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Spatial variation in stage distribution in colorectal cancer in the Netherlands

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ABSTRACT

Background: In the Netherlands the incidence of colorectal cancer has increased, mainly in the eastern part of the country. Patient delay due to unawareness or ignorance of symptoms and differences in use of diagnostic tools could have influence on the stage distribution. The aim of this study was to evaluate geographical differences in stage-specific incidence rates of colon and rectal cancer in the Netherlands.

Methods: Age-adjusted incidence rates for cancers of the colon and rectum diagnosed in 2001–2005 and registered in the Netherlands Cancer Registry were calculated for each municipality and stage. The incidence for each 500 m by 500 m grid was estimated as a weighted average of the incidence rates of the neighbouring municipalities. The incidence rates and the stage distribution are both presented as maps. Geographic variation in stage-specific incidence was evaluated using spatial scan statistic.

Results: In both colon and rectal cancer, significant spatial variation in stage-specific incidences was found, except for colon cancer of stages III and IV. The regions with a higher stage-specific incidence were almost all in the south eastern part of the Netherlands, however, these differences were not seen in the stage distribution. There were no differences in stage distribution between large cities and the rest of the country.

Conclusions: These maps give insight into differences in stage-specific incidences of colon and rectal cancer in the Netherlands. Educational interventions to increase the awareness of symptoms of colorectal cancer may be especially useful for the population in regions with high incidence of advanced stages.

1. Introduction

Colorectal cancer is the second most common cancer in the Netherlands. In 2009, more than 12,300 patients were diagnosed with colorectal cancer. With almost 5000 deaths in 2009, colorectal cancer is the second leading cause of death from cancer in the Netherlands after lung cancer. Investigation of spatial trends have revealed a somewhat higher overall incidence in the eastern part of the Netherlands, suggesting a higher prevalence of risk factors, such as dietary habits, obesity and lack of physical activity, in this area.[1]

Stage at diagnosis is an important indicator for the prognosis of a patient. Overall 5-year relative survival for colorectal cancer was 60% for patients diagnosed in 2003–2007,

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ranging from 93% for patients with stage I (T1-2N0M0) to 9% for patients with stage IV (TanyNanyM1).[2]

Stage at diagnosis is associated with several factors. Older patients have a higher proportion of proximal cancers, which are associated with more advanced disease.[3] In Alabama, black race and lower social economic status were related with a higher incidence of distant disease.[4] Studies from Scotland and France showed that patients living in rural areas had more advanced disease at diagnosis,[5,6] while a study from the US demonstrated a higher proportion of distant disease in urban areas.[7] A poor public awareness of colorectal cancer symptoms may partly explain a late stage presentation.[8]

The aim of this study is to provide insight into geographical differences in stage-specific incidence rates of colorectal cancer in the Netherlands. Monitoring these differences may support the implementation and evaluation of regional educational interventions which could increase the awareness of colorectal cancer symptoms.

2. Methods

2.1. Netherlands Cancer Registry

The Netherlands Cancer Registry (NCR) is a population-based registry in which data about all newly diagnosed in situ and invasive tumours are registered. The NCR have been complete since 1989. Notification is mainly obtained from the automated pathology archive (PALGA) and the haematology departments. Other sources are the National Registry of Hospital Discharge Diagnoses and radiotherapeutic departments. Specially trained registration clerks collect data from the patient files in the hospitals. Information on patient characteristics (e.g. gender and date of birth), tumour characteristics (e.g. morphology, topography and stage) and treatment is recorded. Topography and morphology are coded according the International Classification of Diseases for Oncology.[9] The TNM classification is used for staging of the tumours.[10] Due to thorough training of the registrars, computerised consistency checks and regular quality checks at the national level, quality of the data is high.[11] The completeness of the NCR is approximately 95%.[12]

2.2. Patients

All invasive colon (C18) and rectum carcinomas (C20) diagnosed in the period 2001–2005 were selected (N = 44,607) from the NCR. Pathological stage was used, but if the pathological stage was unknown, the clinical stage was used. We assumed that patients without assessment of regional nodal involvement (NX) or distant metastasis (MX) had no regional nodal involvement (N0) or no distant metastasis (M0), respectively. The pT distributions of patients with NX and MX were comparable with the ones of patients with N0 and M0. Cases with unknown stage were excluded from the analyses (N = 1600; 3.6% of total study population, ranging from 3.2% to 4.4% between regions). Most of these patients were inoperable.

