AARHUS UNIVERSITY
HEALTH

# Increased diagnostic activity in general practice during the year preceding colorectal cancer diagnosis

Research year report

Pernille Libach Hansen

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THE RESEARCH UNIT FOR GENERAL PRACTICE
Aarhus

CaP
Research Centre for Cancer Diagnosis in Primary Care

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**Preface**

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This report is based on the research project which was conducted during my research year at the Research Centre for Cancer Diagnosis in Primary Care (CaP), Aarhus University, from 1st of August 2013 to 1st of August 2014.

I would like to express my sincere gratitude to persons involved in the research project and others who have supported me during the year. An appreciative acknowledgement to:

- My accomplished main supervisor, Peter Vedsted, for giving me the opportunity to perform the research year at a leading research institution as CaP/The Research Unit of General Practice. Thank you for your warm and inspiring personality and the great part of experienced knowledge you have supplied to the project. Despite your fully booked schedule, you have always showed high interest in the study and full reserves of energy which I admire a lot.
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**Contents**

**Abstract (English)**

**Background:** Accurate diagnostic activity in general practice before colorectal cancer (CRC) diagnosis is crucial for early detection of CRC. This study aimed to investigate the rates of daytime consultations, haemoglobin (Hb) measurements and medicine prescriptions for haemorrhoids in general practice in the year preceding CRC diagnosis.

**Methods:** Using Danish registries, we conducted a population-based matched cohort study including CRC patients aged 40-80 years (n=19209) and matched references (n=192090).

**Results:** CRC patients had significantly more consultations from nine months before diagnosis and significantly increased rates of Hb measurements from up to 17 months before diagnosis compared with references. Furthermore, up to 18 months before diagnosis, CRC patients had significantly higher rates of prescriptions for haemorrhoids; and two months before diagnosis, the incidence rate ratio was 12.24 (95% confidence interval (CI) 10.29-14.55) for men. The positive predictive value (PPV) of CRC for having a first-time prescription for haemorrhoids was highest among men aged 70-80 years (PPV=3.2% (95% CI: 2.8-3.7)). High prescription rates were predominantly seen among rectal cancer patients, whereas colon cancer patients had higher rates of consultations and Hb measurements.

**Conclusion:** Activity in general practice was increased during the year preceding CRC diagnosis. An earlier diagnosis of CRC may be possible.

**Abstract (Danish)**

**Baggrund:** For at kunne diagnosticere tarmkræft på et tidligt tidspunkt er det vigtigt at have et hensigtsmæssigt diagnostisk forløb i almen praksis. Formålet med dette studie var at undersøge antallet af konsultationer, hæmoglobinmålinger (Hb målinger) og medicinudskrivelser for hæmorider i almen praksis i året op til en diagnose for tarmkræft (CRC).
**Metode:** Vi udførte et populations-baseret matchet kohortestudie med 19 209 CRC patienter i alderen 40-80 år diagnosticeret fra 2004-2010. For hver patient matchede vi 10 referencer på alder, køn og almen praksis.
**Resultater:** CRC patienter havde signifikant flere konsultationer fra 9 måneder før diagnosen og signifikant flere Hb målinger fra 17 måneder før diagnosen sammenlignet med reference personerne. Op til 18 måneder før diagnosen havde CRC patienter signifikant højere antal af medicinudskrivelser for hæmorider og 2 måneder før diagnosen var incidensrate-ratioen (IRR) for mænd =12.24 (95% sikkerhedsinterval (CI): 10.29-14.55). Den positive prædiktive værdi (PPV) for at have en underliggende CRC, hvis man fik en førstegangs udskrivelse på hæmoridemedicin i løbet af et halvt år op til diagnosen, var højest blandt 70-80 årige mænd (PPV=3.2% (95% CI: 2.8-3.7)). Patienter med endetarmskræft havde generelt mange udskrivelser på hæmoridemidler, mens patienter med en proksimalt lokaliseret tarmkræft havde mange konsultationer og Hb målinger sammenlignet med referencer.
**Konklusion:** Der er en øget diagnostisk aktivitet i almen praksis i året op til CRC diagnose, hvilket antyder en mulighed for at stille tarmkræft diagnosen på et tidligere tidspunkt.

## Introduction

CRC is the third most common cancer in the world with an increasing age-standardised incidence which entails a growing load on the healthcare systems. An earlier diagnosis of CRC is a major focus worldwide as it may yield a more favourable stage distribution at diagnosis and hence improve survival [1, 2]. In many countries, including Denmark, fast-track referrals for suspected CRC patients have been established [3] including national CRC screening programmes using the immunochemical faecal occult blood test (iFOBT). Nevertheless, considering the sensitivity of the iFOBT and the expected participation rate in the screening programme, about 75% of CRC patients will still be detected by symptomatic presentation in general practice [4, 5].

In Denmark, the general practitioner (GP) serves as a gatekeeper who refers patients suspected of cancer for further diagnostic investigation. As the symptoms of CRC are often non-specific and mimic other frequent symptoms seen in general practice, the GP is challenged to discriminate between malignant and benign disease [6-8]. Furthermore, only about 50% of CRC patients present with alarm symptoms [9, 10] such as rectal bleeding, anaemia and change in bowel habits and the positive predictive value (PPV) of these symptoms is often low [11-15].

To achieve an earlier diagnosis of CRC, knowledge is needed regarding the patients' health-seeking behaviour and activities in general practice prior to diagnosis. This could complement the symptom appraisal and help GPs to decide which patients to refer for further diagnostic work-up. In general, cancer patients tend to be seen more often in general practice before their diagnosis [16], but it is unknown how this applies to CRC patients and whether diagnostic activity in general practice is increased prior to cancer diagnosis.

We aimed to investigate the rate of daytime face-to-face consultations, Hb measurements and prescriptions of medicine for haemorrhoids in general practice among CRC patients compared with a reference group 12 months prior to diagnosis. Furthermore, we aimed to investigate whether this diagnostic activity differed between patients with rectal cancer, distal and proximal colon cancer.

## Method

*Study design and study population*

We performed a population-based matched comparative study using historical registry data. Information was collected from nationwide registries linked at the individual level using the unique civil registration number assigned to all Danish citizens at birth [17].

The cases were Danish cancer patients diagnosed with a primary colon cancer (ICD-10 code: C18-C19) or rectal cancer (ICD-10 code: C20) from 1 January 2004 to 31 December 2010 aged 40-80 years at diagnosis (n = 23 544). Patients were identified in the Danish Cancer Registry, which holds information on the date of diagnosis and tumour characteristics [18]. Patients were excluded if they had a previous diagnosis of any cancer except for non-melanoma skin cancer (n = 3623), if they had an incorrect civil registration number (n = 107), had lived outside Denmark at some point during the 12 months preceding diagnosis (n = 151), or were not listed with a general practice (n = 454). A total of 19 209 cases were eligible.

Using incidence density sampling, ten references were selected matched on age, gender and general practice. The index date was defined as the date of the cancer diagnosis of the corresponding case. Persons were not eligible as references if they were registered with any cancer diagnosis except for non-melanoma skin cancer in the Danish Cancer Registry before the index date and until two years after, or if they had been living outside Denmark at some point during the 12 months leading up to the index date. We were able to match 182 930 references (95.2%) with a maximum one-year age difference to the case and 190 596 (99.2%) references with a maximum age difference of two years. It was not possible to match 1494 references (0.8%) within a two-year age interval to a case in the same general practice. For these cases, references from other practices were matched within a two-year age interval. A total of 192 090 references were included.

Information about general practice affiliation was available from the Patient List Register, which is an administrative database that contains information on which general practice each person is registered with at any given time.

*Outcome variables*

The main outcomes of the study were rates of daytime face-to-face consultations incl. home visits, point-of-care Hb measurements using photometry, and prescriptions of haemorrhoid medication issued by a general practitioner in the year preceding diagnosis. These measures were chosen as proxies for symptoms and signs that could be caused by an underlying CRC. Data regarding consultations and Hb measurements in general practice were extracted from the Danish National Health Service Register [(19)], which holds information on all contacts and services provided by general practice for the purpose of remuneration. For analysis where rates differed between cases and references for all 12 months prior to diagnosis, the study period was extended by a year to comprise a total of 24 months. Information on medicine prescriptions was collected from The Danish National Prescription Registry[(20)], and included all redeemed medicine prescriptions for haemorrhoids (ATC: C05AA01, C05AA08, C05AE01) prescribed for each individual by a GP. The medicaments are all available by prescription only.

*Characteristics of the study population*

Demographic and socioeconomic information was collected from Statistics Denmark. This included country of origin categorised into "Danish", "Immigrant/descendant from a Western country" and "Immigrant/descendant from a non-Western country" (Table 1). Marital status was categorised into "Living alone" or "Married/cohabitating" including couples regardless of their civil status. Data on taxable income was extracted for the calendar year preceding the index date to eliminate the risk of any influence from the CRC diagnosis on income. Income was categorised into three groups using the OECD-modified scale: the lowest 20% "Low", the middle 50% "Middle" and the highest 30% "High" [(21)]. The highest attained level of education was categorised into "Basic", "Short", "Long" and "Unknown" according to the International Standard Classification of Education [(22)]. Labour market affiliation based on the main employment during the preceding 12 months was categorised into "Working", "Unemployed", "Retirement pension" and "Other" including social welfare recipients. The Charlson Comorbidity Index (CCI) was used to account for comorbidity [(23)]. A CCI score was calculated on the basis of diagnoses registered in The Danish National Patient

Register [24] in the ten-year-period preceding study entry. Only nine years of data were available for persons with an index date in 2004. We computed the total CCI score for each patient and grouped levels of comorbidity into "Low" (CCI score = 0), "Moderate" (CCI score = 1-2) and "Severe" (CCI score ≥ 3).

The study was approved by the Danish Data Protection Agency (J. no. 2008-41-2956).

*Statistical analysis*

Odds ratios (ORs) of having a consultation, Hb measurement or a medicine prescription for haemorrhoids were calculated using a conditional logistical regression model to account for the matched design. A negative binomial regression model applying cluster robust variance at the patient level was used to calculate incidence rate ratios (IRRs) for comparison of the monthly rates of consultations, Hb measurements and medicine prescriptions between cases and references. The PPV of CRC for a first-time prescription six months before the index date was estimated on the basis of Bayes' theorem using the STATA programme "diagt" [25]. For the PPV calculations we only included patients and references who had consulted their GP in the six months period as only these persons were in risk of having a prescription in general practice on the basis of a face-to-face contact. From the NORDCAN database [26] we gathered national incidence rates which were stratified by age, sex and tumour type and multiplied with an age and gender specific ratio of the consulting population. A prescription was defined as a first-time prescription if no similar prescription was observed in the previous 12 months.

