Cancer Epidemiology 60 (2019) 23–30

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

# Rational targeting of population groups and residential areas for colorectal cancer screening

Ulf Strömberg[a,*], Stefan Peterson[b], Anders Holmén[c], Erik Holmberg[d,e], Rolf Hultcrantz[f], Anna Martling[g], Mef Nilbert[h,i,j]

[a] Health Metrics Unit, Institute of Medicine, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden
[b] Regional Cancer Center South, Lund, Sweden
[c] Department of Research and Development, Region Halland, Halmstad, Sweden
[d] Regional Cancer Center West, Gothenburg, Sweden
[e] Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[f] Department of Gastroenterology and Hepatology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden
[g] Department of Molecular Medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden
[h] Institute of Clinical Sciences, Division of Oncology and Pathology, Lund University, Lund, Sweden
[i] Clinical Research Centre, Hvidovre Hospital, Copenhagen University, Hvidovre, Denmark
[j] The Danish Cancer Society Research Center, Copenhagen University, Copenhagen, Denmark

ARTICLE INFO

*Keywords:*
Socioeconomic inequalities
Population groups
Incidence mapping
Mortality
Cancer prevention

ABSTRACT

*Background:* Sociodemographic and spatial disparities in incidence and mortality burden of colorectal cancer (CRC) are important to consider in the implementation of population screening, in order to achieve expected benefit and not increase health inequities. Analytic methods should be adapted to provide rational support for targeted interventions.

*Methods:* CRC incidence rates by tumor stage (I-IV) and location (colon vs. rectum) were analyzed for the time period 2008–2016 within a screening-relevant age interval of 55–74 years for the population of South and West Sweden, where screening is planned for. The study population was stratified by sex, country of birth, educational level (for Swedish-born citizens) and residential area. We also estimated disparities in excess mortality from CRC across groups of patients accordant to relevant population groups.

*Results:* The analyses were based on 8961 patients with a first CRC diagnosis. There were marked socioeconomic gradients in the stage II-IV CRC incidence rates among Swedish-born men and women. Compared to men with high educational level, the incidence rate ratios (IRRs) of stage II, III, and IV CRC in men with low educational level were 1.38 (95% confidence interval 1.18, 1.62), 1.09 (0.95, 1.26), and 1.18 (1.02, 1.37), respectively. In women, the corresponding figures were 1.26 (1.06, 1.51), 1.19 (1.01, 1.39), and 1.45 (1.20, 1.80). The groups of patients with low educational level showed relatively high excess mortality burdens from CRC.

*Conclusions:* Our analytic approach provided rational support for targeted intervention when implementing CRC screening, aiming at optimizing participation in groups with low educational level.

## 1. Introduction

The disease and mortality burden from colorectal cancer (CRC) is considerable. The global burden is expected to increase by 60% to more than 2.2 million new cases and 1.1 million deaths by 2030 [1]. There is a 10-fold variability in incidence worldwide with some of the highest incidences in the Nordic countries, South Korea, Slovakia, Hungary and the Netherlands [1].

Socioeconomic disparities related to incidence of CRC have been documented in several countries [2–4]. Later stage CRC at diagnosis may be the major cause of the lower survival observed in individuals with low socioeconomic status (SES) [5]. Socioeconomic inequities in CRC survival may vary in relation to age, sex, and tumor location [6]. Nevertheless, neighborhood deprivation may constitute a marker to

*Abbreviations:* CRC, colorectal cancer; CI, confidence interval; EMRR, excess mortality rate ratio; FOBT, fecal occult blood test; FIT, fecal immunochemical test; IRR, incidence rate ratio; SCRCR, Swedish Colorectal Cancer Registry; SES, socioeconomic status; SSHCR, Southern Swedish Health Care Region; WSHCR, Western Swedish Health Care Region

* Corresponding author at: Sahlgrenska Academy, PO Box 463, SE-405 30 Gothenburg, Sweden.
*E-mail address:* ulf.stromberg@gu.se (U. Strömberg).

https://doi.org/10.1016/j.canep.2019.01.009
Received 20 June 2018; Received in revised form 8 November 2018; Accepted 17 January 2019
Available online 18 March 2019
1877-7821/ 

define underserved populations for initiatives directed at timely diagnosis, access to treatment, and postoperative care [7]. Overall, variable tumor stage distribution seems to have a larger impact on survival disparity than treatment-related disparities, though more favorable surgical treatment characteristics and a lower 30-day postoperative mortality in patients with colon cancer and high socioeconomic status has been demonstrated from the Netherlands [8,9].

Organized screening programs using fecal occult blood tests (FOBT) or immunohistochemically based tests (FIT) effectively reduce CRC mortality and are recommended by international health organizations. Organized CRC screening, in contrast to opportunistic screening, actively invite all individuals in a specific geographical area within predefined age limits to take part in a protocol-based screening. Mortality rates from CRC have dropped by half in the latest decades after the implementation of screening programs, but mortality drops primarily apply to population groups with high SES, and lower uptake in groups with lower SES increases CRC disparity [10]. If screening participation varies by subgroup, screening programs may create or exacerbate socioeconomic and ethnic health inequities. Equity of access and high coverage are therefore important to consider in the planning phases of CRC screening.

Herein, our focus is on rational targeting of high-risk groups in a general population within a specified region without organized CRC screening, but where such screening will be implemented. We consider rational targeting based on the existing associations (assessed herein) between sociodemographic variables, on the on hand, and CRC incidence and excess mortality, on the other hand. We take into account relevant prognostic factors, i.e. tumor stage and location. The a priori sociodemographic variables of interest are: sex, educational level, country of birth, and residential area. These factors are associated and may also reflect other risk factors. For example, educational level is an important indicator of SES and an essential factor affecting life circumstances and health. Educational attainment, largely reached before the age of 30, is associated with gender, occupation, income, residence area, major risk factors for adverse health outcomes, health literacy, etc. Adverse health behaviors and higher body mass index has together been suggested to explain 44% of the association of education with the risk of CRC, based on data from the US [11].

