non-follow-up group (time until first follow-up) and then to the follow-up group (time after first follow-up until end of study period). The distribution of person years between the sexes were 66% male for adenoma patients without follow-up and 67% male for patients with one or more follow-up visits.

Adenoma risk groups

Based on the EU guidelines, about half (47%) of adenoma patients belonged to the intermediate group, while 23% belonged to the low-risk group and 30% to the high-risk group. The optional EU guidelines, that also take histological and morphological characteristics into account, resulted in reclassification of 24 patients from the low-risk group to the intermediate group due to either high-grade dysplasia or villous characteristics. The

ESGE guidelines' low-risk group is similar to the optional EU guidelines resulting in 20% of adenoma patients belonging to this group, and the remaining 80% belonging to the high-risk group (Table 2).

Risk of CRC after screen detected adenoma

The median follow-up period was 10.7 years for the adenoma patients in the EU low-risk and intermediate risk groups, 10.6 years for adenoma patients in the EU high-risk group, and 10.8 years for the reference population. A total of 22 cases of CRC were detected among the 704 adenoma patients during the follow-up period of 6,836 person years. Table 2 shows the distribution of CRC cases between the adenoma risk groups, as well as the percentage of adenoma patients who went for follow-up visit, the number of follow-up visits and median time to first follow-up.

The CRC incidence among all adenoma patients was 322 cases per 100,000 person-years (95% CI: 212-489). The CRC incidence was 251 (95% CI: 94-671), 218 (95% CI: 104-456) and 542 (95% CI: 300-978) cases per 100,000 person-years for patients in the EU low-risk, intermediate risk and high-risk groups, respectively. The CRC incidence among patients in the optional EU and the ESGE low-risk groups was 220 (95% CI: 71-681), while the CRC incidence for high-risk adenoma patients was 542 (95% CI: 300-978) and 347 (95% CI: 222-545) for the optional EU guidelines and the ESGE guidelines, respectively (Table 3).

We used the reference population as basis to calculate adjusted Hazard Ratios (aHR) for incident CRC for each of the adenoma sub-groups (Table 3). In the reference population, the CRC incidence was 244 (95% CI: 242-247) per 100,000, which was not significantly different from the overall group of adenoma patients (aHR 1.32, 95% CI: 0.87-2.01).

The aHR for incident CRC was significantly higher for the high-risk groups defined by both versions of the EU guidelines at 1.80 (95% CI: 1.00-3.26) compared to the reference population. For the ESGE high-risk group, the incidence of CRC was slightly higher than the reference population, however insignificantly (aHR 1.15, 95% CI: 0.74-1.81).

Follow-up colonoscopy

We found no significant association between the proportion of patients who went for a follow-up visit in the low risk compared to the high-risk adenoma groups (EU guidelines p = 0.072, optional EU guideline p = 0.069 and ESGE guidelines p = 0.851). Patients belonging to the optional EU guidelines' high-risk group had shorter median time to first follow-up visit compared to patients in the low risk group (Low vs. High risk, p = 0.049), but the association was insignificant for the basic EU guidelines (p = 0.052) and the ESGE guidelines (p = 0.23).

Adenoma patients with one or more follow-up visits had significantly lower CRC incidence than adenoma patients with no follow-up visits (aHR 0.33, 95% CI: 0.12-0.88). The effect of follow-up visits was no longer significant when the analysis was performed separately for each adenoma risk group.

Compared to the reference population, adenoma patients, who did not undergo any follow-up visit, had significantly higher long-term risk of CRC with an aHR of 1.65 [95% CI: 1.01-2.69] (Table 3 and Figure 1). The risk further increased for adenoma patients belonging to any of the guidelines' high-risk groups (aHR 3.34, 95% CI: 1.67-6.69 for EU and optional EU guidelines, aHR 1.80, 95% CI: 1.07-3.04 for ESGE guidelines). For patients with one or more follow-up visits, the long-term risk of CRC did not significantly differ from the reference population, regardless of the adenoma risk group.