2.3. Mapping

Maps were made of the stage-specific cancer incidence and of the stage distribution for colon and rectal cancer separately using the mapping method developed by the Finnish Cancer Registry.[13] The stage-specific cancer incidence maps were based on the World Standardised Rates (WSR) which were calculated for each municipality (N = 443) and each stage. The stage distribution maps were based on the proportion of each stage per municipality. For cities with more than 100,000 inhabitants, the rates were presented as coloured circles on the maps. The radius of the circle indicates the size of the population and the colour, the WSR or the percentage. The rates for the remaining municipalities were smoothed to decrease visibility of change variation. For each 500 m by 500 m grid, a weighted average of the WSRs or the percentages of the neighbouring municipalities within a 100 km radius was calculated to define the colour of that grid. The rates were directly weighted with the population size of the municipality and inversely weighted in relation to the distance.

2.4. Spatial analyses

Geographic variation in stage-specific incidence of colon and rectal cancer was evaluated using spatial scan statistic calculated by the SatScan software.[14] This describes significant spatial variation in the rate of a disease under assumptions of a Poisson model searching one or more areas where the occurrence of cases deviated from the null hypotheses that the incidence was randomly distributed. The country was scanned to identify areas where the stage-specific incidence within the circle differed most from the incidence outside the circle.[15] All circles containing at least one municipality and having a radius that is less or equal to what is needed to cover 25 percent of the total population, were tested. Areas with a higher or lower relative risk of stage-specific age-adjusted incidence compared to the rest of the country were

Table 1 – Number of new cases and age-standardised incidence rate per 100,000 person-years (World Standardised Rate, WSR) of rectal and colon cancer in the Netherlands in the period 2001–2005 according to stage.

Stage	Rectum			Colon		
	N	%	WSR	N	%	WSR
Total	12,428	100	9.1	30,579	100	20.6
I	3585	29	2.6	4647	15	3.1
II	3114	25	2.2	10,995	36	7.1
III	3389	27	2.5	8000	26	5.5
IV	2340	19	1.7	6937	23	4.9