Sociodemographic as well as spatial variations in stage- and location-specific incidences of CRC are relevant to consider for targeting of high-risk groups. Area-level statistics on sociodemographic characteristics for high-risk groups may be used to identify appropriate residential areas to be targeted. Neighborhood deprivation has been suggested to play a role, which reinforces the need to define underserved populations [12]. Although spatial variations in risk are often linked to sociodemographic inequalities between residential areas, contextual factors such as access to health care may have an independent influence on the chance of timely diagnostics.

Our general aim is to provide results to support rational cancer prevention on a population level by adapting epidemiologic and statistical methods to (i) target population groups and residential areas with elevated incidence rates of advanced-stage cancers and (ii) estimate excess mortality burden in corresponding patient groups. Specifically, herein, disparities in tumor stage- and tumor location-specific incidences of CRC within a screening-relevant age interval of 55–74 years are linked to sociodemographic and spatial groups of the population of South and West Sweden. Furthermore, we estimate sociodemographic disparities in excess mortality burden due to CRC.

## 2. Methods

### 2.1. Study population

The study comprised the population of the Southern and the Western Swedish Health Care Regions (SSHCR and WSHCR) with a population of 3.8 million, which corresponds to 37% of the Swedish population. For incidence mapping, the study area was subdivided into 101 municipalities. No organized screening program for CRC was available in these regions during the time of the study. In Sweden, CRC screening was partly implemented in 2008, but only within the Stockholm-Gotland Health Care Region. The screening age interval applied in that region is 60–69 years [13], although the European guidelines for quality assurance in colorectal cancer recommends screening between 50 and 74 years [14]. Age cut-off at 74 years is motivated by data on the effectiveness of screening in elderly people [15]. Our analyses focused on individuals within a screening-relevant age interval of 55–74 years and encompassed the time period 2008–2016. In SSHCR there were 406,000 inhabitants between 55–74 years in 2016. The corresponding population size in WSHCR was 417,000.

### 2.2. Patient data

Eligible patients for this study were all individuals who resided in the study area and were diagnosed with a first CRC between January 1, 2008, and December 31, 2016, when aged 55–74 years. Patients were identified by using the records of the incident CRC cases in each region for the population-based national Cancer Register. Data on sex, age, residential municipality, time of diagnosis, and tumor location (colon vs. rectum) were obtained from this Cancer Register. Based on unique Swedish identity numbers [16] patient data were linked to the Swedish Colorectal Cancer Register (SCRCR) and the Statistics Sweden's population registers. Information on tumor stage (I-IV) was obtained from the SCRCR. We used data on the pathologic (postoperative) stage, as data on clinical stage before surgery were insufficient. Data on country of birth and educational level were obtained from Statistics Sweden and patients were classified as Swedish-born/foreign-born (referred to as immigrant status) and in relation to the number of school years completed at the end of the year of diagnosis ("low" $\leq$9 years [primary school], "intermediate" 10–12 years [high school/pre-university level] and "high" $\geq$13 years [university level]). Information on vital status was obtained from Statistics Sweden and the follow-up data were assessed by the survival times censored at 5 years after diagnosis, date of emigration or December 31, 2016, whichever occurred first.

### 2.3. Population data

Statistics Sweden provided the population data needed for incidence calculations, i.e. population size by municipality, year, sex, and 5-year age groups (55–59, 60–64, 65–69, and 70–74). We obtained data that allowed for additional population stratification by immigrant status and educational level. We decided to disregard registered information on educational level for the foreign-born individuals because of considerable misclassification [17].

### 2.4. Statistical methods

#### 2.4.1. Analysis of stage-specific incidences across population groups

Poisson regression was employed to estimate the stage-specific incidence rates of CRC [18]. Incidences between eight different population groups were compared: (i) Swedish-born women with high educational level, (ii) Swedish-born women with intermediate educational level, (iii) Swedish-born women with low educational level, (iv) foreign-born women, (v) Swedish-born men with high educational level, (vi) Swedish-born men with intermediate educational level, (vii) Swedish-born men with low educational level, and (viii) foreign-born men. The stage-specific incidence rates in each population group were estimated by model-based marginal means. The average stage-specific incidence rates in the whole study population were estimated by the grand means. We also analyzed stage-specific incidences according to tumor location.

#### 2.4.2. Analysis of spatial variation in stage-specific incidences

We estimated the spatial variation in the stage-specific incidence rates across the 101 residential municipalities by hierarchical Bayes modeling. More specifically, the standardized incidence rate ratios, $\lambda_i$ (municipality i = 1, 2, …, 101), were estimated using the Besag-York-Mollié (BYM) modelling [19]. For a given stage category (I, II, III, or IV), the expected number of cases in each municipality was calculated from the year-, sex-, age-, immigrant status, and educational level specific incidence rates in the total population. Thereby, the spatial incidence patters were adjusted for potential confounding by sociodemographic factors (sex, age, immigrant status, and educational level). Statistical certainty maps based on estimated posterior probabilities were used for depicting stage-specific incidence variations of CRC across the municipalities, visualizing each area having an elevated incidence rate with a posterior probability above 0.80 [20].