Analyses were performed for each gender separately because differences exist in the use of general practice among men and women [27, 28]. Furthermore, analyses on rates were stratified on type of tumour by dividing the CRC patients into patients with rectal cancer (ICD code: C20.9), patients with distal colon cancer (C18.5-C18.7, C19.9) and patients with proximal colon cancer (C18.0-C18.4). Patients diagnosed with a CRC localised at multiple sites or without specification were not included in the tumour-specific analyses. All analyses except PPV calculations were adjusted for socioeconomic and demographic variables, age and comorbidity. Data were analysed using the statistical software Stata 13.0 (StataCorp LP, TX, USA).

**Results**

The study included a total of 19 209 incident colorectal cancer patients and 192 090 references from a total of 2424 general practices. Among the CRC patients, 36.5% had a rectal cancer (n = 7007) and 63.5% had a colon cancer (n = 12 202) of whom 49.2% had a distal colon cancer (n = 6006), 42.8% a proximal colon cancer (n = 5217); and 8.0% of the colon cancers were registered without a specific localisation or at multiple sites in the colon (n = 979). The cases and references were comparable regarding socio-demographic variables and comorbidity (Table 2). The mean age at the index date was 66.6 years for women and 66.5 years for men.

*CRC patients vs. references*

During the year preceding diagnosis 98% of the female CRC patients and 97.4% of the male patients had a consultation in general practice and the odds for having more than five consultations were higher among CRC patients compared to references (Table 3). From nine months prior to diagnosis the CRC patients had significantly higher rates of consultations and the consultation rate rose consistently with a peak in the last month prior to diagnosis (IRR=3.20, 95%CI (3.12-3.28) among males) (Figure 1).

A total of 38.6% female patients and 35.6% male patients had a Hb measurement in the year preceding diagnosis and the odds of having several Hb measurements were higher among the patients (OR=3.96 (3.68-4.27) for females) (Table 3). Female CRC patients had significantly higher rates of Hb measurements compared to references in all 12 months prior to diagnosis (Figure 2) and an inclusion of an additional year revealed significantly increased rates from 17 months before diagnosis (data not shown). During the last six months prior to diagnosis, the rates of Hb measurements increased resulting in an IRR=8.27 (7.76-8.81) for male patients in the month before diagnosis (Figure 2).

In the year preceding diagnosis 11.4% of female patients and 10.0% of male patients had a medicine prescription for haemorrhoids and the odds of having one or more medicine prescriptions were higher among CRC patients than references (Table 3). Female CRC patients had

significantly higher prescription rates from 18 months before diagnosis and male patients from 15 months before diagnosis. The highest prescription rate was two months before diagnosis with an IRR=9.53 (8.03-11.32) for female patients and IRR=12.24 (10.29-14.55) for male patients (Figure 3).

In total, 7.3% of the CRC patients had a first-time prescription of medicine for haemorrhoids within the last six months. The PPVs for CRC when having a first-time medicine prescription for haemorrhoids in the six months prior to diagnosis differed according to age and gender. The highest PPV for CRC when having a first-time medicine prescription for haemorrhoids was seen for men aged 70-80 years (PPV 3.2% (2.8-3.7)), whereas the PPVs of the women were slightly lower than those for men in all age groups (Table 4).

*Colon cancer patients vs. rectal cancer patients*

The timing of the increase in rates of consultations, Hb measurements and medicine prescriptions differed between patients with various tumour types. Overall, patients with a proximal colon cancer had long time intervals with increased rates of consultations and Hb measurements compared to references (Figure 4-5). Female patients with a proximal colon cancer had significantly higher consultation rates during all 24 months compared with references (data not shown). In contrary to this, female patients with distal colon cancer or rectal cancer had higher consultation rates from seven and four months before diagnosis, respectively (Figure 4). Male patients with a proximal colon cancer had significantly higher Hb measurement rates from 21 months before diagnosis compared to references (data not shown), whereas patients with a distal colon cancer or rectal cancer had higher rates from five months before diagnosis (Figure 5).

Rectal cancer patients had long intervals with higher prescription rates than references. Female rectal cancer patients had significantly higher prescription rates than references from 19 months before diagnosis, whereas corresponding figures for distal colon cancer patients were significantly increased from nine months before diagnosis and four months before for proximal colon cancer patients (Figure 6)

## Discussion

CRC patients consulted their GP significantly more than a reference group from ten months prior to diagnosis. Up to 18 months before diagnosis, CRC patients had more Hb measurements performed than their references and two months before, prescription rates for haemorrhoids were up to 12 times higher for CRC patients compared to references. The activity pattern in general practice prior to diagnosis differed according to the localisation of the tumour. The more distally a tumour was situated in the colon, the longer intervals with higher rates of prescription for haemorrhoids were seen among the patients. In contrast, patients with more proximally situated tumours had longer intervals with increased rates of consultations and Hb measurements than the references.

### *Strengths and limitations*

This population-based study achieved a high statistical precision owing to the large study population.

All data were collected from nationwide Danish registries, which are considered to have a high quality [17-20, 24]. Cancer patients were included from The Danish Cancer Registry, which is known to have an almost complete registration of cancers diagnosed in Denmark [18]. Furthermore, the information on healthcare services provided in general practice is considered valid because the registration of these services forms the basis of fee-for-service remuneration of the GPs [19]. Additionally, the medicine included is only available on prescription, which eliminates the risk of bias due to over-the-counter sale. Overall, as data were not collected for the purpose of the present study and were independent of the memory of the GP and the enrolees, selection bias and information bias in relation to diagnosis and healthcare services were negligible.

By matching references and CRC patients according to gender, age and general practice, we diminished confounding by these factors. Moreover, cases and references were comparable regarding socioeconomic and demographic factors, which also minimised any potential bias. Despite this, the results might have been influenced by residual confounding such as comorbidity

because the CCI does not include diseases only managed in general practice. Persons with a diagnosis of hereditary non-polyposis colorectal cancer, familial adenomatous polyposis or inflammatory bowel disease, such as ulcerative colitis and Crohn's disease, were not excluded which potentially could have influenced our results, but exclusion of these patients from our analyses did not alter the results. We restricted the CRC population to first-time cancers only to avoid the influence of an increased alertness of the GP among patients with a former history of cancer.

A limitation of this study was the lack of information on the reasons for and the contents of the consultations with the GPs. Furthermore, the indications for the Hb measurements and the actual test results were not available. Some general practices may only use hospital laboratories for Hb measurements, and thus we may have underestimated the actual use of Hb measurements in general practice.

The results of this nationwide study are considered generalisable to other countries with healthcare systems in which GPs serve as the first point of contact or as gatekeepers.

*Comparison with other studies*

Our finding of an increased consultation frequency in general practice prior to CRC diagnosis is consistent with the study by Christensen et al., which showed increasing consultation rates prior to cancer diagnosis for all types of cancer [16]. Furthermore, we were able to demonstrate an increased clinical activity even before the consultation rates rose, which - to our knowledge - has not been shown before. This may reflect that GPs observe signs indicating disease and begin the diagnostic work-up even before changes in patients' health seeking behaviour. As previously stated by Hamilton, this innate sense of the GP to react on "red flags" seems important in cancer diagnostics [5].

The increased use of Hb measurements and medicine prescriptions before diagnosis corroborates the findings of previous studies on symptom presentation [7, 14, 15, 29-31] as Hb measurements and prescriptions for haemorrhoids can be interpreted as proxies for anaemia and rectal bleeding;

symptoms qualifying for referral to diagnostic fast-tracks for CRC. The long interval with increased rates of Hb measurements is consistent with the study by Singh et al. which found that anaemia was an important missed clue in CRC diagnostics and which reported a median interval of 393 days from the detection of anaemia to endoscopic referral [32].

The PPVs for CRC in our study when prescribing medicine for haemorrhoids are comparable with the PPVs on rectal bleeding found in recent studies using data from general practices. Jones et al. found that the PPV of rectal bleeding six months before a diagnosis of CRC was 1.8% (1.5-2.2)[15], whereas Hamilton et al. found a PPV of approximately 3.5% for men aged 70-79 years[11]. These figures are comparable with the results of this study as we found a PPV of 3.2% (2.8-3.7) for having a first-time prescription for haemorrhoids six months prior to diagnosis for men aged 70-79 years. We do not know whether this indicates lack of attention to CRC when patients present with symptoms associated with haemorrhoids. However, the high proportion of CRC patients receiving treatment with medicine for haemorrhoids calls for further investigation. As rectal bleeding is an alarm symptom which, according to guidelines, should trigger further diagnostic workup through a colonoscopy; the results of this study question whether a first-time prescription for haemorrhoids should also be followed by a referral to colonoscopy, especially in certain older age groups.

Lyratzopoulos et al. found that colon cancer patients had an increased risk of three or more consultations prior to diagnosis compared with rectal cancer patients [33]. This coincides well with the findings of the present study where colon cancer patients had higher consultation rates compared to references for a more extensive period than rectal cancer patients. Conversely, rectal cancer patients had an increased prescription rate for haemorrhoids that was several months longer than that of colon cancer patients which indicates some diagnostic activity among rectal cancer patients as well.

Our results reflect the clinical aspects of the two diseases with colon cancer patients presenting with uncharacteristic symptoms such as fatigue, whereas rectal cancer patients more frequently report rectal bleeding. Furthermore, we also recognised a difference between patients with proximal and distal colon cancer which support the conception of CRC as different diseases where symptomatic presentation varies substantially.

## Conclusion

In this population-based study, we found an increased use of general practice several months before CRC diagnosis, which indicates an increase in healthcare seeking among CRC patients and the opportunity of an earlier diagnosis of CRC. We also revealed an increased clinical activity in general practice for these patients in the year prior to their diagnosis, which indicates that GPs recognise signs and symptoms and that a 'diagnostic time window' for earlier diagnosis exists. Furthermore, the early increase in the use of medicine for haemorrhoids prior to CRC diagnosis highlights the importance of ruling out CRC as a possible diagnosis when patients present with symptoms qualifying for a prescription of medicine for haemorrhoids. Future studies should focus on the contents of the consultations prior to diagnosis and the indications for initiation of diagnostic investigations in general practice. Furthermore, knowledge on the association between tumour stage and activity prior to diagnosis is needed.