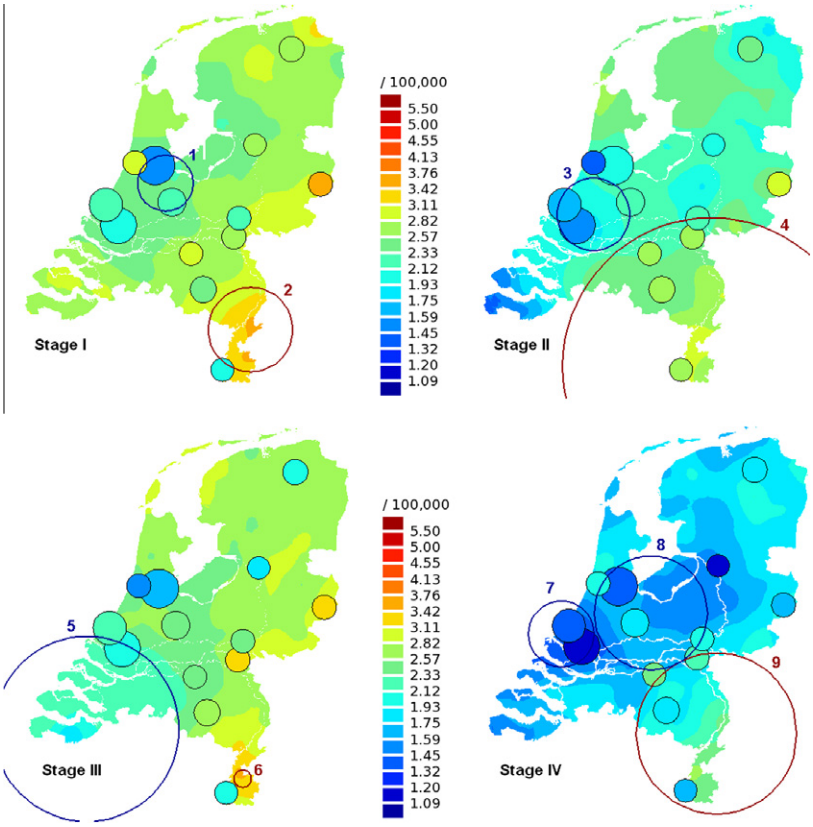

Fig. 1 – Spatial pattern of age-adjusted incidence of rectal cancer per 100,000 persons-years in the Netherlands 2001–2005, by stage.

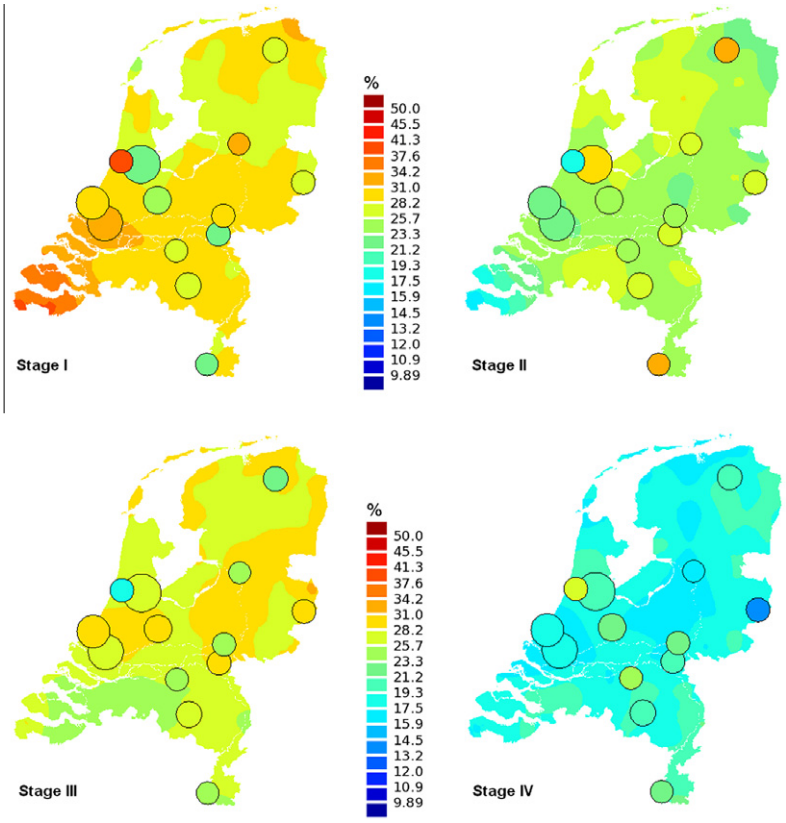

Fig. 2 – Spatial pattern of stage distribution of rectal cancer in the Netherlands 2001–2005, presented as proportions.

Table 2 – Areas with a significant higher or lower stage-specific rectal and colon cancer incidence compared with the rest of the country.

Tumour	Stage	Area	Radius of circle (km)	Crude rate (per 100,000 persons)	Relative risk	P-value*
Rectum						
	I	1	23	3.2	0.7	0.001
		2	35	6.0	1.4	0.003
	II	3	30	3.0	0.7	0.001
		4	123	4.7	1.3	0.001
	III	5	76	3.4	0.8	0.002
		6	7	7.7	1.9	0.002
	IV	7	27	2.1	0.7	0.002
		8	47	2.4	0.8	0.033
		9	66	3.9	1.4	0.001
Colon						
	I	10	48	4.7	0.8	0.002
		11	13	3.1	0.5	0.023
		12	17	8.0	1.4	0.042
	II	13	57	11.0	0.8	0.001
		14	60	15.2	1.1	0.009
	III	–				
	IV	–				

* Accounted for multiple testing.

identified for colon and rectal cancer separately. These are shown as transparent circles on the maps. The blue circles are the areas with a significantly lower incidence, the red circles are those with a significantly higher incidence.