#### 2.4.3. Analysis of excess mortality burden in different patient groups

Patients' excess mortality rate was estimated based on a model taking into account the following predictors: year of diagnosis, age at diagnosis, tumor location, tumor stage, and patient group (8 different groups, analogous to the population groups specified above) [21]. Each patient's reference mortality rate was calculated from the life tables for the total Swedish population stratified by calendar year, sex, age (1-year groups), and educational level (foreign-born patients, without reliable data on educational level, were classified as "intermediate"). The excess mortality burden in a specified group of patients was quantified by the number of excess deaths, i.e. the sum of each patient's excess risk up to 5 years after diagnosis (model-based estimates, with the excess-risk equal to zero for patients that did not die during follow-up), in relation to the number of patients. In order to assess a 95% CI for the quantified mortality burden, a bootstrapping method was employed replicating excess mortality estimation 10,000 times.

#### 2.4.4. Computing

The analyses were carried out by using the Rapid Inquiry Facility [22], R programs (http://www.R-project.org/) and IBM Statistics for Windows version 25.0 (IBM Corp.: Armonk, NY, USA).

## 3. Results

### 3.1. Stage distribution by tumor location

After the exclusion 27 Swedish-born patients with missing data on educational level, 8961 patients with assessed tumor stage remained (Table 1). There were additionally 762 patients with insufficient data for assessing tumor stage. There were 158 patients with synchronous colon cancer and rectal cancer; in the following, we classify these patients into the colon cancer group.

### 3.2. Stage-specific incidences across population groups

The stage-specific incidence rates of CRC in the total population of the study area exceed 20 per 100,000/year in the age groups 55–59 (stage III), 60–64 (stage II and IV) or 65–69 (stage I) (Fig. 1). Swedish-born men with low educational level had the highest incidence rates of stage II-IV CRC (Fig. 2). There were marked educational level gradients in the stage II, III, and IV CRC incidence rates among Swedish-born men as well as among Swedish-born women (Fig. 2). Compared to men with high educational level, the incidence rate ratios (IRRs) of stage II, III, and IV CRC in men with low educational level were 1.38 (95% CI: 1.18, 1.62), 1.09 (0.95, 1.26), and 1.18 (1.02, 1.37). In women, the corresponding figures were: 1.26 (1.06, 1.51), 1.19 (1.01, 1.39), and 1.45 (1.20, 1.80). In men, the socioeconomic gradient was more pronounced for stage III rectal cancer than for stage III colon cancer, whereas in women the socioeconomic gradient was more pronounced for stage II-III colon cancer than for stage II-III rectal cancer (Supplementary Figs. S1 and S2). As should be expected, women had lower incidence rates of rectal cancer than men.

Foreign-born women had significantly lower incidence rates of stage I and II CRC, compared with Swedish-born women combined: 0.75 (0.59, 0.95) and 0.79 (0.66, 0.97). We found no such significant differences for stage III and IV CRC. Comparisons of foreign- vs. Swedish-born men showed no significant differences in the stage-specific incidences of CRC.

### 3.3. Spatial variations in stage-specific incidences

The incidence maps visualize the spatial variations in the stage-specific CRC incidence rates (Fig. 3). In the SSHCR, an elevated stage IV CRC incidence rate was indicated in five municipalities. Such spatial patterns may be of potential concern if they reflects delayed detection linked to certain residential areas. In the WSHCR, variability in the certainty maps were apparent for the stage I and II CRC incidence rates. In the northern area of this health care region, the stage I incidence rate tended to be lower whereas the stage II incidence rate was higher. We reinforce that the incidence maps in Fig. 3 were adjusted for confounding by sociodemographic variables, thereby indicating areas where contextual factors such as access to health care may have had an independent influence on the chance of timely diagnostics. By contrast, area-level statistics on sociodemographic characteristics for high-risk groups, e.g. the proportion of men with low educational level, may reveal different spatial patterns (Supplementary Fig. S3).

### 3.4. Excess mortality in different patient groups

During follow-up, 2763 (31%) of the 8961 CRC patients with assessed tumor stage died. Table 2 presents the fitted excess mortality rate model. Stage was the strongest predictor of excess mortality. We found a significant interaction between stage and calendar period of diagnosis ($p = 0.016$). In the latter period 2011–2016, as compared to the earlier period 2008–2010, the excess mortality rate increased less pronouncedly with more advanced tumors according to the pathologic stage. For example, the excess mortality rate ratio (EMRR) for stage II vs. I equals 1.3 ( = 2.25/1.72) in the latter period, whereas the corresponding EMRR in the earlier period equals 4.0.

In total, we estimated that 2246 patients died due the excess risk up to 5 years after diagnosis or until December 31, 2016, whichever occurred first. The number of excess deaths among Swedish-born male patients with low educational level represented the highest share (20%) of the total excess deaths (Table 2). The highest excess mortality burden was estimated for Swedish-born female patients with low education level: 0.29 (95% CI: 0.26, 0.33), i.e. 29% of these patients died due to their excess risk from CRC. By comparison, the corresponding estimate for Swedish-born female patients with high educational level became 0.20 (0.17, 0.23), i.e., in this group, an evidently lower proportion (20%) died due to an excess risk.

## 4. Discussion

### 4.1. Summary of key findings

Using data from a high-incidence population of 3.8 million and a publicly funded health-care system in which organized screening for CRC has not yet been endorsed, our analytic approach demonstrated most elevated stage II-IV CRC incidence rates within a screening-relevant age interval of 55–74 years in Swedish-born men with low educational level. There were marked socioeconomic gradients in the stage II-IV CRC incidence rates among Swedish-born men and women. The groups of patients with low educational level showed relatively high excess mortality burdens from CRC.