**Table 1:** *Categorisation and definition of the sociodemographic and economic indicators*

| Demographic and socioeconomic indicators | Categorisation | Definition |
|---|---|---|
| **Age** | 40-53 | The age at date of diagnosis for the cancer patients and the age at index date for the references. |
| | 54-67 | |
| | 68-80 | |
| **Country of origin** | Danish | Western countries defined as: Nordic countries, European Union countries, Andorra, Liechtenstein, Monaco, San Marino, Switzerland, the Vatican State, Canada, USA, Australia, New Zealand. An immigrant is born outside Denmark and a descendant is born in Denmark with none of the parents being Danish citizens nor born in Denmark. |
| | Immigrant/descendant from Western Country | |
| | Immigrant/descendant from non-Western Country | |
| **Marital status** | Married/cohabitating | Married/cohabitating includes married couples, registered partnership, cohabitants with min. 1 shared child and cohabitant couples with a max. age difference on 15 years. |
| | Living alone | |
| **Education** | | Highest attained education categorised according to the International Standard Classification of Education |
| | Basic | - Primary and lower secondary, 0-10 years of education |
| | Short | - Upper secondary and post-secondary non-tertiary, 11-15 years. |
| | Long | - Tertiary and advanced research programmes, >15 years |
| | Unknown | - Missing information on 2.1% of the participants of whom 71% were on retirement pension. |
| **Labour market affiliation** | | Based on the main employment during the preceding 12 months |
| | Working | - self-employed, salary earner |
| | Unemployed | - unemployed, unemployment benefit claimant, undergoing education, trainee |
| | Retirement pension | - pensioner, voluntarily retired person receiving a special pension |
| | Other | - recipient of cash benefits, other persons receiving special claimants |

| | | |
|---|---|---|
| **Income** | | Taxable income during the year preceding the year of the index date |
| | Lowest 20% | - Annual income < 123.570,7 kr |
| | Middle 50% | - Annual income from 123.570,7 kr to 217.044,7 kr |
| | Highest 30% | - Annual income > 217.044,7 kr |
| **Charlson Comorbidity Index Score** | 0 - Low | CCI calculated using the Quan version of the CCI score based on the registration of ICD-codes on 17 disease categorisations in the ten year period preceding study entry. |
| | 1-2 - Moderate | |
| | ≥3 - Severe | |

**Table 2.** *Characteristics of the 19 209 patients diagnosed with colorectal cancer (CRC) and the 192 090 matched references*

| | Women | | | | Men | | | |
|---|---|---|---|---|---|---|---|---|
| | References | | CRC patients | | References | | CRC patients | |
| | n | % | n | % | n | % | n | % |
| **Total** | 83 730 | | 8373 | | 108 360 | | 10 836 | |
| **Age*** | | | | | | | | |
| 40-53 | 8791 | 10.5 | 877 | 10.5 | 10 014 | 9.2 | 1002 | 9.3 |
| 54-67 | 32 015 | 38.2 | 3192 | 38.1 | 44 417 | 41.0 | 4439 | 41.0 |
| 68-80 | 42 924 | 51.3 | 4304 | 51.4 | 53 929 | 49.8 | 5395 | 49.8 |
| **Country of origin** | | | | | | | | |
| Danish | 79 599 | 95.1 | 8095 | 96.7 | 103 214 | 95.3 | 10 447 | 96.4 |
| Immigrant/descendant Western country | 2337 | 2.8 | 178 | 2.1 | 2472 | 2.3 | 227 | 2.1 |
| Immigrant/descendant non-Western country | 1793 | 2.1 | 100 | 1.2 | 2674 | 2.5 | 162 | 1.5 |
| **Marital status** | | | | | | | | |
| Married/cohabitating | 49 287 | 58.9 | 4893 | 58.4 | 80 496 | 74.3 | 8024 | 74.1 |
| Living alone | 34 443 | 41.1 | 3480 | 41.6 | 27 864 | 25.7 | 2812 | 26.0 |
| **Education**** | | | | | | | | |
| Basic | 41 286 | 49.3 | 4125 | 49.3 | 39 163 | 36.1 | 3933 | 36.3 |
| Short | 28 659 | 34.2 | 2961 | 35.4 | 50 720 | 46.8 | 5184 | 47.8 |
| Long | 12 117 | 14.5 | 1162 | 13.9 | 15 956 | 14.7 | 1497 | 13.8 |
| Unknown | 1668 | 2.0 | 125 | 1.5 | 2521 | 2.3 | 222 | 2.1 |
| **Labour market affiliation** | | | | | | | | |
| Working | 22 012 | 26.3 | 2285 | 27.3 | 35 831 | 33.1 | 3564 | 32.9 |
| Unemployed | 1326 | 1.6 | 127 | 1.5 | 1635 | 1.5 | 171 | 1.6 |
| Retirement pension | 58 949 | 70.4 | 5838 | 69.7 | 69 827 | 64.4 | 7017 | 64.8 |
| Other | 1443 | 1.7 | 123 | 1.5 | 1067 | 1.0 | 83 | 0.8 |
| **Income** | | | | | | | | |
| Low | 18 583 | 22.2 | 1772 | 21.2 | 19 984 | 18.4 | 1921 | 17.7 |
| Middle | 42 567 | 50.8 | 4300 | 51.4 | 53 299 | 49.2 | 5484 | 50.6 |
| High | 22 580 | 27.0 | 2301 | 27.5 | 35 077 | 32.4 | 3431 | 31.7 |
| **Charlson Comorbidity Index score** | | | | | | | | |
| 0 - Low | 66 218 | 79.1 | 6635 | 79.2 | 80 518 | 74.3 | 7949 | 73.4 |
| 1-2 - Moderate | 15 066 | 18.0 | 1472 | 17.6 | 22 702 | 21.0 | 2306 | 21.3 |
| ≥3 - Severe | 2446 | 2.9 | 266 | 3.2 | 514 | 4.7 | 581 | 5.4 |

* Age: Due to the sampling method, the age-group "40-53 years" includes references aged 39 years and the age-group "68-80 years" includes references aged 82 years.

**Education is defined according to the International Standard Classification of Education(22).

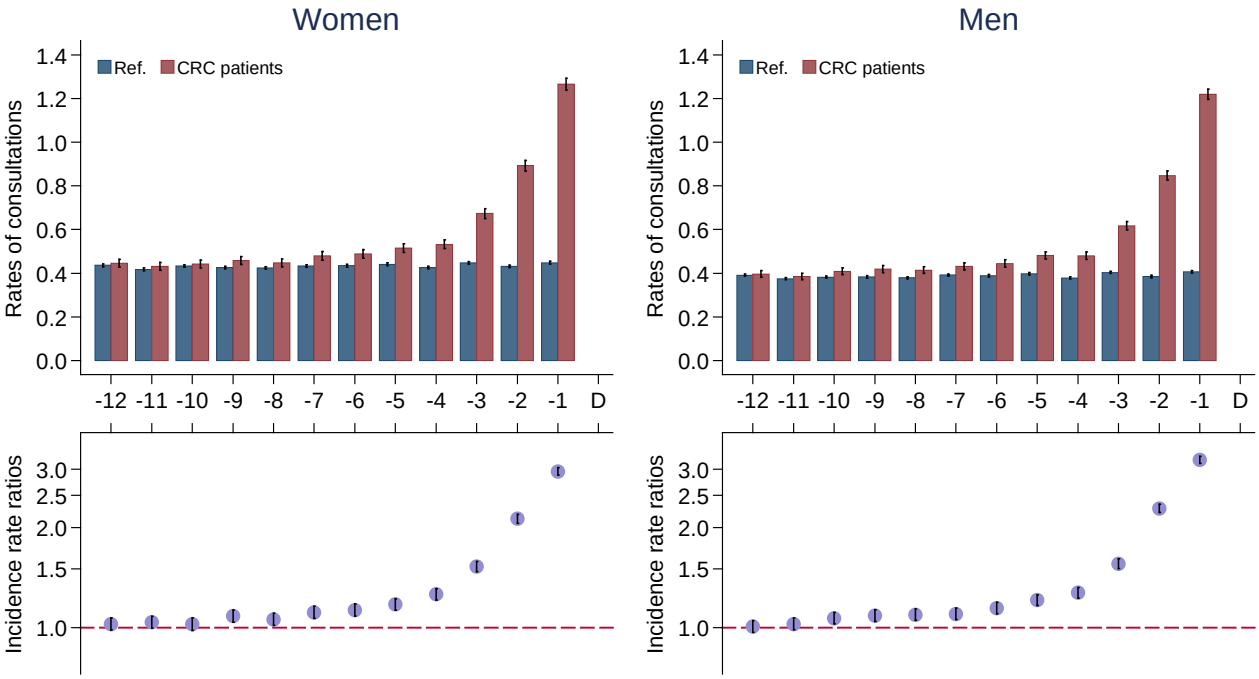
**Table 3.** *Proportions of persons with face-to-face consultations, point-of-care Hb measurements and prescriptions of medicine for haemorrhoids during the 12 months prior to the index date. Adjusted* analyses comparing the activity between cases and references*

| | Women | | | | | Men | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Consultations** | **CRC patients** | | **References** | | **OR (95% CI)*** | **CRC patients** | | **References** | | **OR (95% CI)*** |
| **0** | 167 | 2.0% | 11 093 | 13.3% | 0.13 (0.11-0.15) | 277 | 2.6% | 19 941 | 18.4% | 0.11 (0.10-0.12) |
| **1-4** | 3047 | 36.4% | 36 183 | 43.2% | 0.74 (0.70-0.77) | 4556 | 42.0% | 48 067 | 44.4% | 0.91 (0.87-0.95) |
| **5-8** | 2723 | 32.5% | 20 747 | 24.8% | 1.48 (1.41-1.55) | 3333 | 30.7% | 23 008 | 21.2% | 1.67 (1.59-1.74) |
| **≥ 9** | 2436 | 29.1% | 15 707 | 18.8% | 1.89 (1.80-2.00) | 2670 | 24.7% | 17 344 | 16.0% | 1.83 (1.74-1.92) |
| **Hb measurements** | | | | | | | | | | |
| **0** | 5143 | 61.4% | 68 315 | 81.6% | 0.25 (0.23-0.26) | 6975 | 64.4% | 90 920 | 83.9% | 0.23 (0.22-0.25) |
| **1** | 1841 | 22.0% | 10 177 | 12.2% | 2.23 (2.10-2.37) | 2358 | 21.8% | 11 750 | 10.8% | 2.60 (2.47-2.75) |
| **≥2** | 1389 | 16.6% | 5238 | 6.3% | 3.96 (3.68-4.27) | 1503 | 13,9% | 5690 | 5.3% | 3.68 (3.44-3.95) |
| **Prescriptions** | | | | | | | | | | |
| **0** | 7421 | 88.6% | 81 106 | 96.9% | 0.25 (0.23-0.27) | 9757 | 90.0% | 105 645 | 97.5% | 0.23 (0.21-0.25) |
| **1** | 630 | 7.5% | 1939 | 2.3% | 3.44 (3.14-3.78) | 726 | 6.7% | 2018 | 1.9% | 3.80 (3.48-4.13) |
| **≥2** | 322 | 3.9% | 685 | 0.8% | 5.01 (4.37-5.75) | 353 | 3.3% | 697 | 0.6% | 5.32 (4.66-6.06) |