DISCUSSION

To our knowledge this is the first long-term follow-up study that assess CRC incidence of persons diagnosed with adenomas after testing positive in a population-based FOBT screening programme. In total, 183,238 persons invited to screening; 80,563 persons participated; 1,924 (2.4%) had positive FOBT; and of those 711 (37%) had adenomas detected. The gFOBT positivity rate and distribution between low risk adenomas and medium/high risk adenomas (advanced adenomas) in our adenoma population fell within distribution reported by others [6, 16]. Patients with screen detected high-risk adenomas after a positive FOBT had an almost doubled risk of CRC compared to the general population, and the incidence in those with no follow-up visits was over 3.3 times the incidence in the general population. Of the adenoma patients, 64% went for one or more follow-up visits, where new/previously overlooked adenomas could be removed. Our data showed that the increased CRC risk could be controlled if the patients underwent follow-up colonoscopy, as the CRC incidence in patients followed up was in line with that of the general population. In this study, we applied three different guidelines for stratifying adenoma patients into risk groups. The European guidelines for quality assurance in colorectal cancer screening and diagnosis (EU guidelines) base risk stratification on the count of adenomas and the size of the largest adenoma [14]. The optional EU guidelines and the guidelines developed by European Society of Gastrointestinal Endoscopy (ESGE guidelines) take histologic features into account in addition to count and size [14, 15]. We found that the categorization of adenoma patients into high-risk groups in both versions of the EU and the ESGE guidelines effectively identified those with a long-term increased risk of CRC based on adenoma findings at baseline during screening; when not followed up these excess risks amounted to 3.3 and 1.8 times, respectively, of the incidence in the general population. The CRC incidence in adenoma patients categorized into the low- or intermediate risk groups was the same as in the general population even among those not followed up.

From clinical data sets and from primary colonoscopy screening, it is well established that most cases of CRC develop from adenomatous polyps [7], and that removal of these cancer

precursor lesions prevent cancers and reduce mortality [10, 17, 18]. The strength of our study was that we selectively included adenoma patients identified through FOBT screening and subsequent colonoscopy. Adenoma patients identified through FOBT screening constitute a selected group whose risk profile may differ from adenoma patients found by primary colonoscopy screening or symptom triggered colonoscopy. Therefore, the adenoma patients in our study will be comparable with adenoma patients identified in screening programmes with similar design. Since many countries are implementing CRC screening using FOBT, evidence gathered under these conditions could prove useful.

In the Pathology Register, part of the information is provided in free text and codes, that may not always have been used consistently. Therefore, to ensure consistent classification for all adenoma patients, the same pathologist (JL) manually checked their records after the screening colonoscopy in the Pathology Register. We believe this reduced the risk of classification bias compared to automatic register searches based on algorithms. Nevertheless, our results relied on health service register data submitted by Danish health providers. While the quality of Danish register data is considered to be high[19], we found some discrepancies between registers, especially with respect to date of CRC diagnosis, date of colonoscopy, and date of pathological record, which could introduce some classification bias.

The risk of CRC and new advanced adenomas has been shown to depend on findings during baseline colonoscopy [9, 11-13, 18, 20] as well as the completeness of the colonoscopy and removal of metachronous lesions. In our study, the colonoscopies were performed in the routine health care setting and we did not have access to data on the quality of the colonoscopic examination, preparation, completeness or withdrawal time. Since the time when the colonoscopies in our study were performed, there has been increasing attention to the quality of the colonoscopic procedure and to the development of quality standards [21, 22], and our findings may therefore not fully reflect the quality of colonoscopies in today's screening programme.

As CRC is a gradually developing disease, lead time can cause earlier detection of CRC in the population undergoing colonoscopy surveillance than in the reference population. This should

be taken into consideration when comparing the observed CRC incidence in the follow-up group with that of the non-follow-up group. The fact that our data showed that adenoma patients with follow-up had a lower CRC incidence, HR 0.56 [0.25-1.25], than the general population therefore indicate a truly protective effect of follow-up.