**Table 1**
Tumor stage distributions by tumor location (colon, rectal) and 8 different groups of the study patients from South and West Sweden, diagnosed in 2008–2016 when aged 55–74 years.

| Tumor location<br>Patient group | Stage I<br>*n* (%) | Stage II<br>*n* (%) | Stage III<br>*n* (%) | Stage IV<br>*n* (%) | All stages<br>*n* (%) | Unknown<br>*n* |
|---|---|---|---|---|---|---|
| **Colon cancer** | | | | | | |
| Swedish-born women, high education | 86 (14.6) | 164 (27.9) | 192 (32.7) | 146 (24.8) | 588 (67)[a] | 61 |
| Swedish-born women, intermed. education | 141 (13.9) | 299 (29.5) | 316 (31.1) | 259 (25.5) | 1015 (68)[a] | 75 |
| Swedish-born women, low education | 91 (12.4) | 229 (31.2) | 235 (32.0) | 180 (24.5) | 735 (70)[a] | 72 |
| Foreign-born women | 41 (11.9) | 88 (25.6) | 125 (36.3) | 90 (26.2) | 344 (70)[a] | 28 |
| Swedish-born men, high education | 91 (14.3) | 158 (24.8) | 211 (33.2) | 176 (27.7) | 636 (61)[a] | 60 |
| Swedish-born men, intermed. education | 164 (16.0) | 268 (26.2) | 321 (31.3) | 271 (26.5) | 1024 (59)[a] | 108 |
| Swedish-born men, low education | 124 (13.2) | 271 (28.8) | 284 (30.1) | 263 (27.9) | 942 (58)[a] | 89 |
| Foreign-born men | 49 (12.6) | 120 (30.8) | 123 (31.6) | 97 (24.9) | 389 (57)[a] | 37 |
| **TOTAL** | **787 (13.9)** | **1597 (28.2)** | **1807 (31.9)** | **1482 (26.1)** | **5673 (63)**[a] | **530** |
| **Rectal cancer** | | | | | | |
| Swedish-born women, high education | 88 (31.0) | 62 (21.8) | 95 (33.5) | 39 (13.7) | 284 (33)[b] | 25 |
| Swedish-born women, intermed. education | 118 (24.6) | 104 (21.7) | 148 (30.9) | 109 (22.8) | 479 (32)[b] | 38 |
| Swedish-born women, low education | 80 (26.0) | 61 (19.8) | 93 (30.2) | 74 (24.0) | 308 (30)[b] | 26 |
| Foreign-born women | 36 (25.0) | 35 (24.3) | 45 (31.2) | 28 (19.4) | 144 (30)[b] | 10 |
| Swedish-born men, high education | 100 (24.9) | 79 (19.7) | 118 (29.4) | 104 (25.9) | 401 (39)[b] | 24 |
| Swedish-born men, intermed. education | 172 (24.4) | 160 (22.7) | 209 (29.6) | 164 (23.3) | 705 (41)[b] | 48 |
| Swedish-born men, low education | 143 (21.3) | 170 (25.3) | 190 (28.3) | 168 (25.0) | 671 (42)[b] | 40 |
| Foreign-born men | 66 (22.3) | 71 (24.0) | 89 (30.1) | 70 (23.6) | 296 (43)[b] | 21 |
| **TOTAL** | **803 (24.4)** | **742 (22.6)** | **987 (30.0)** | **756 (23.0)** | **3288 (37)**[b] | **232** |

[a] The percentage of colon cancer cases among the colorectal cancer patients in the specified patient group.
[b] The percentage of rectal cancer cases among the colorectal cancer patients in the specified patient group.

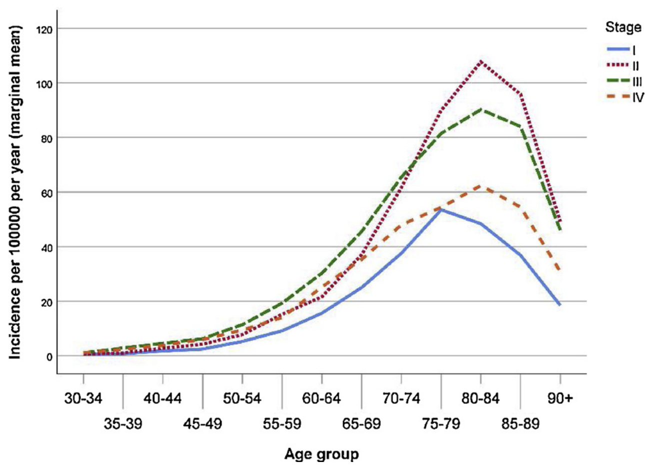


**Fig. 1.** Age-specific incidence rates of colorectal cancer by tumor stage. Data from the population of the Southern and Western Swedish Health Care Regions (2008–2016).

### *4.2. Educational level and incidence of advanced-stage colorectal cancer*

Notably, in the period 2008–2016, we observed that the stage IV CRC incidence rate among 55–74 year old Swedish-born women was 45% (95% CI: 20%, 80%) higher than the corresponding rate among Swedish-born women with high educational level. A report based on participants in the European Prospective Investigation into Cancer and Nutrition (EPIC), with follow-up until 2002–2006 (depending on country), has indicated lower overall CRC incidence with lower educational level in women in Sothern Europe, but not in Northern and Middle Eurouope [23]. In a previous study from Sweden based on individuals diagnosed between 1992–2010, Brooke et al. [24] demonstrated modest variations, if any, in CRC incidence ratios across population groups according to educational level. Nevertheless, Brooke et al. raised awareness of the need for strategies for cancer prevention and health promotion in groups with lower educational levels. We underline that these other two studies included women in wider age spans and did not estimate stage-specific incidence rates.