3. Results

The Netherlands has more than 16 million inhabitants. In total, 12,428 rectal tumours and 30,579 colon tumours were diagnosed in the period 2001–2005 in the Netherlands (Table 1). For rectal tumours, the proportion was highest (29%) for stage I disease. For colon tumours, the proportion of patients with stage II disease was the highest (36%).

3.1. *Rectal cancer*

Areas in the south eastern part of the Netherlands had a significantly higher incidence rate of all stages of rectal cancer, whereas areas in the western or south western part of the country had a significantly lower incidence rate of all stages (Fig. 1, Table 2). Focussing on stage distribution, the south western part of the country had a high proportion of stage I disease and a low proportion of stage II disease (Fig. 2). No large differences in stage distribution between the large cities and the rest of the country were found.

3.2. *Colon cancer*

The south western part of the Netherlands had a significantly lower incidence rate and an area in the south eastern part had a significantly higher incidence rate of stage II disease (Fig. 3, Table 2). There were no areas with significantly lower or higher incidence rate of stages III or IV colon cancer. There were no differences in stage distribution between the large cities and the rest of the country (Fig. 4).

4. Discussion

This study showed modest spatial variation in stage-specific incidence and stage distribution of rectal cancer but almost no variation in colon cancer. A publication about time–space trends in the Netherlands revealed a slightly higher baseline incidence level and relative increase in the overall incidence rate of colorectal cancer in the east.[1] This could be explained by a high prevalence of risk factors in this region such as obesity, dietary habits and lack of physical activity.[16–18] The spatial variation in stage-specific cancer incidence rates reported in this study are partly related to the differences in overall incidence and the related risk factors. However, there are some other factors that could affect the stage-specific incidence and the stage distribution.

Differences in *diagnostic activity* among non-symptomatic persons influences overall incidence, stage-specific incidence and stage distribution. The mass screening is expected to increase the incidence of stage I and decrease the incidence of advanced stages. Furthermore, due to the detection and removal of adenomatous polyps and adenomas, it should lead, finally, to a decrease in the overall incidence of colorectal cancer. However, the pilot studies for organised screening with faecal occult blood testing have been started in the Netherlands only since 2006, after the closing date of our study. Therefore, organised screening cannot affect the incidence rates shown in this study. The minister of Health, Welfare and Sport postponed the decision about the introduction of colorectal cancer screening to 2019 due to financial reasons and insufficient colonoscopy capacity. After implementation

