

# Incidence and histological features of colorectal cancer in the Northern Cape province, South Africa

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## Summary

*Aim.* The purpose of this study was to determine the incidence of colorectal cancer (CRC) in the Northern Cape province of South Africa, and to identify patients with histological and demographic features suggestive of hereditary non-polyposis colon cancer (HNPCC).

*Method.* This is a retrospective review of all cases of primary adenocarcinoma of the colon or rectum diagnosed by the two pathology laboratories operating in the Northern Cape between January 2002 and February 2009. Demographic data were collected, as well as pathological staging of the tumours and histological features suggestive of HNPCC (according to the revised Bethesda guidelines for microsatellite instability testing). Population census data for the Northern Cape were obtained from Statistics South Africa.

*Results.* The annual incidence of CRC in the Northern Cape was 3.7/100 000 population (3.5/100 000 for men and 3.9/100 000 for women). The median age at which colorectal cancer was diagnosed was 59 years (range 16 - 90 years). On pathological and demographic criteria, 75/206 (36%) of the patients met at least one of the criteria of the revised Bethesda guidelines for microsatellite instability testing.

*Conclusion.* CRC is rare in the Northern Cape, and one-third of the patients had demographic or tumour histological features suggestive of HNPCC.

Each year approximately 1 million people are diagnosed with colorectal cancer (CRC) worldwide, but the incidence varies greatly. The disease is commonest among Japanese men, and lowest in Africa.<sup>1</sup> Colorectal cancer is reported to have a low incidence in South Africa, although it appears to have increased over the past decade. CRC is now the fourth commonest cancer in men in South Africa, and the third commonest in women.<sup>2,3</sup>

Hereditary non-polyposis colorectal cancer (HNPCC) is the commonest inherited colorectal cancer. It is an autosomal dominant condition caused by germline mutations of the mismatch repair genes, and is characterised by young-onset CRC as well as extracolonic malignancies.<sup>4,5</sup> These tumours display microsatellite instability (MSI-h), and have distinctive pathological features. The suggestive clinical and pathological features of these tumours are summarised in the revised Bethesda criteria for the diagnosis of HNPCC6 (Table I). The purpose of these criteria is to select patients for genetic testing for HNPCC.

Previous studies of colorectal cancer in black South Africans have reported that colorectal cancer affects a disproportionately large number of younger patients,<sup>7,8</sup> and that pathological and immunohistochemical features suggestive of HNPCC were

**TABLE I. THE REVISED BETHESDA GUIDELINES FOR TESTING COLORECTAL TUMOURS FOR MICROSATELLITE INSTABILITY (MSI)<sup>6</sup>**

**Tumours from individuals should be tested for MSI in the following situations:**

- 1. Colorectal cancer diagnosed under the age of 50 years of age**
- 2. Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumours,\* regardless of age**
- 3. Colorectal cancer with the MSI-h histology<sup>†</sup> diagnosed in a patient under 60 years of age**
- 4. Colorectal cancer diagnosed with one or more first-degree relatives with an HNPCC-related tumour, with one of the cancers being diagnosed under age 50 years**
- 5. Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumour, regardless of age.**

\*Hereditary non-polyposis colorectal cancer (HNPCC)-related tumours include colorectal, endometrial, stomach, ovarian, pancreas, bladder, ureter and renal pelvis, biliary tract, brain (usually glioblastoma as seen in Turcot syndrome), sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.

<sup>†</sup>Presence of tumour infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern.

common in CRC in this group of patients.<sup>7</sup> In the mid-1980s the first familial cases of CRC to be reported in South Africa were identified in Kleinsee, a remote town in the Northern Cape. The family was found to have HNPCC, with a unique mutation of the hMLH1 gene. Since then we have identified over 1 500 subjects (many of whom live in the Northern Cape) from a number of different families as being at risk for HNPCC on the basis of their family trees. We have identified 13 different germline mismatch repair gene mutations in these subjects, but the mutations in the majority of these subjects remain unknown.<sup>9,10</sup>

The Northern Cape has an estimated population of just over 1.1 million people and is the least populated province of South Africa, with an average of 3 persons per square kilometre.<sup>11</sup> The incidence of colorectal cancer in this area has not been documented, and the prevalence of HNPCC in the population is unknown.

The purpose of this study was to determine the incidence of colorectal cancer in the Northern Cape, and to identify patients with histological and demographic features of HNPCC in order to guide further genetic screening in this population.

## Methods

All cases of primary adenocarcinoma of the colon or rectum diagnosed in the Northern Cape province of South Africa between January 2002 and February 2009 were retrospectively reviewed. All pathology reports of colorectal adenocarcinoma from both pathology laboratories operating in the Northern Cape (the National Health Laboratory Services (NHLS), which provides a service to the state hospitals, and Pathcare, which serves the

private sector) were requested. The patients from the state and private health systems were analysed separately, as this is a surrogate marker for affluence in the South African health care system.

Tumours were staged according to the Duke's staging system<sup>12</sup> (staging was based only on the histological findings – no information regarding distant metastases was available except when metastases were biopsied or resected for histological examination), and graded as poorly, moderately or well differentiated. The site of the tumour was noted, as were histopathological features suggestive of microsatellite instability.

Wherever possible the address and postal codes of the subjects were obtained, and any subjects found to be living outside the Northern Cape were excluded from the study. In the absence of any information to the contrary, subjects were assumed to be residents of the Northern Cape if they had undergone their colorectal cancer operations in that area.

When a patient was diagnosed with a metachronous colon cancer within the study period, only the first cancer was included in the study.