### *4.3. Country of birth and incidence of colorectal cancer*

The sex-specific incidence comparisons between the foreign- and Swedish-born groups revealed significantly lower incidence rates of stage I-II CRC for foreign-born women. This difference may be due lower incidences in minority ethnic groups. However, the group of foreign-born female patients was relative small and ethnically heterogeneous; 37% were born in a Nordic country, 50% in another European country, and 13% outside Europe.

### *4.4. Spatial disparities in stage-specific incidences of colorectal cancer*

Our incidence maps identified spatial variations in CRC incidence after controlling for sociodemographic confounders. Residential areas with an overrepresentation of stage I tumors and an underrepresentation of stage II tumors may potentially reflect populations with higher rates of wild screening and/or having access to health care providing newer treatment programs leading to down-staging before surgery. Residential areas with an increased incidence of stage IV CRC cancer may raise concern related to CRC awareness or access to health care and may signify areas of special concern for targeted interventions. We did not recognize a clear-cut difference between urban and nonurban areas. A recent study from Switzerland reported similar stage distributions between urban and nonurban areas, but poorer prognosis among CRC patients in nonurban areas after adjustments for sociodemographic characteristics and stage at diagnosis [5].

Geo-mapping may also be used for addressing another question: which areas should be targeted for an intervention trial? We encourage randomized health service trials, designed to evaluate new strategies in a randomized fashion [25]. In the present context of opportunistic screening, but where organized screening will be implemented, investigators may consider a trial on strategies for optimizing CRC screening attendance targeted towards disadvantaged population groups (achievements through written materials alone will be challenging, however) [26]. Area-level statistics on SES may be used for identifying appropriate target areas. Another approach to identifying appropriate target areas for a trial could be geo-mapping of stage-specific incidences without adjustment for sociodemographic variables, visualizing residential areas with elevated incidences of late-stage CRC.

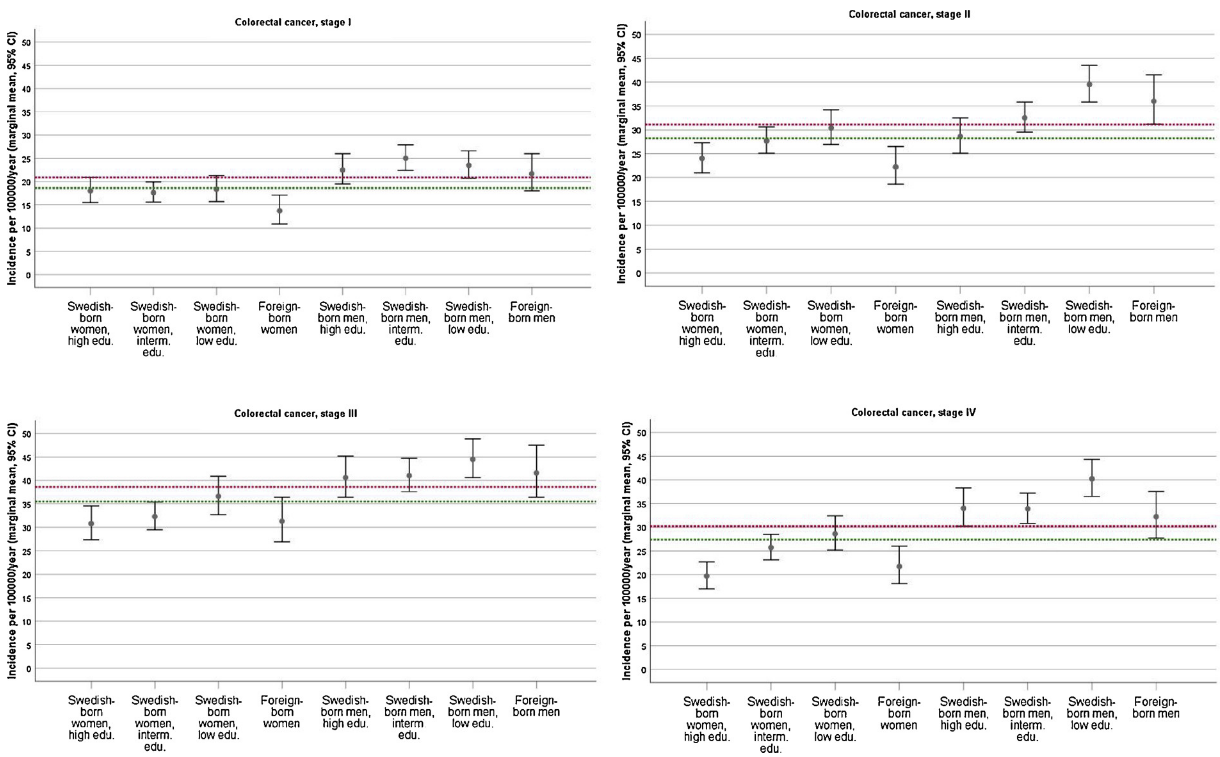


**Fig. 2.** Stage-specific incidence rates of colorectal cancer within the age interval 55–74 years for different population groups specified by sex, educational level and immigrant status. Data from the population of the Southern and Western Swedish Health Care Regions (2008–2016). The dotted horizontal reference lines indicate the lower (green color) and upper (red color) limits of the 95% CI around the average incidence rate in the study population (model-based estimate). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

### *4.5. Consideration of possible down-staging*

A down-staging effect of radiotherapy could potentially influence the interpretation of the excess mortality in stage I tumors in the latter period 2011–2016, as compared to the earlier period 2008–2010. Our analysis indicated that the excess mortality rate increased less pronouncedly with more advanced tumors in the latter time-period.