**Abbreviations: OR = odds ratio; CI = confidence interval**

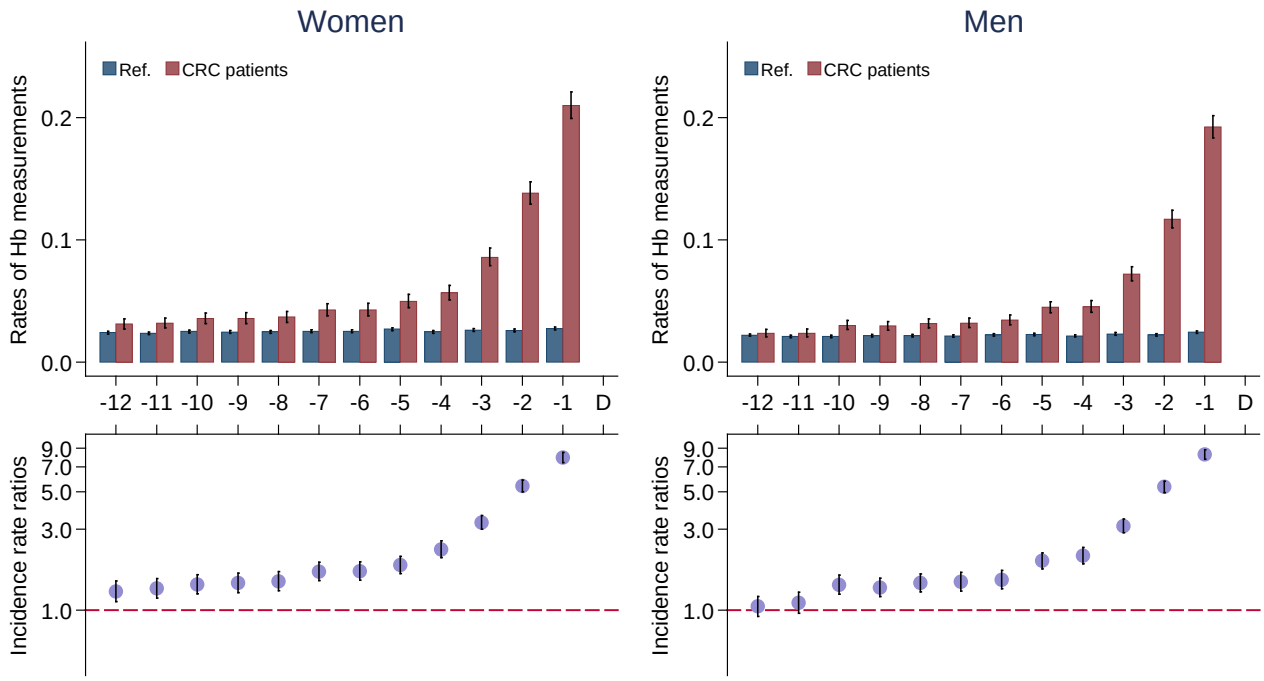
***** ORs adjusted for age, country of origin, marital status, education, labour market affiliation, income and comorbidity according to the Charlson Comorbidity Index.

**Figure 1.** ***Daytime face-to-face consultations in general practice.*** *Upper part: Rates of consultations (mean consultations per month) in general practice for CRC patients and references 12 months prior to diagnosis/index date. Lower part: The incidence rate ratios (IRR) for consultations with 95% confidence intervals*



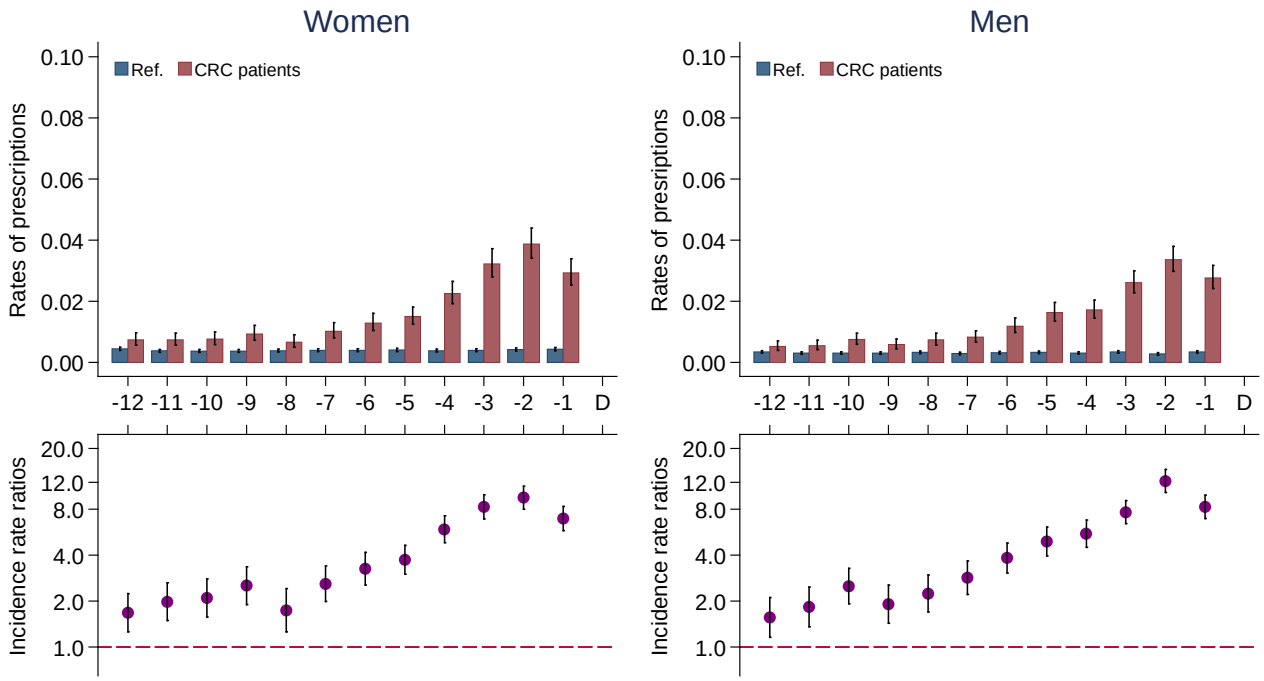

**Note**: The IRRs with 95% confidence intervals are adjusted for age, country of origin, marital status, education, labour market affiliation, income and comorbidity according to the Charlson Comorbidity Index.

**Figure 2.** ***Point of care Hb measurements (photometry) in general practice.*** *Upper part: Rates of Hb measurements (mean Hb measurements per month) in general practice for CRC patients and references 12 months prior to diagnosis/index date. Lower part: The incidence rate ratios (IRR) for Hb measurements with 95% confidence intervals*




**Note**: The IRRs with 95% confidence intervals are adjusted for age, country of origin, marital status, education, labour market affiliation, income and comorbidity according to the Charlson Comorbidity Index.

**Figure 3.** ***Prescriptions of medicine for haemorrhoids in general practice.*** *Upper part: Rates of prescriptions (mean prescriptions per month) in general practice for CRC patients and references 12 months prior to diagnosis/index date. Lower part: The incidence rate ratios (IRR) for prescriptions with 95% confidence intervals*

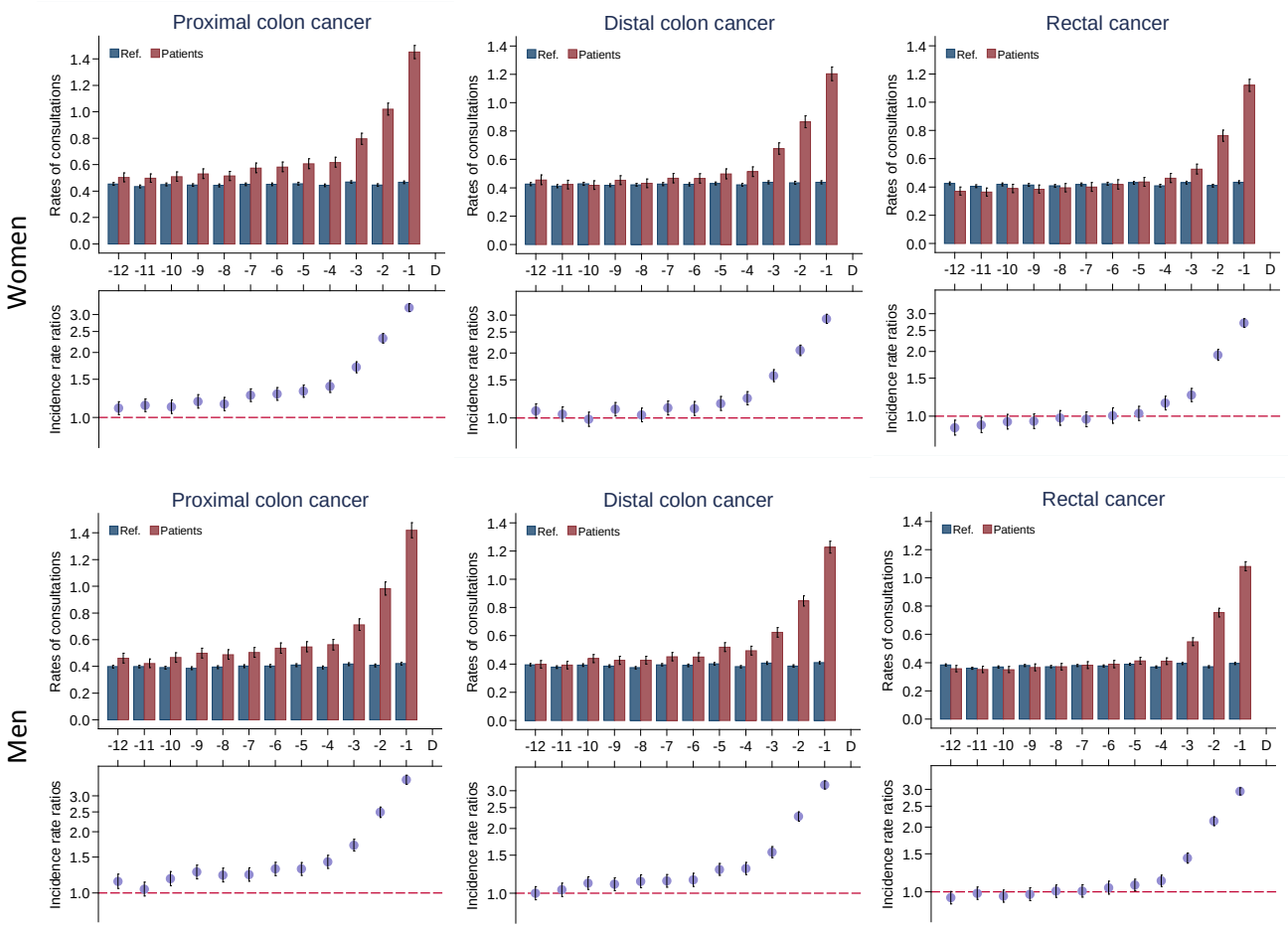



**Note:** The IRRs with 95% confidence intervals are adjusted for age, country of origin, marital status, education, labour market affiliation, income and comorbidity according to the Charlson Comorbidity Index.