Since patients in the screening cohort all underwent systematic colonoscopy before entry in this study, it is reasonable to assume that all were free of CRC at study entry. The observed CRC incidence in the study population therefore represents incidence of new CRC. In the reference population, the observed incidence represents cases that became symptomatic after study entry. We find it reasonable to assume that the incidence of symptomatic disease in the screen-naïve population, and incidence of new CRC among adenoma patients reflect the same underlying CRC incidence (provided other factors being equal).

Others have shown that healthy lifestyle factors reduce the risk of CRC [23-25] and participation in CRC screening is greater among those engaging in more healthy behaviours [26, 27]. It would be reasonable to assume that adherence to adenoma surveillance is also greater among persons with healthy lifestyle. Adenoma patients with high risk behaviour for CRC may therefore be less prone to undergo follow-up colonoscopy than healthier and more health-conscious patients. The observed excess risk of CRC among adenoma patients without follow-up visits may therefore be affected by a more unhealthy lifestyle in this group than in those followed up. The observed effect of follow-up visits on CRC incidence may be prone to this bias. Meanwhile, all adenoma patients in this study constitute a population that previously opted in for screening and opted in for colonoscopy following their positive gFOBT.

At the time of the feasibility study, there was no national guidelines for adenoma surveillance, and post-polypectomy surveillance was performed in accordance with the local clinical practice. Since the implementation of the Danish nationwide FOBT screening program in 2014, the EU guidelines for follow-up of adenoma patients have been used. According to these guidelines, high risk patients are recommended an extra examination within 12 months followed by 3-yearly surveillance; patients with intermediate risk are offered 3-yearly

surveillance; while low-risk patients are returned to screening [14]. Previously, Atkin et al found that patients in the intermediate risk group may benefit from further division into a higher-risk subgroup that benefit from surveillance and a lower-risk subgroup for whom additional surveillance may not be necessary [28]. It is noteworthy that our study found that the patients from the intermediate group without follow-up have the same CRC risk as the general population. If this observation is confirmed in other settings, the guidelines for follow-up colonoscopy of the intermediate groups may require revision.

We used the Danish population from the areas not included in the feasibility study as reference population. Since the feasibility study, Denmark underwent an administration reform where several counties were merged into larger regions. In the South and Capital Regions, where the feasibility study took place, the age-standardized (Nordic Standard Population) CRC incidence rate for persons aged 50-74 years was 171.2 and 177.1 per 100,000 person years for men, respectively, and 133.8 and 125.0 for women in the period from 2007 to 2016[1]. This is comparable to the national average incidence for Denmark of 179.1 for men and 133.0 for women. On this basis we do not expect regional difference in background CRC incidence to have distorted the results.

In conclusion, our study showed that patients identified with high-risk adenomas after a positive FOBT during screening were at increased risk of later developing CRC. This risk could be reduced to a risk similar to that of the general population, if the high-risk adenoma patients were identified as outlined in the EU guidelines and followed up with colonoscopic surveillance.

The authors declare no conflict of interest.