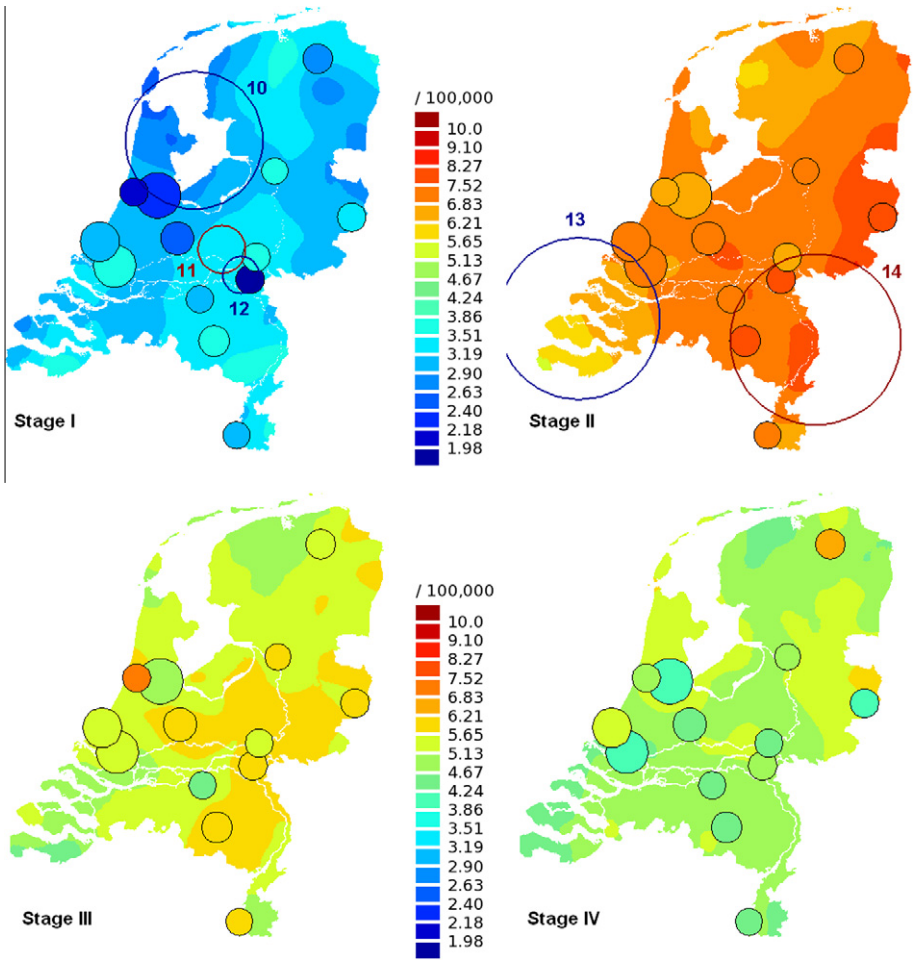

Fig. 3 – Spatial pattern of age-adjusted incidence of colon cancer per 100,000 persons-years in the Netherlands 2001–2005, by stage.

of the screening in the whole country, it would be interesting to study the incidence patterns again.

Differences in stage-specific incidences and stage distribution between regions can be a reflection of the variation between hospitals in adherence of the recommendations in the guidelines about the use of *diagnostic tools*. Nowadays, according to the Dutch guidelines of diagnosis and treatment of colon and rectal cancer, patients should be screened for distant metastases using spiral Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) of the liver, combined with chest X-ray.[19,20] CT scanning will lead to upgrading due to a shift of early metachronic distant disease to synchronic disease.[21] A study in the central southern part of the Netherlands found no optimal adherences to clinical guidelines, showing a large variation in diagnostic assessment between hospitals.[22] Hospitals with a higher quality of diagnostic assessment may find more patients with advanced disease. However, the maps in our study demonstrated no clear differences in stage distribution in the central southern part. Furthermore, large variation is seen in lymph node evaluation between hospitals and pathology laboratories leading to differences in stage distribution.[23,24] Regions with a high proportion of stages I and II and a low proportion of stage III could be regions with hospitals and pathology laboratories which perform more suboptimal lymph node evaluations.

In this study we used the pathological stage. Downstaging might occur in patients with rectal cancer who received a long course of preoperative radiotherapy.[25] A regional population-based study reported large variation between hospitals in the central southern part of the Netherlands in radiotherapy use for patients with rectal cancer[26], possible leading to differences in stage distribution. Regions with a high proportion of low stages of rectal cancer, e.g. the south western area, could be regions with a high use of preoperative radiotherapy leading to downstaging.

Above mentioned explanations could lead to differences between regions, but are all related to variation in methods of staging or variation in treatment and do not explain real differences in stage-specific incidence.

Patient delay also affects differences in stage distribution. Factors influencing patient delay, such as non-recognition of the seriousness of symptoms, lack of knowledge about the disease, fear and not worrying, often affect the behaviour of the patient.[27–30] These factors might vary between areas, causing differences in health utilisation, and could lead to differences in stage distribution. For example, difficult access to health care can change people's attitude. An inverse relation