**Table 4.** *Positive predictive values (PPVs) for CRC of having a first-time prescription of medicine for haemorrhoids in the six months prior to CRC diagnosis with 95% confidence intervals (95% CI)*

| | Women | Men |
|---|---|---|
| **Age** | **PPV (95% CI)** | **PPV (95% CI)** |
| 40-49 | 0.2 (0.1-0.2) | 0.2 (0.2-0.4) |
| 50-59 | 0.6 (0.5-0.7) | 0.9 (0.7-1.1) |
| 60-69 | 1.1 (0.9-1.3) | 1.7 (1.5-2.0) |
| 70-79 | 2.0 (1.7-2.3) | 3.2 (2.8-3.7) |

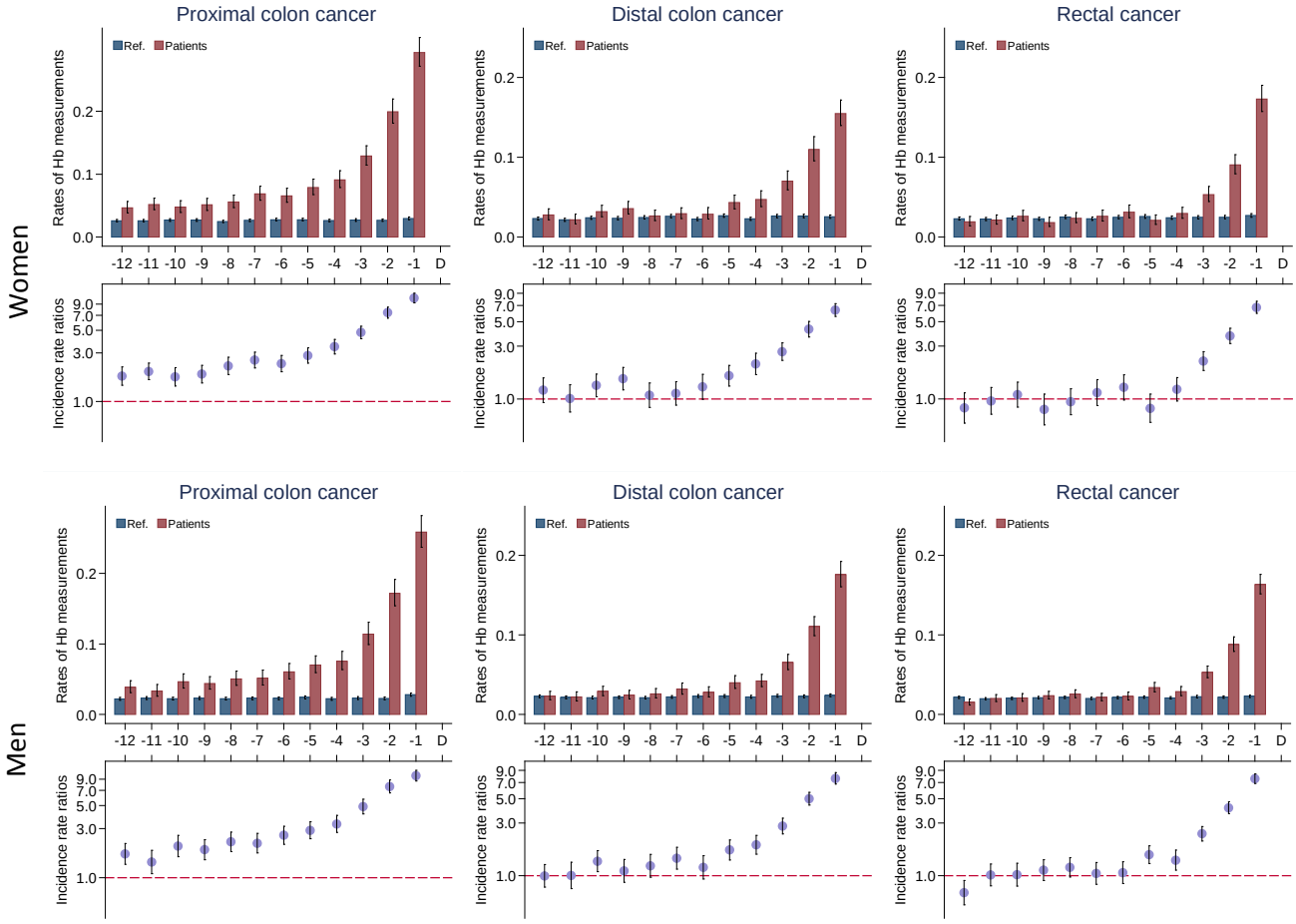
**Figure 4.** ***Daytime face-to-face consultations in general practice according to tumour type.*** *Upper part: Rates of consultations (mean consultations per month) in general practice for CRC patients according to tumour type and references 12 months prior to diagnosis/index date. Lower part: The incidence rate ratios (IRR) for consultations with 95% confidence intervals (95% CI)*




**Note**: The IRRs with 95% confidence intervals are adjusted for age, country of origin, marital status, education, labour market affiliation, income and comorbidity according to the Charlson Comorbidity Index.

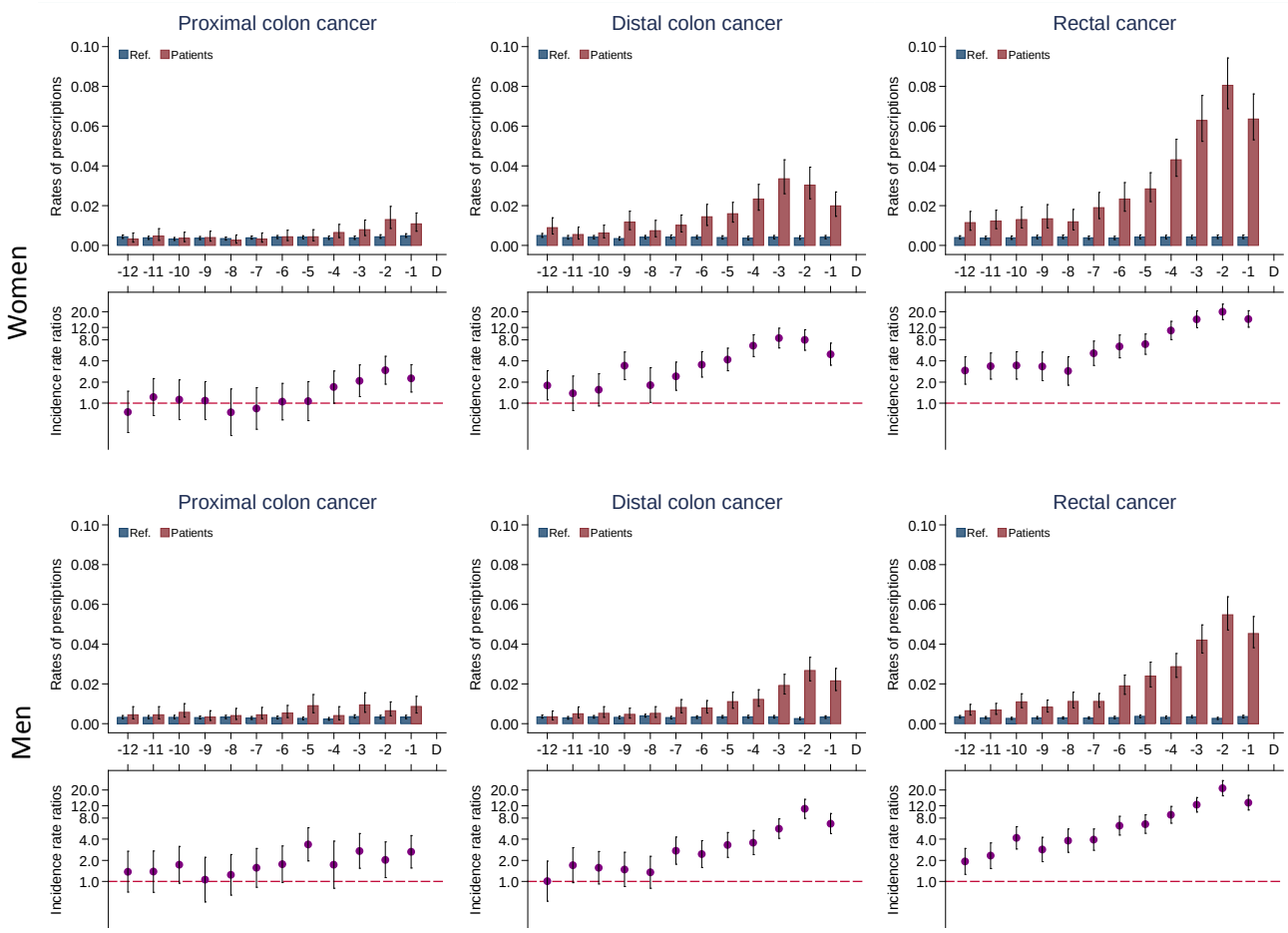
**Figure 5.** ***Point of care Hb measurements (photometry) in general practice according to tumour type.***

*Upper part: Rates of Hb measurements (mean Hb measurements per month) in general practice for CRC patients according to tumour type and references 12 months prior to diagnosis/index date. Lower part: The incidence rate ratios (IRR) for Hb measurements with 95% confidence intervals*




**Note:** The IRRs with 95% confidence intervals are adjusted for age, country of origin, marital status, education, labour market affiliation, income and comorbidity according to the Charlson Comorbidity Index.

**Figure 6.** ***Prescriptions of medicine for haemorrhoids in general practice according to tumour type.*** *Upper part: Rates of prescriptions (mean prescriptions per month) in general practice for CRC patients according to tumour type and references 12 months prior to diagnosis/index date. Lower part: The incidence rate ratios (IRR) for prescriptions with 95% confidence intervals*



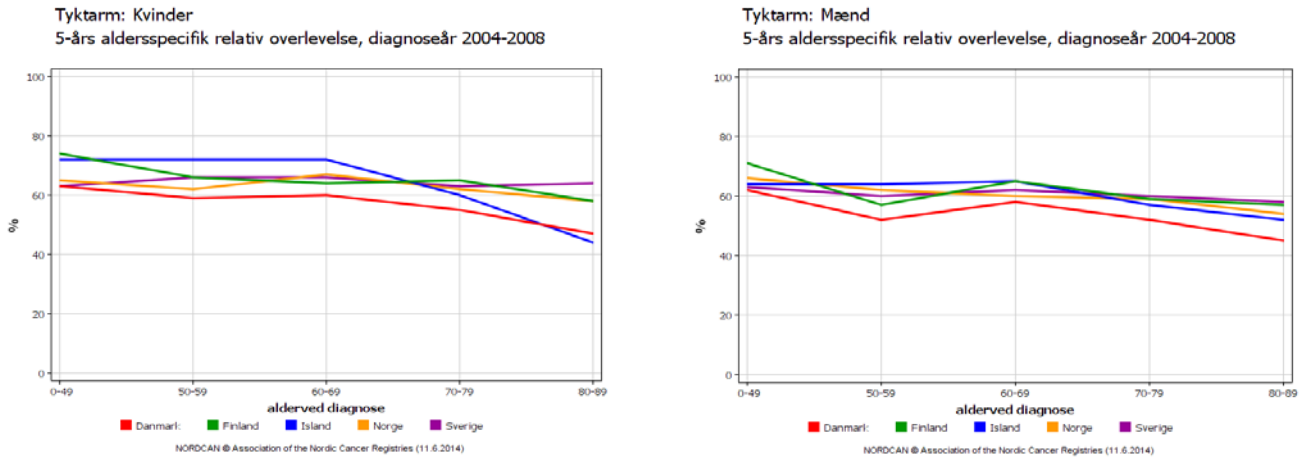

**Note:** IRR with 95% CI are adjusted for age, country of origin, marital status, education, labour market affiliation, income and comorbidity according to the Charlson Comorbidity Index.