REFERENCES

1. NORDCAN. Standardised rates by cancers (Incidence/Mortality), vol. 2019, 2019.
2. Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, Ederer F. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *The New England journal of medicine* 1993;**328**: 1365-71.
3. Lindholm E, Brevinge H, Haglind E. Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer. *Br J Surg* 2008;**95**: 1029-36.
4. Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, James PD, Mangham CM. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996;**348**: 1472-7.
5. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996;**348**: 1467-71.
6. van Rossum LG, van Rijn AF, Laheij RJ, van Oijen MG, Fockens P, van Krieken HH, Verbeek AL, Jansen JB, Dekker E. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. *Gastroenterology* 2008;**135**: 82-90.
7. Muto T, Bussey HJ, Morson BC. The evolution of cancer of the colon and rectum. *Cancer* 1975;**36**: 2251-70.
8. Hol L, Wilschut JA, van Ballegooijen M, van Vuuren AJ, van der Valk H, Reijerink JC, van der Togt AC, Kuipers EJ, Habbema JD, van Leerdam ME. Screening for colorectal cancer: random comparison of guaiac and immunochemical faecal occult blood testing at different cut-off levels. *British journal of cancer* 2009;**100**: 1103-10.
9. Bjerrum A, Milter MC, Andersen O, Fischer A, Lynge E. Risk stratification and detection of new colorectal neoplasms after colorectal cancer screening with faecal occult blood test: experiences from a Danish screening cohort. *European journal of gastroenterology & hepatology* 2015;**27**: 1433-7.
10. Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, Shi W, Bond JH, Schapiro M, Panish JF, Stewart ET, Waye JD. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *The New England journal of medicine* 2012;**366**: 687-96.
11. Winawer SJ, Zauber AG, Fletcher RH, Stillman JS, O'Brien MJ, Levin B, Smith RA, Lieberman DA, Burt RW, Levin TR, Bond JH, Brooks D, et al. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. *Gastroenterology* 2006;**130**: 1872-85.
12. Martinez ME, Baron JA, Lieberman DA, Schatzkin A, Lanza E, Winawer SJ, Zauber AG, Jiang R, Ahnen DJ, Bond JH, Church TR, Robertson DJ, et al. A pooled analysis of advanced colorectal neoplasia diagnoses after colonoscopic polypectomy. *Gastroenterology* 2009;**136**: 832-41.
13. Loberg M, Kalager M, Holme O, Hoff G, Adami HO, Bretthauer M. Long-term colorectal-cancer mortality after adenoma removal. *The New England journal of medicine* 2014;**371**: 799-807.
14. Dancourt V, Lejeune C, Lepage C, Gailliard MC, Meny B, Faivre J. Immunochemical faecal occult blood tests are superior to guaiac-based tests for the detection of colorectal neoplasms. *European journal of cancer* 2008;**44**: 2254-8.
15. Hassan C, Quintero E, Dumonceau JM, Regula J, Brandao C, Chaussade S, Dekker E, Dinis-Ribeiro M, Ferlitsch M, Gimeno-Garcia A, Hazewinkel Y, Jover R, et al. Post-polypectomy

colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2013;**45**: 842-51.

16. Guittet L, Bouvier V, Mariotte N, Vallee JP, Levillain R, Tichet J, Launoy G. Comparison of a guaiac and an immunochemical faecal occult blood test for the detection of colonic lesions according to lesion type and location. *British journal of cancer* 2009;**100**: 1230-5.

17. Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, Waye JD, Schapiro M, Bond JH, Panish JF, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *The New England journal of medicine* 1993;**329**: 1977-81.

18. Atkin WS, Morson BC, Cuzick J. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. *The New England journal of medicine* 1992;**326**: 658-62.

19. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;**7**: 449-90.

20. Bouvier AM, Latournerie M, Jooste V, Lepage C, Cottet V, Faivre J. The lifelong risk of metachronous colorectal cancer justifies long-term colonoscopic follow-up. *European journal of cancer* 2008;**44**: 522-7.

21. Rees CJ, Thomas Gibson S, Rutter MD, Baragwanath P, Pullan R, Feeney M, Haslam N, on behalf of: the British Society of Gastroenterology tJAGoGIEtAoCoGB, Ireland. UK key performance indicators and quality assurance standards for colonoscopy. *Gut* 2016;**65**: 1923-9.

22. Kaminski MF, Regula J, Kraszewska E, Polkowski M, Wojciechowska U, Didkowska J, Zwierko M, Rupinski M, Nowacki MP, Butruk E. Quality indicators for colonoscopy and the risk of interval cancer. *The New England journal of medicine* 2010;**362**: 1795-803.