### *4.6. Excess mortality burden in different patient groups*

We underline that the expected mortality rate for each patient was calculated from the national population reference rates stratified by calendar year, sex, age, and educational level. In Sweden, life expectancy at age 30 is about 5 years shorter for individuals with a low educational level compared to those with a high educational level. In other study settings than ours, reference mortality rates according to SES may not be available on a population level. Alternatively, information from a cohort (control population) may be used to adjust reference mortality rates with regard to SES [27].

The highest number of excess deaths from CRC was estimated among Swedish-born male patients with low educational level, who accounted for 20% of the total number of excess deaths due to excess risk up to 5 years after a CRC diagnosis in the age span 55–74 years. This result reinforces that the effectiveness of the organized CRC screening to be implemented in the study area will largely depend on optimization of participation with special regard to this population group. It is also important to optimize participation with regard to female patients with low education level, in order to prevent that socioeconomic inequity is exacerbated by the screening program to be implemented. The highest excess mortality burden, in relation to the number of patients, was estimated for Swedish-born female patients with low education level.

### *4.7. Limitations*

Weaknesses of our study include lack of data on wild screening behaviors in the population studied, a potential stage migration during the study time due to improved diagnostics and therapeutic changes such as increasing use of neoadjuvant therapy, and us not being able to further investigate differential effect in the various national and ethnic groups of foreign-born individuals because of limited-sized material in this group.

### *4.8. Conclusions*

Our analytic approach provided rational support for targeted intervention when implementing CRC screening, aiming at optimizing participation in groups with low educational level.

## Author contributions

US, SP and MN conceived and designed the study. US, SP, AH and EH analyzed the data. US, SP and AH carried out the statistical analysis. All authors interpreted the data. US and MN drafted the manuscript and all authors critically revised the manuscript.

## Funding

The Swedish Cancer Society (grant 2017/355); the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement (grant ALFGBG-621241).

## Ethical approval

The study was approved by the Regional Ethical Review Board (EPN 2414/372) in Lund, Sweden

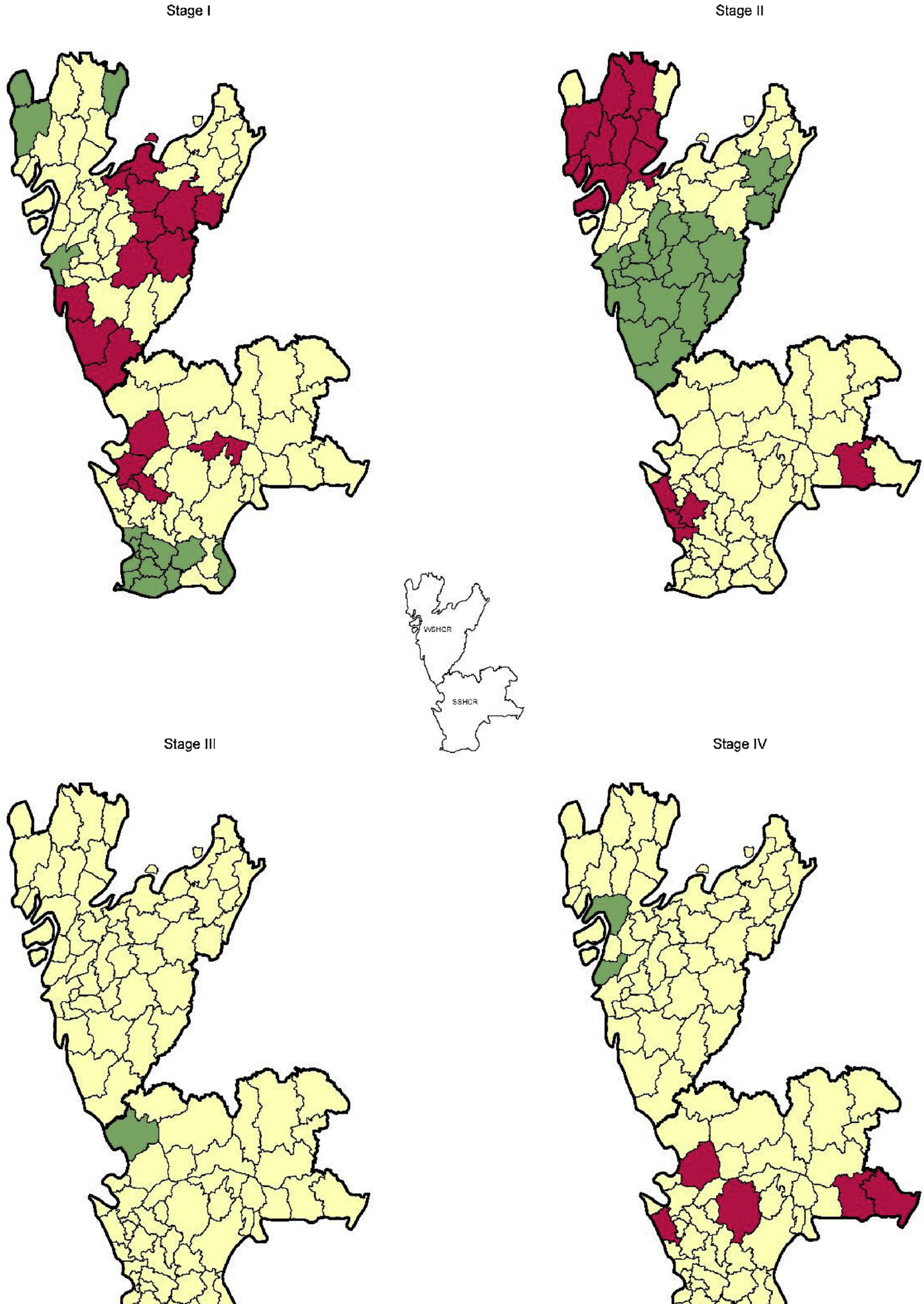


**Fig. 3.** Statistical certainty maps showing spatial variations in the stage-specific incidence rates of colorectal cancer over 101 municipalities within the Southern and Western Swedish Health Care Regions (SSHCR and WSHCR; see legend map), after controlling for calendar year, sex, age (55–59, 60–64, 65–69, 70–74), immigrant status (Swedish- vs. foreign-born) and educational level (for Swedish-born inhabitants) by population stratification. The municipalities with elevated incidence rates are colored red and the municipalities with lowered incidence rates are colored green. Data for the period 2008–2016.