# Supplementary Information

**Background**

Colorectal cancer (CRC) is the third most common cancer in Denmark with approximately 4400 new diagnoses every year and an increasing incidence. The prognosis of CRC is severe with a five year-relative survival on 54-57 % [26]. This is 6-8 percentage points lower than in the other Nordic countries (Figure 7) which is partly due to a more advanced tumour stage at diagnosis among Danish patients [34, 35].

Figure 7. The five year age-specific relative survival among female and male CRC patients [26]

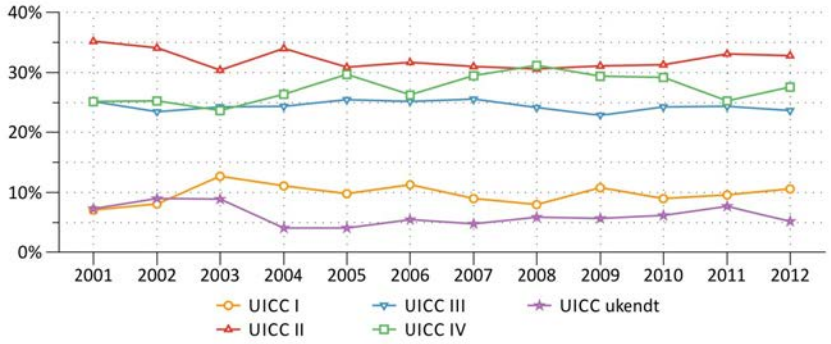



CRC is typically categorized into one of four tumour stages at time of diagnosis (UICC stage I-IV) with 25% of the patients being diagnosed with distant metastasis (stage IV) and 23% being diagnosed with lymph node metastasis (stage III)[36]. The distribution of the tumour stages has not changed substantially the past ten years (Figure 8). As mortality from CRC is highly dependent on tumour stage at diagnosis, an earlier diagnosis of CRC is crucial in the pursuit of lowering stage of disease at time of diagnosis and hence reducing mortality.

Earlier diagnosis will not only have an impact on survival but also limit the patient related consequences of CRC regarding physical, mental and economical aspects. Furthermore, the increasing incidence of CRC and the ageing population accentuate the overall treatment costs of

CRC involving surgical, adjuvant and palliative treatment, for which reason an earlier diagnosis is also desirable from a welfare economic viewpoint.

Figure 8. The distribution of tumour stages among Danish colon cancer patients [36]



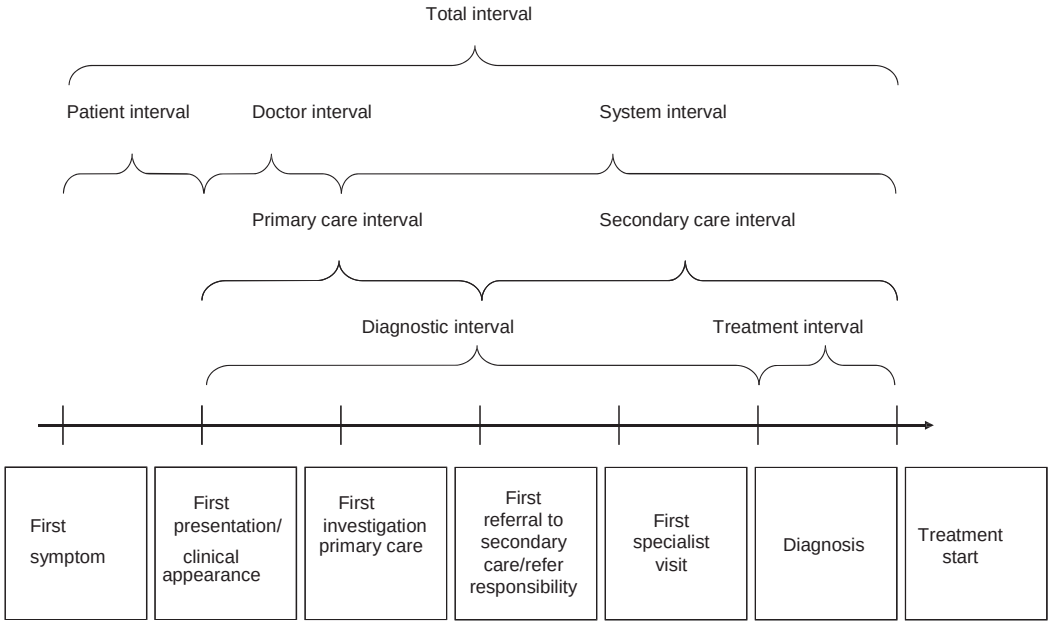

*Diagnosis of colorectal cancer*

In March 2014 a Danish national screening program for CRC was initiated to diagnose CRC at an earlier tumour stage. The screening method includes an iFOBT test, a type of fecal occult blood test which uses an immunohistochemical reaction to check for the presence of non-visible blood in the stool. It is estimated that only up to 25% of CRC patients will be diagnosed by the screening program because of the sensitivity of the test (60%), the limited included patient population (people aged 50-74 years) , and the estimated participation rate (40%)[4, 5]. Therefore, still 75% of CRC patients have to be diagnosed on the basis of symptomatic presentation and most often in general practice [37].

In Denmark, as in the UK and other Nordic countries, general practice provides first-line medical advice and the general practitioner (GP) serves as a gatekeeper deciding whether to refer patients suspected of cancer for further diagnostic work-up [38]. Due to the often vague symptoms of CRC, the disease can be difficult to diagnose. Symptoms as rectal bleeding and anaemia are known alarm symptoms of CRC but the positive predictive values (PPVs) are relative low and many patients present with non-specific symptoms as fatigue, weight loss and change in bowel habits which can mimic common benign conditions in general practice [7, 11, 13, 15]. Furthermore, the GP's opportunity to gain familiarity with CRC diagnosing is hampered by the low incidence of CRC which is equivalent to approximately one new CRC diagnosis per GP per year [26].

The diagnostic pathway for cancer patients can be divided into different time intervals from first symptom appearance/sensation to start of treatment as shown in figure 9. In order to achieve an earlier diagnosis, the entire course from first symptom to diagnosis needs to be as short as possible. This is based on a theory, that the longer interval from first symptom appearance until start of treatment, the worse disease stage at diagnosis and poorer prognosis [(39)]. In 2008-2009 fast tracks for all cancer types were implemented in Denmark to minimise the time from referral to end of treatment. These fast tracks have accelerated the secondary care interval but knowledge is lacking regarding the primary care interval. A Danish study by Hansen et al [(40)] investigated delay in cancer diagnoses based on information from GP questionnaires. They found that the median GP interval before referral was 0 days in contrast to the findings of Christensen et al [(16)] who found an increased health care use among cancer patients in general practice. In order to obtain more knowledge about the patient interval and the primary care interval we focused on the activities in general practice in the period prior to a CRC diagnosis. As the symptoms of CRC often are non-specific, the patient and doctor interval can be quite confluent for which reason precise distinctions between the different pre-diagnostic intervals will not be made. The aim of this study was to investigate the activity in general practice before CRC diagnosis to reveal patterns reflecting the actions of the patient and the GP as this may guide the GPs to diagnose CRC at an earlier time and minimise the primary care interval.

Figure 9. The intervals in the route from first cancer symptom until start of treatment [(3)]



**Discussion of the methods**

In the following sections I will discuss the methodological issues of the study in relation to study design, study population outcome variables and statistical analysis. The validity of the study is discussed in terms of internal validity (selection bias, information bias and confounding) and external validity (generalisability).

*Study Design*

We conducted a national population-based cohort study of CRC patients and a matched reference population. As all data were available from registers we performed a retrospective cohort study using prospectively recorded registry data. Since the life risk of CRC is relatively small, a prospective follow-up study would have been more time-consuming and costly. We made a comparative study to be able to compare the baseline activities in general practice between a reference population and CRC patients to evaluate the possible association to a CRC diagnosis.

*Selection of the study population*

In a cohort study it is important that the study population is representative of the population of interest with regards to the research subject to eliminate the risk of selection bias and strengthen the generalizability of the results. On the other hand, some restriction in the selection process is often applied to be able to compare homogeneous populations and prevent confounding.

We included patients with a primary diagnosis of CRC according to ICD codes C18-C20 (table 5). The proportion of included colon cancer patients (63.5%) and rectal cancer patients (36.5%) in the study is comparable with the distribution of all diagnosed CRC from 2008-2012 (64% vs. 36%)[(26)].