23. Kirkegaard H, Johnsen NF, Christensen J, Frederiksen K, Overvad K, Tjonneland A. Association of adherence to lifestyle recommendations and risk of colorectal cancer: a prospective Danish cohort study. *Bmj* 2010;**341**: c5504.

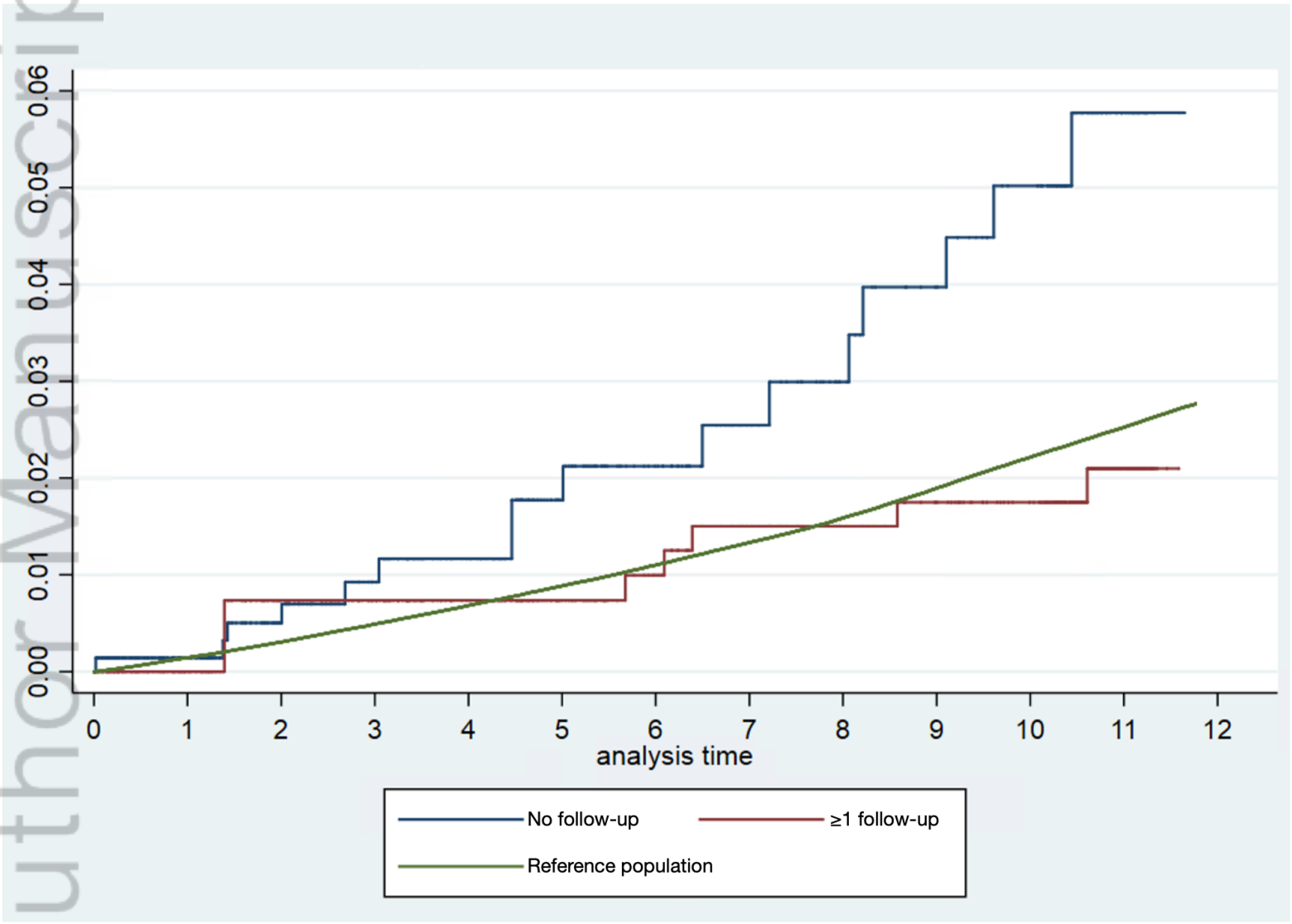
24. Carr PR, Weigl K, Jansen L, Walter V, Erben V, Chang-Claude J, Brenner H, Hoffmeister M. Healthy Lifestyle Factors Associated With Lower Risk of Colorectal Cancer Irrespective of Genetic Risk. *Gastroenterology* 2018;**155**: 1805-15 e5.