**Table 2**
Estimated effects [EMRR (95% CI)] of patient variables on the excess mortality up to 5 years after diagnosis of colorectal cancer, together with number of patients, estimated excess deaths and proportion of excess deaths among the patients.

| Patient variable | Category | EMRR (95% CI) [a] | *p* for variable | Patients (*n*) | Excess deaths (*n*) [b] | Excess deaths/patients (95% CI) [c] |
|---|---|---|---|---|---|---|
| Age at diagnosis (y) | 55-59 [d] | 1.00 (-) | < 0.001 | 1138 | 252 | 0.22 (0.20, 0.25) |
| | 60-64 | 1.12 (0.95, 1.31) | | 1865 | 476 | 0.25 (0.24, 0.28) |
| | 65-69 | 1.21 (1.04, 1.40) | | 2758 | 693 | 0.25 (0.23, 0.27) |
| | 70-74 | 1.43 (1.24, 1.66) | | 3200 | 825 | 0.26 (0.24, 0.28) |
| Tumor location | Colon [d] | 1.00 (-) | < 0.001 | 5673 | 1528 | 0.27 (0.26, 0.28) |
| | Rectum | 0.84 (0.77, 0.92) | | 3288 | 718 | 0.22 (0.20, 0.23) |
| Stage at diagnosis in two time periods | I in 2008-2010 [d] | 1.00 (-) | < 0.001 | 429 | 14 | 0.03 (0.00, 0.07) |
| | II in 2008-2010 | 4.03 (1.73, 9.38) | | 749 | 104 | 0.14 (0.11, 0.17) |
| | III in 2008-2010 | 7.78 (3.41, 17.7) | | 862 | 213 | 0.25 (0.21, 0.28) |
| | IV in 2008-2010 | 53.1 (23.5, 120) | | 688 | 571 | 0.83 (0.80, 0.86) |
| | I in 2011-2016 | 1.72 (0.69, 4.28) | | 1161 | 41 | 0.03 (0.02, 0.05) [e] |
| | II in 2011-2016 | 2.25 (0.95, 5.31) | | 1590 | 81 | 0.05 (0.04, 0.07) [e] |
| | III in 2011-2016 | 7.56 (3.33, 17.2) | | 1932 | 295 | 0.15 (0.14, 0.17) [e] |
| | IV in 2011-2016 | 48.3 (21.4, 109) | | 1550 | 927 | 0.60 (0.57, 0.62) [e] |
| Patient group | Swedish-born women, high edu.[d] | 1.00 (-) | 0.002 | 872 | 174 | 0.20 (0.17, 0.23) |
| | Swedish-born women, intermed. edu. | 1.20 (0.99, 1.44) | | 1494 | 360 | 0.24 (0.22, 0.26) |
| | Swedish-born women, low education | 1.42 (1.17, 1.72) | | 1043 | 299 | 0.29 (0.26, 0.33) |
| | Foreign-born women | 0.89 (0.69, 1.14) | | 488 | 106 | 0.22 (0.18, 0.26) |
| | Swedish-born men, high education | 1.14 (0.93, 1.39) | | 1037 | 267 | 0.26 (0.23, 0.28) |
| | Swedish-born men, intermed. edu. | 1.17 (0.97, 1.40) | | 1729 | 431 | 0.25 (0.23, 0.27) |
| | Swedish-born men, low education | 1.19 (0.98, 1.43) | | 1613 | 442 | 0.27 (0.25, 0.30) |
| | Foreign-born men | 1.12 (0.90, 1.41) | | 685 | 165 | 0.24 (0.21, 0.27) |

[a] Excess mortality rate ratio estimate based on the multi-variable model presented.
[b] Estimated number of excess deaths due to the excess risk up to 5 years after diagnosis (median value based on 10,000 bootstrap replications).
[c] Ratio between the estimated number of excess deaths and the number of patients (95% CI obtained by using the 2.5th and 97.5th percentiles of the excess death estimates from 10,000 bootstrap replications).
[d] Reference category.
[e] The proportions of excess deaths were lower among the patients diagnosed in the later period 2011–2016, partly because of incomplete 5-year follow-up.

## Conflicts of interest

None to declare.


## Acknowledgements

Analytics support has been granted by the Regional Cancer Center South, Sweden.


## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.01.009.