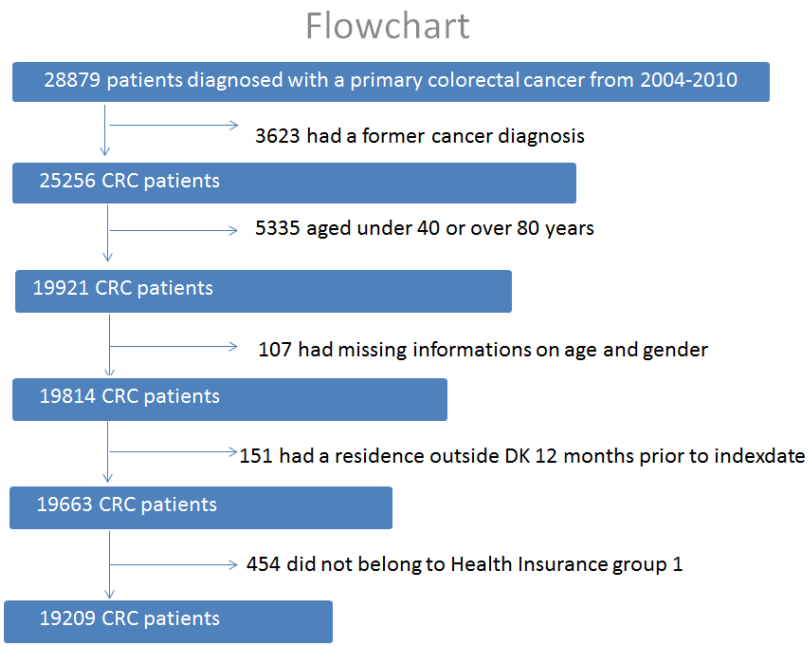
Table 5. The numbers of eligible CRC patients according to tumour localisation [41]

| | Code | Localisation | Numbers |
|---|---|---|---|
| o | DC180 | Cancer in caecum | 1972 |
| o | DC181 | Cancer in the appendix | 170 |
| o | DC182 | Cancer in colon ascendens | 1655 |
| o | DC183 | Cancer in flexura coli dextra | 524 |
| o | DC184 | Cancer in colon transversum | 896 |
| o | DC185 | Cancer in flexura coli sinistra | 364 |
| o | DC186 | Cancer in colon ascendens | 524 |
| o | DC187 | Cancer in colon sigmoideum | 4840 |
| o | DC188 | Cancer in colon located at multiple sites | 122 |
| o | DC189 | Cancer in colon without specification | 857 |
| o | DC199 | Cancer in the recto-sigmoidal junction | 278 |
| | | • Patients with a colon cancer in total | 12202 |
| o | DC209 | Rectal cancer | 7007 |

The inclusion process and the numbers of non-eligible patients are shown in figure 10. We decided to exclude CRC patients with a former diagnosis of cancer except non-melanoma skin cancer (DC44.0) because these patients might have had a different health seeking pattern due to their former cancer diagnosis and because it is reasonable that the GPs also had an increased awareness to the symptoms presented by these patients. We chose to include only patients aged 40-80 years old as both younger and older patients were suspected to have different tumour characteristics following different presentations which were not in the interest of this study.

We included patients diagnosed from the 1st of January 2004 to 31st of December 2010 as the precise date of the registration of cancer diagnosis in the Danish Cancer Registry is available from year 2004. Until 2004, only the month of the date of diagnosis was available; this could have made time intervals prior to diagnosis inaccurate. We only included persons with a residence in Denmark in the 12 month study period and patients registered at a general practice (Health Insurance Group I) to have an equal exposure to general practice among all participants in the study period.

Figure 10. Flowchart of the selection process to eligible CRC patients.




*Selection of the reference population*

For each CRC patient ten references were matched on gender, age and general practice to eliminate the effect of these factors on the association between health care use and CRC diagnosis. The references were matched using incidence density sampling which involves that every time a case was diagnosed, ten references were selected from the eligible cohort. When using incidence density sampling persons could be selected as references more than once and could also subsequently become a case [(42)]. Persons were not eligible if they had a diagnosis of cancer or were diagnosed with cancer within the next two years to eliminate the potential effect of a developing cancer disease on health care use.

*Selection of outcome variables*

Data on all outcome variables were collected from Danish registries. We chose only to include daytime face-to-face consultations (code 0101, 0102) including home visits (code 0411, 0421, 0431, 0441, 0451, 0461, 0491) to focus on a setting in general practice where most contacts are initiated by the patients and where the GP actually sees the patient and observe signals from the

patient. To investigate the amount of haemoglobin (Hb) measurements performed in general practice we obtained information on point-of-care Hb measurements using photometry (coded: 7108). We only focused on the Hb measurements performed using photometry in general practice as the GP has a clear intention of performing a Hb measurement when using photometry. In contrast, some blood samples in general practice are administered and analysed in hospital laboratories where the intention does not necessarily only concern haemoglobin for which reason these blood samples were not included in the study.

The medicine prescriptions included were on the medicine: Proctosedyl (Steroid (group I) + antibiotic), Doloproct (Steroid (group II) + local anaesthetic) and Rectogesic (local anaesthetic) which are prescribed for the indications of haemorrhoids, anal pruritus and anal fissures. We also investigated the rate of prescriptions on medicine for obstipation, but this medicine are often bought without a prescription and thus not registered in the Danish Prescription Registry. Therefore, the estimates of rates of prescriptions of obstipation medicine were imprecise and clinically irrelevant for which reason these analysis will not be discussed any further.

**Study validity**

The validity of the study will be discussed in terms of precision, internal validity (selection bias, information bias and confounding) and generalisability (external validity). The precision of the results is high if several repeated measurements of the same object will have the same result or with a minimum of difference. Even with a high degree of precision the results can be systematically incorrect which results in a low degree of internal validity of the estimates.

*Statistical precision*

We chose a significance level on 5% and calculated 95% confidence intervals to report the statistical precision of the results. Due to the large study population with 19209 CRC patients we obtained a high statistical precision of the estimates, which can be noticed in the narrow confidence intervals of the estimates.

*Internal validity*

The internal validity is divided into selection bias, information bias and confounding and indicates to what extent the results of the study are valid regarding the representative target population. The internal validity of a result estimate is high if the estimate does not under- or overestimates the true value and if a result is not influenced by a confounder. It relies on the risk of bias of the results based on errors in the selection of the study population (selection bias), in the gathering of data (information bias) or on the risk of confusion of effects (confounding).

1) *Selection bias:*

A systematic under- or overestimation of the result estimate can occur due to procedures in the selection process. In comparative studies the references must resemble the target population from which cases are collected and must be representative of the population in interest regarding the research subject. Furthermore, selected cases must be representative of cases from the target population.

Given the high completeness in the registration of cancer diagnoses in the Danish Cancer Registry[18], selection bias due to an incomplete registration of cases seem negligible. As we obtained complete information on use of general practice, all eligible cases were included in the study for which reason selection bias due to eligible non-participants were absent in this study. To obtain an equal baseline exposure to general practice among references and cases, age- and gender matched references were selected from the same GP as the corresponding case to limit the risk of selection bias. This was important since variation is known in the amount of activity between general practices [43]. Furthermore, references seem representative of the target population due to the limited amount of inclusion criteria.

*2) Information bias:*

The results of a study can be biased when systematic error occurs in the collection of data regarding outcome or exposure variables, so-called information bias. This may lead to a misclassification of the results which furthermore can be divided into differential and non-differential misclassification depending on the whether the error is systematically related to both the outcome and exposure.

Despite a high completeness in registration of cancer patients in the Danish Cancer Registry [18] errors in the registration might occur. Though, as the registration of cancer diagnosis were not related to the registration of prospective health care services, the potential bias would be non-differential and pull the association towards the null [44]. Information bias in relation to the outcome variables (health care services) would occur if errors were present in the registrations of the outcomes. The registration of health care services in general practice relies on a remuneration of the general practitioner and as up to 75% of the salary of the GP relies on registration of such health care services the completeness of registration in the Danish National Health Service Register is estimated as high [19]. The registration of the medicine prescriptions in the Danish Prescription Register is also estimated as high as the prescriptions were electronically registered when redeemed by the patient at the pharmacy. Furthermore, since the health care services were prospectively recorded and hence not associated with the cancer diagnosis, a potential information bias would be non-differential. Given the retrospective design of the study recall bias was eliminated.

*3) Confounding:*

Confounding means a confusion of associations. A confounder is a variable which is a predictor of the outcome and associated with the exposure variable without being a part of the causal pathway. In the statistical model, e.g. a regression model, a confounder can be adjusted for, but still residual confounding can be present due to a crude division of variables into too few categories. Furthermore, unknown and unmeasured confounding can also be present.

In this comparative study we minimised the degree of confounding by selecting the study participants on the basis of restrictions and by matching the cases with references on age, gender and general practice. We also controlled for confounders such as socioeconomic variables, demographic variables and comorbidity by including the confounders as covariates in the multivariable regression analysis used. Still, residual confounding might be present e.g. according to comorbidity. We used the Charlson Comorbidity Index (CCI) to account for different comorbidity between study persons but the use of the CCI score is debatable because of the limited included diagnoses and the selection of these (Table 6). The CCI is based on hospital diagnoses for which reason diseases managed in general practice are not included even though they influence the use of general practice. Other variables such as obesity, food intake, smoking and alcohol consumption might have confounded the results but we were not able to adjust for these factors, as information was not available.

Table 6. The 17 ICD10 diagnosis and categories for calculation of the Charlson Comorbidity Index Score

| Points | Disease | ICD10 code |
|---|---|---|
| 1 point | Acute myocardial infarction | I21; I22; I23 |
| | Congestive heart failure | I50; I11.0; I13.0; I13.2 |
| | Peripheral vascular disease | I70; I71; I72; I73; I74; I77 |
| | Cerebrovascular disease | I60-I69; G45; G46 |
| | Dementia | F00-F03; F05.1; G30 |
| | Chronic pulmonary disease | J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3 |
| | Connective tissue disease | M05; M06; M08; M09; M30; M31; M32; M33; M34; M35; M36; D86 |
| | Peptic ulcer disease | K22.1; K25-K28 |
| | Mild liver disease | B18; K70.0-K70.3; K70.9; K71; K73, K74; K76.0 |
| | Diabetes without end organ damage | E10.0; E10.1; E10.9; E11.0; E11.1; E11.9 |
| 2 points | Diabetes with end organ damage | E10.2-E10.8; E11.2_E11.8 |
| | Hemiplegia | G81; G82 |
| | Moderate to severe renal disease | I12; I13;N00-N05; N07; N11; N14; N17-N19; Q61 |
| | Non-metastatic cancer | C00-C75 |
| 3 points | Moderate to severe liver disease | B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85 |
| 6 points | Metastatic cancer | C76-C80 |
| | AIDS | B21-B24 |

*External validity*

The external validity of a study relies on the generalizability of the results to other populations than the target population. In order to gain a high degree of intern validity, a study population is often selected on the basis of restrictions at the expense of a lower representativeness to the target population which weakens the generalizability.

The national approach of this study implied that every CRC patient in Denmark was expected to be included in the study when meeting the inclusion criteria. As only limited restrictions were made in the selection process of the study population, a large heterogeneous group of patients and references with different health care patterns were included which strengthens the degree of external validity. In general, the CRC patients included in this study were 6 years younger at time of diagnosis compared to all CRC patients (66 years vs. 72 years) and with a male/female ratio on 1.3 we included relatively more male patients compared to the national gender ratio for CRC patients (1.16) [(26)]. This was explained by the exclusion of patients above 80 years. Despite these differences, the results of this large population-based study have a high degree of external validity to populations with comparable health care systems where general practice provides first-line medical advice.

**Statistical considerations**

The association between rates of outcomes (consultations, Hb measurements and medicine prescriptions) and having a diagnosis of CRC was estimated using negative binomial regression model. This model was chosen because we are modelling count data for which the variance is greater than the mean [(45)].

Since an observation on a person in our study were likely to be dependent on a previous observation, we applied cluster robust variance estimation to account for heterogeneity between persons. Persons were also clustered in the respective general practices which we accounted for by matching cases and references on general practice level. We were not able to use cluster robust variance estimation on general practice level as 0.8% of the references had another GP than their belonging case.