25. Erben V, Carr PR, Holleczek B, Stegmaier C, Hoffmeister M, Brenner H. Strong associations of a healthy lifestyle with all stages of colorectal carcinogenesis: Results from a large cohort of participants of screening colonoscopy. *Int J Cancer* 2019;**144**: 2135-43.

26. Carey RN, El-Zaemey S. Lifestyle and occupational factors associated with participation in colorectal cancer screening among men and women in Australia. *Preventive medicine* 2019;**126**: 105777.

27. Blanks RG, Benson VS, Alison R, Brown A, Reeves GK, Beral V, Patnick J, Green J. Nationwide bowel cancer screening programme in England: cohort study of lifestyle factors affecting participation and outcomes in women. *British journal of cancer* 2015;**112**: 1562-7.

28. Atkin W, Brenner A, Martin J, Wooldrage K, Shah U, Lucas F, Greliak P, Pack K, Kralj-Hans I, Thomson A, Perera S, Wood J, et al. The clinical effectiveness of different surveillance strategies to prevent colorectal cancer in people with intermediate-grade colorectal adenomas: a retrospective cohort analysis, and psychological and economic evaluations. *Health Technol Assess* 2017;**21**: 1-536.



IJC_32850_Figure 1.tiff

Novelty & Impact Statement: IJC-19-2415.R2

About half of individuals who have a positive fecal occult blood test (FOBT) will have one or more adenomas, potentially increasing their risk of later developing colorectal cancer (CRC). While surveillance is recommended to detect and remove these precursor lesions, evidence of surveillance effectiveness on CRC incidence is scarce. This study shows that in persons with high-risk adenomas detected following positive FOBT screening, long-term risk of CRC is nearly doubled, relative to the general population. This risk could be controlled, however, if high-risk patients were identified via European guidelines for CRC screening and diagnosis and underwent follow-up colonoscopic surveillance.

	Adenoma characteristics
EU Guidelines	
Low risk	≤ 2 small adenomas (< 10mm)
Intermediate risk	3-4 small adenomas OR 1 adenoma (≥10mm < 20mm)
High risk	≥5 adenomas OR 1 large adenoma (≥ 20mm)
Optional EU guidelines	
Low risk	≤ 2 small, tubular adenomas (< 10mm) with low grade neoplasia
Intermediate risk	3-4 small adenomas OR 1 adenoma (≥10mm < 20mm) OR villous OR high-grade neoplasia
High risk	≥5 adenomas OR 1 large adenoma (≥ 20mm)
ESGE guidelines	
Low risk	≤ 2 small, tubular adenomas (< 10mm) with low grade neoplasia
High risk	3-4 small adenomas OR 1 adenoma (≥10mm < 20mm) OR villous OR high-grade neoplasia

Table 1: Risk stratification by EU guidelines, optional EU guidelines and ESGE guidelines.