## References


[1] M. Arnold, M.S. Sierra, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global patterns and trends in colorectal cancer incidence and mortality, Gut 66 (2017) 683–691.
[2] C.A. Doubeni, A.O. Laiyemo, J.M. Major, M. Schootman, M. Lian, Y. Park, B.I. Graubard, A.R. Hollenbeck, R. Sinha, Socioeconomic status and the risk of colorectal cancer: an analysis of more than a half million adults in the National Institutes of Health-AARP Diet and Health Study, Cancer 118 (2012) 3636–3644.
[3] M. Garcia-Gil, J.M. Elorza, M. Banque, et al., Linking of primary care records to census data to study the association between socioeconomic status and cancer incidence in Southern Europe: a nation-wide ecological study, PLoS One 9 (2014) e109706.
[4] E.J. Tweed, G.M. Allardice, P. McLoone, D.S. Morrison, Socio-economic inequalities in the incidence of four common cancers: a population-based registry study, Public Health 154 (2018) 1–10.
[5] A. Feller, K. Schmidlin, A. Bordoni, et al., Socioeconomic and demographic inequalities in stage at diagnosis and survival among colorectal cancer patients: evidence from a Swiss population-based study, Cancer Med. 7 (2018) 1498–1510.
[6] U. Nur, G. Lyratzopoulos, B. Rachet, M.P. Coleman, The impact of age at diagnosis on socioeconomic inequalities in adult cancer survival in England, Cancer Epidemiol. 39 (2015) 641–649.
[7] H. Fowler, A. Belot, E.N. Njagi, et al., Persistent inequalities in 90-day colon cancer mortality: an English cohort study, Br. J. Cancer 117 (2017) 1396-140.
[8] Y. Lai, C. Wang, J.M. Civan, J.P. Palazzo, Z. Ye, T. Hyslop, et al., Effects of cancer stage and treatment differences on racial disparities in survival from colon cancer: a United States population-based study, Gastroenterology 150 (2016) 1135–1146.
[9] V.K. Dik, M.J. Aarts, W.M. Van Grevenstein, M. Koopman, M.G. Van Oijen, V.E. Lemmens, P.D. Siersema, Association between socioeconomic status, surgical treatment and mortality in patients with colorectal cancer, Br. J. Surg. 101 (2014) 1173–1182.
[10] N. Breen, D.R. Lewis, J.T. Gibson, M. Yu, S. Harper, Assessing disparities in colorectal cancer mortality by socioeconomic status using new tools: health disparities calculator and socioeconomic quintiles, Cancer Causes Control 28 (2017) 117–125.
[11] C.A. Doubeni, J.M. Major, A.O. Laiyemo, M. Schootman, A.G. Zauber, A.R. Hollenbeck, R. Sinha, J. Allison, Contribution of behavioral risk factors and obesity to socioeconomic differences in colorectal cancer incidence, J. Natl. Cancer Inst. 104 (2012) 1353–1362.
[12] P. Hagedoorn, H. Vandenheede, K. Vanthomme, S. Gadeyne, Socioeconomic position, population density and site-specific cancer mortality: a multilevel analysis of Belgian adults, 2001-2011, Int. J. Cancer 142 (2018) 23–35.
[13] J. Blom, S. Kilpeläinen, R. Hultcrantz, S. Törnberg, Five-year experience of organized colorectal cancer screening in a Swedish population - increased compliance with age, female gender, and subsequent screening round, J. Med. Screen. 21 (2014) 144–150.
[14] European Colorectal Cancer Screening Guidelines working Group, European guidelines for quality assurance in colorectal cancer screening and diagnosis: overview and introduction to the full supplement publication, Endoscopy 45 (2013) 51–59.
[15] X. García-Albéniz, J. Hsu, M. Bretthauer, M.A. Hernán, Effectiveness of screening colonoscopy to prevent colorectal cancer among medicare beneficiaries aged 70 to 79 years: a prospective observational study, Ann. Intern. Med. 166 (2017) 18–26.
[16] J.F. Ludvigsson, P. Otterblad-Olausson, B.U. Pettersson, A. Ekbom, The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research, Eur. J. Epidemiol. 24 (2009) 659–667.
[17] J. Saarela, R. Weber, Assessment of educational misclassification in register-based data on Finnish immigrants in Sweden, Scand. J. Public Health 45 (17_suppl) (2017) 20–24.
[18] D. Clayton, M. Hills, Statistical Models in Epidemiology, Oxford University Press, Oxford, 1993.
[19] J. Besag, J. York, A. Mollié, Bayesian image restoration with applications in spatial statistics, Ann. Inst. Math Stat. 43 (1991) 1–20.
[20] S. Richardson, A. Thomson, N. Best, P. Elliott, Interpreting posterior relative risk estimates in disease-mapping studies, Environ. Health Perspect. 112 (2004) 1016–1025.
[21] M. Pohar Perme, Relsurv: Relative Survival, R package version 2.1. URL (2017) http://CRAN.R-project.org/package = relsurv.
[22] L. Beale, J.J. Abellan, S. Hodgson, L. Jarup, Methodologic issues and approaches to spatial epidemiology, Environ. Health Perspect. 116 (2008) 1105–1110.
[23] A.M. Leufkens, F.J. Van Duijnhoven, H.C. Boshuizen, P.D. Siersema, A.E. Kunst, T. Mouw, et al., Educational level and risk of colorectal cancer in EPIC with specific

reference to tumor location, Int. J. Cancer 130 (2012) 622–630.
[24] H.L. Brooke, M. Talbäck, A. Martling, M. Feychting, R. Ljung, Socioeconomic position and incidence of colorectal cancer in the Swedish population, Cancer Epidemiol. 40 (2016) 188–195.
[25] M. Hakama, N. Malila, J. Dillner, Randomised health services studies, Int. J. Cancer 131 (2012) 2898–2902.
[26] J. Wardle, C. von Wagner, I. Kralj-Hans, S.P. Halloran, S.G. Smith, L.M. McGregor, et al., Effects of evidence-based strategies to reduce the socioeconomic gradient of uptake in the English NHS Bowel Cancer Screening Programme (ASCEND): four cluster-randomised controlled trials, Lancet 387 (2016) 751–759.
[27] H. Bower, T.M. Andersson, M.J. Crowther, P.W. Dickman, M. Lambe, P.C. Lambert, Adjusting expected mortality rates using information from a control population: an example using socioeconomic status, Am. J. Epidemiol. 187 (2018) 828–836.