We also investigated differences in the total amount of the outcomes per year to compare the patients and references having a certain amount of the outcomes. We divided the outcomes into three or four graduations and compared the proportion of cases and references within each graduation. For this we used conditional logistic regression model as the groups were matched (cases and references) for every graduation of the outcome.

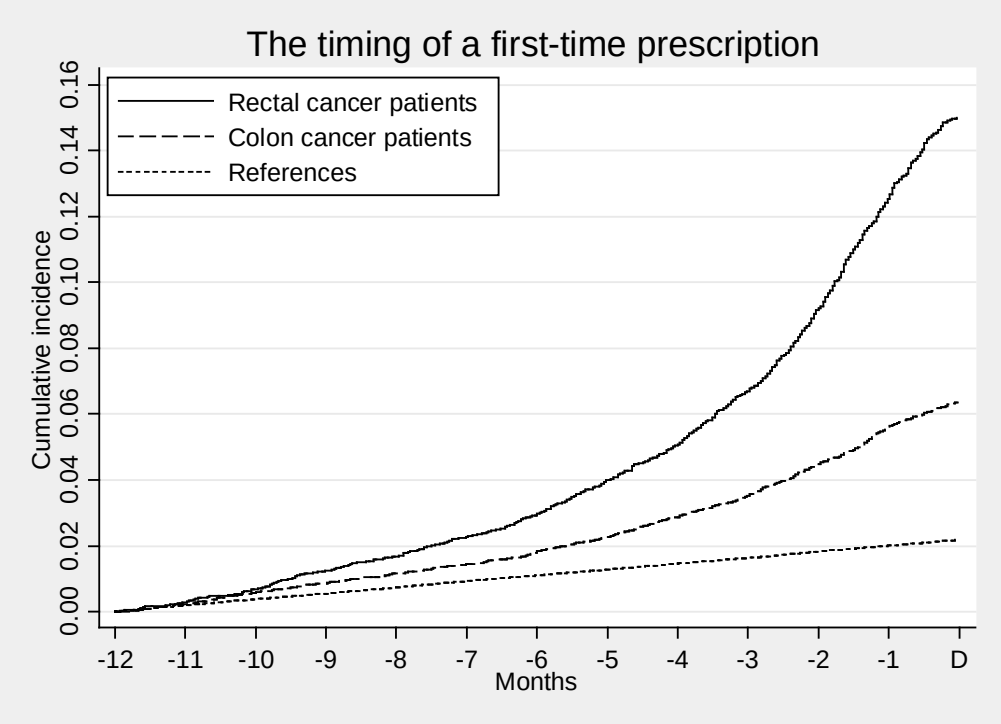
The positive predictive values (PPVs) on prescription of medicine for haemorrhoids were calculated using the STATA command "diagt"[(25)] which calculates PPVs based on Bayes Theorem (posterior odds= prior odds x likelihood ratio) using a 2x2 table and the background incidence. Age was stratified into four groups (40-49, 50-59, 60-69, and 70-79 years) and PPVs were estimated for every combination of gender and age group. The prior odds were derived from national incidence rates [(26)] and we multiplied the national incidence rates with the age and gender specific ratios of the consulting population in the six month period (proportion of consulting CRC patients/proportion of consulting references) to estimate predictive values of the incidence rates of CRC in the consulting population.

**Supplementary method and result**

As we found high rates of first-time prescriptions on medicine for haemorrhoids in the year prior to CRC diagnosis we were interested in knowing the time at which the patients had their first-time prescription. To estimate the timing of the first-time-prescription we analysed data using a Kaplan Meier Failure function to produce a curve showing the cumulative incidence of having a first-time prescription. We calculated the time from the first-time prescription to the index date for colon cancer patients, rectal cancer patients and references.

Figure 11 shows that references have a constant cumulative incidence of first time prescriptions whereas the incidence of having a first time prescription among rectal cancer patients increases approximately ten months before diagnosis with a steep increase the last four months before diagnosis. Overall, in the year preceding diagnosis about 15% of the rectal cancer patients had a first-time prescription for haemorrhoids with only 3% of the rectal cancer patients having a first-time prescription in the period from 12 to 6 months before diagnosis.

Figure 11. The cumulative incidence of a first-time prescription in the year prior to index date



**Strengths and limitations**

A major strength of this study is the national approach including all eligible CRC patients diagnosed over a seven year period and matched references which provided a high statistical precision to the study results due to the high number of participants (n=211299). The data was collected from Danish registries which are known to have a high degree of quality [18-20] and with complete and accurate information on prospectively recorded healthcare use, we eliminated the risk of bias of the results. Furthermore, we gained near complete information on potential confounding factors such as socio-demographic and economic factors and comorbidity. Overall, the results of this study gained high degree of precision and validity.

A limitation of the study was the missing information on the indications for the consultations, Hb measurements and medicine prescriptions. This limits the interpretation of the results as we do not know the spectrum of the symptoms and complaints which made the patients contact their GP. In addition, some consultations could also be initiated by the GP. The indications for the Hb measurement are also lacking. The patient might have suffered from fatigue, dizziness or just have a Hb measurement performed as a status test related to a known chronic disease. Such supplementary information would be relevant in the future research of symptoms and signs related to CRC diagnosis. Still, it would be very difficult to select and exclude the Hb measurements not associated to a CRC suspicion and the risk of underestimating the amount of Hb measurements would be inevitable.

As some of the patients (2-2.6%) and references (13.3-18.4%) did not have a consultation in the year preceding index date they were not in risk of having a Hb measurement or a medicine prescription. However, given the matched design of the study it was not possible to make analysis solely on the consulting population except for the PPV calculations where we adjusted the national incidences for CRC to the consulting population. As more references than CRC patients did not consult their GP our results may overestimate the actual association.

We did not take changes to another general practitioner during the study period into account, however only few persons did shift to another general practitioner and it is unlikely to have influenced our estimates.

**Discussion of the results**

The study showed an increased use of general practice among CRC patients compared to a matched reference group in the year preceding diagnosis. The increasing rates of consultations and diagnostic activity in the months prior to date of diagnosis are hardly unexpected as they reflect the diagnostic work-up leading up to a CRC diagnosis.

However, the significantly increased consultation rates up to 10 months before diagnosis indicates that some patients react on bodily signs several months before diagnosis. Furthermore, as a symptomatic patient interval often precedes the first symptom presentation to general practice it is likely that the patient may have recognised the first symptom of CRC several days or months earlier [(40)] which extends the potential for earlier diagnosis.

Surprisingly, the diagnostic activity initiated by the GP increased several months before an increase in the patients' healthcare seeking was observed. This may indicate that some GPs have a longer "wait and see" interval where they use time as a diagnostic tool, which extends the primary care interval. It could also reflect that some patients worry wasting the time of the GP and postpone seeking medical advice [(46)].

More than one third of all CRC patients had a Hb measurement in the year prior to diagnosis and the odds of having several Hb measurements were higher among CRC patients than references. Since we found increased rates of Hb measurements from 17 months before diagnosis among female CRC patients, the Hb level may have been in the normal range as a low Hb measurement with iron deficiency anaemia allows for the entering in a fast track diagnostic work-up for CRC. If the Hb levels were sub normal, the results would indicate a missed opportunity of diagnosing CRC earlier which is consistent with the findings by Singh et al [(32)]. Since the indications and the results of the Hb measurements are unknown it is difficult to interpret the increased rates of Hb measurements more specifically but overall we observed an increased diagnostic activity from the GP.

We also found that about 10% of the CRC patients had a prescription for haemorrhoids in the year prior to diagnosis and that some female patients started having significantly more prescriptions than references already 18 months before diagnosis which signifies an increased activity from the

GP. Furthermore, as we only included prescriptions from general practice and only the redeemed prescriptions our results may underestimate the actual use of medicine for haemorrhoids. Overall, the results of this study show a clear association between use of medicine for haemorrhoids and CRC.

When we separated analysis according to tumour type a strong association appeared between activities in general practice and tumour type. The patients with a proximal colon cancer had long intervals with increased amount of consultations and Hb measurements in agreement with the vague symptoms of proximal situated colon tumours. Conversely, rectal cancer patients had a short consultation pattern but a long interval with high rates of medicine prescriptions for haemorrhoids. As some rectal cancers can be detected by a digital examination these findings highlights the importance of performing a relevant examination of the patient presenting rectal bleeding or other anal complaints before initiating treatment for haemorrhoids.

**Conclusion**

The findings of this large population-based study revealed an increase in the patients' healthcare seeking and the diagnostic activity in general practice prior to CRC diagnosis. Furthermore, we found a clear association between these outcomes and tumour type in agreement with the known symptomatic presentations according to tumour type. Overall, the results indicate that a "diagnostic time window" is present in general practice which opens the opportunity for diagnosing CRC at an earlier tumour stage and hence improve survival.

**Perspectives**

The new information on increased activity before CRC diagnosis can be useful in the pursuit of an earlier detection of CRC and guide GPs in their diagnostic way of thinking when patients present with symptoms not eligible for a fast track referral. Furthermore, the findings of this study should be considered when developing new referral guidelines for CRC, especially as PPVs from this study on first-time prescriptions for haemorrhoids were comparable with PPVs from former studies on

rectal bleeding [11, 15]. As the presence of rectal bleeding allows for a fast diagnostic work-up with a colonoscopy, the results of this study propose whether, an examination such as a sigmoidoscopy should be a requirement before prescribing a first-time medicine prescription for haemorrhoids. On the other hand, even though a colonoscopy may lead to an earlier diagnosis of CRC for up to every tenth patient, it would require a large amount of colonoscopies as the annual incidence for having a first-time prescription for haemorrhoids in the Danish population aged 40-80 years is 2%. The answer of the question remains political and a decision clearly depends on cost benefit analyses. However, in screening programs the screening is based on a risk of cancer of about 0.15% which is much lower than the PPVs found in our studies.

As we were able to find a correlation between medicine prescriptions for haemorrhoids and CRC, future studies should focus on the amount of medicine prescriptions for constipation prior to diagnosis to investigate if the patient interval prior to diagnosis is extended due to the alleviation of abdominal symptoms by self-administered constipation medicine. This type of medicine can be bought over-the-counter why future studies could be based on patient questionnaires.

As the results differed according to tumour type it might be interesting to investigate the CRC disease as different diseases according to tumour localisation. Many former studies have only investigated symptom presentation for CRC patients as a whole group but the results of this study underpins the importance of looking at these diseases as different complexes of symptoms.

Furthermore, as the survival from CRC is dependent on tumour stage at diagnosis future studies should focus on the association between activities in general practice and tumour stage at diagnosis to investigate if the long intervals are associated with more advanced tumour stage.

The implementation of fast track referral for suspected cancer disease in 2008 and the increased cancer awareness may have an impact on the clinical behaviour of the GPs for which reason it could be relevant to repeat this study in the future to measure potential changes in the duration of pre-diagnostic activity.

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