	Risk group after index colonoscopy								
	EU Guidelines			Optional EU Guidelines			ESGE Guidelines		Total
	Low (%)	Interm. (%)	High (%)	Low (%)	Interm. (%)	High (%)	Low (%)	High (%)	n (%)
Adenoma patients after index colonoscopy†	163 (23)	337 (47)	211 (30)	139 (20)	361 (51)	211 (30)	139 (20)	572 (80)	711 (100)
At least 1 follow-up colonoscopy‡	104 (64)	198 (59)	153 (73)	88 (63)	214 (59)	153 (73)	88 (63)	367 (64)	455 (64)
1 follow-up colonoscopy	64 (39)	107 (32)	68 (32)	54 (39)	117 (32)	68 (32)	54 (39)	185 (32)	239 (34)
2 follow-up colonoscopies	31 (19)	59 (18)	50 (24)	26 (19)	64 (18)	50 (24)	26 (19)	114 (20)	140 (20)
3 follow-up colonoscopies	7 (4.3)	25 (7.4)	26 (12)	6 (4.3)	26 (7.2)	26 (12)	6 (4.3)	52 (9.1)	58 (8.1)
≥4 follow-up colonoscopies	2 (1.2)	7 (2.1)	9 (4.3)	2 (1.4)	7 (1.9)	9 (4.3)	2 (1.4)	16 (3.8)	18 (2.5)
Median time to first follow-up colonoscopy (years)	3.7	3.7	3.2	3.8	3.6	3.2	3.8	3.5	3.6
No follow-up colonoscopy‡	59 (36)	139 (41)	58 (27)	51 (37)	147 (41)	58 (27)	51 (37)	205 (36)	256 (36)
CRC‡	4 (2.4)	7 (2.1)	11 (5.2)	3 (2.2)	8 (2.2)	11 (5.2)	3 (2.2)	19 (3.3)	22 (3.1)
1 or more follow-up colonoscopies	1 (0.6)	2 (0.6)	3 (1.4)	1 (0.7)	2 (0.6)	3 (1.4)	1 (0.7)	5 (0.9)	6 (0.8)
No follow-up colonoscopy	3 (1.8)	5 (1.5)	8 (3.8)	2 (1.4)	6 (1.7)	8 (3.8)	2 (1.4)	14 (2.4)	16 (2.3)

Table 2: CRC by index risk group. † (%) Percentage of all adenoma patients. ‡ (%) Percentage of adenoma patients in given risk group.

	EU Guidelines			Optional EU Guidelines			ESGE Guidelines		Total
	Low	Intermediate	High	Low	Intermediate	High	Low	High	
Incidence of CRC†	251	218	542	220	233	542	220	347	322
	[94-671]	[104-456]	[300-978]	[71-681]	[116-465]	[300-978]	[71-681]	[222-545]	[212-489]
Follow-up	134	141	267	161	129	267	161	187	182
	[19-951]	[35-562]	[86-828]	[23-1,141]	[32-517]	[86-828]	[23-1,141]	[78-450]	[82-406]
No follow-up	356	279	882	269	317	882	269	500	451
	[115-1,104]	[116-669]	[441-1,763]	[67-1,076]	[142-705]	[441-1,763]	[67-1,076]	[296-844]	[277-737]
Adjusted HR for CRC‡	0.88	0.72	**1.80**	0.77	0.77	**1.80**	0.77	1.15	1.08
	[0.33-2.35]	[0.34-1.51]	**[1.00-3.26]**	[0.25-2.39]	[0.39-1.54]	**[1.00-3.26]**	[0.25-2.39]	[0.74-1.81]	[0.71-1.64]
. Follow-up	0.43	0.43	0.81	0.52	0.40	0.81	0.52	0.57	0.56
	[0.06-3.07]	[0.11-1.73]	[0.26-2.51]	[0.07-3.68]	[0.10-1.60]	[0.26-2.51]	[0.07-3.68]	[0.24-1.38]	[0.25-1.25]
No follow-up	1.35	0.98	**3.34**	1.02	1.12	**3.34**	1.02	**1.80**	**1.65**
	[0.44-4.19]	[0.41-2.35]	**[1.67-6.69]**	[0.26-4.08]	[0.50-2.48]	**[1.67-6.69]**	[0.26-4.08]	**[1.07-3.04]**	**[1.01-2.69]**

Table 3: Incident CRC by index risk group. † Incidence per 100,000 person-years. ‡ Hazard Ratios adjusted for sex and age, reference population as controls.