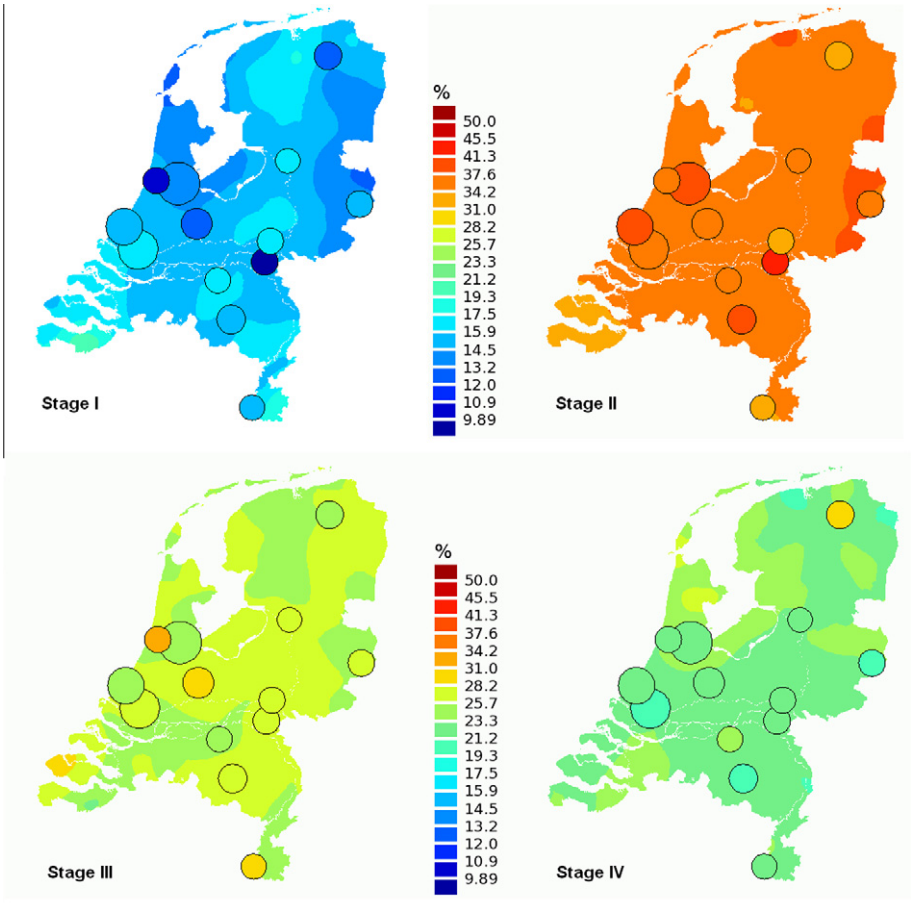

Fig. 4 – Spatial pattern of stage distribution of colon cancer in the Netherlands 2001–2005, presented as proportions.

between perceived need and remoteness has been found.[31] In the United Kingdom patients living in rural areas presented with advanced stage disease often assessed their symptoms to be trivial, suggesting lower expectations of care for patients living in these areas.[32] In our study, there was no clear association between rural areas and advanced disease. In the Netherlands, opposite to many other European countries, people with a higher socioeconomic status generally live outside the big cities.

High health care costs also could have influence on using health care. In countries with a poor insurance system, such as the United States of America, uninsured people have to pay the health care costs themselves which could lead to a delay in going to the hospital. However, in the Netherlands, everyone has a healthcare insurance. Educational interventions might be especially useful in the regions with a high incidence of advanced disease of colorectal cancer. A review on this topic concluded that these interventions should not focus on the patient's awareness of symptoms, but on their recognition and understanding of the possible seriousness of those symptoms and possibilities to gain from an early disease.[30]

A study from Denmark showed an association between delay in treatment and advanced stage for rectal cancer, but not for colon cancer.[33] However, the results about delayed diagnosis and stage are not consistent. Results from a review showed that diagnostic delay had no association with advanced disease or even an opposite association when colon and rectal tumours were analysed separately.[34] A study from the United Kingdom showed that symptomatic colorectal cancer patients with delay between referral and diagnosis have less aggressive tumours and markedly better long-term cure compared to earlier diagnosed tumours.[35] This suggests that other factors, such as *tumour biology*, may also be important.

In conclusion, in this study we demonstrated spatial variation in stage-specific cancer incidence. Knowledge about this variation can support policymakers in the planning of local educational interventions and in the planning of care facilities.

5. Conflict of interest statement

None declared.

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