To calculate the incidence of colorectal cancer, census data for the population of the Northern Cape were obtained from Statistics South Africa.<sup>13</sup> In order to allow comparison with cancer rates in populations with different age demographics, the age-standardised rate (ASR) for colorectal cancer was calculated using the World Standard Population.<sup>14</sup>

## Statistics

Statistical analysis was performed using Statistica 8 software. Categorical data were compared using the chi-square or two-sided Fisher's exact tests as appropriate. Normally distributed continuous data were compared using Student's *t*-test and continuous data with a skewed distribution using the Mann-Whitney U-test. A value of  $p < 0.05$  was considered to be significant.

## Ethics

Anonymity of the subjects was assured and patient information was only available to the investigators. Ethical approval for the study was granted by the Health Sciences Faculty Research Ethics Committee of the University of Cape Town.

## Results

We identified 206 patients with adenocarcinoma of the colon or rectum between January 2002 and February 2009. Of these, 101 were men and 105 women.

### Incidence of colorectal cancer

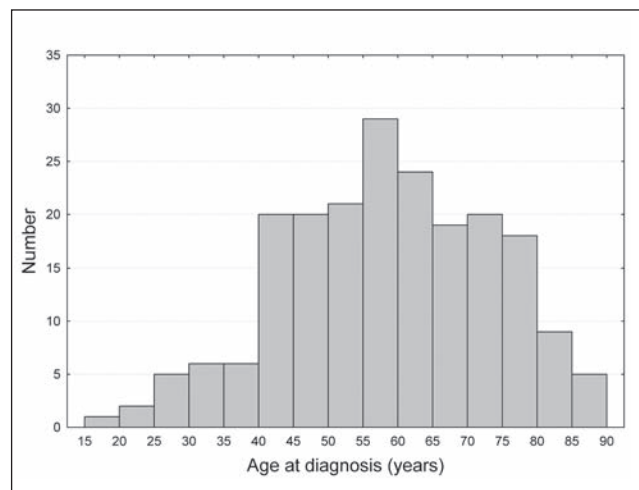
Records could only be obtained from the Pathcare laboratory for the period 2006 - 2008, so the incidence of colorectal cancer in the Northern Cape could only be calculated for that time. During that period, 113 patients were diagnosed with colorectal cancer (73 patients (65%) in the public sector, and 40 (35%) in the private sector). The population of the Northern Cape in 2007 was 1 102 200, so the annual incidence of colorectal cancer in that period was 3.7/100 000 population (3.5/100 000 for men, and 3.9/100 000 for women). The ASR was calculated to be 4.2/100 000 world standard population per year (this was similar for men and women).

**Age**

The median age at which colorectal cancer was diagnosed was 59 years (range 16 - 90 years). The age of one of the 206 patients was unknown. The age distribution is illustrated in Fig. 1. The age of diagnosis was lower in men than women (57 v. 61 years,  $p=0.033$ ). Patients treated in the public health sector were diagnosed with colorectal cancer at a younger age than those treated in the private sector (57 v. 63 years,  $p=0.024$ ).

**Site**

The site of the colorectal cancer could be clearly identified by the pathology report in 190 cases. Of these tumours, 58 (31%) were located in the right side of the colon and 132 (69%) in the left side. Subjects who were diagnosed with colorectal cancer before the age of 50 years were more likely to have right-sided cancers than those who were diagnosed when they were older than 50 (23/48 (48%) v.



**Fig. 1. Age of diagnosis of colorectal cancer in the Northern Cape Province.**

**TABLE II. SITE DISTRIBUTION OF COLORECTAL CANCERS**

Location	N	%
<b>Caecum</b>	<b>26</b>	<b>12.6</b>
<b>Ascending colon including hepatic flexure</b>	<b>8</b>	<b>3.9</b>
<b>Transverse colon</b>	<b>21</b>	<b>10.2</b>
<b>Descending colon including splenic flexure</b>	<b>9</b>	<b>4.4</b>
<b>Sigmoid</b>	<b>38</b>	<b>18.4</b>
<b>Rectosigmoid</b>	<b>7</b>	<b>3.4</b>
<b>Rectum</b>	<b>74</b>	<b>35.9</b>
<b>Right hemicolon*</b>	<b>3</b>	<b>1.5</b>
<b>Left hemicolon*</b>	<b>4</b>	<b>1.9</b>
<b>Unknown</b>	<b>16</b>	<b>7.8</b>
<b>Total cancers</b>	<b>206</b>	<b>100</b>

\*The site was not described more specifically than this in the pathology report.

35/141 (25%),  $p=0.007$ ). The sites of the cancers were similar for men and women ( $p=0.55$ ). The sites of the colorectal cancers are shown in Table II.

**Stage**

Pathological staging information was complete in 125 patients. The stage distribution of colorectal cancers is shown in Table III. There was no significant difference in stage of diagnosis between patients who were cared for in the public and private sectors. There was also no difference in stage distribution between males and females ( $p=0.83$ ), younger (<50 years) and older (>50 years) subjects ( $p=0.27$ ), or right- versus left-sided cancers ( $p=0.63$ ).

**Microsatellite instability features**

Table IV shows the frequency of demographic and histological features suggestive of microsatellite instability (MSI) in the colorectal cancers. Patients were younger than 50 years of age in 54/205 cases (26%). Patients who were under 50 years were more likely to have mucinous tumours than older patients (10/54 (19%) v. 11/151 (7%),  $p=0.038$ ).

On pathological and demographic criteria alone, 75/206 (36%) of the patients met at least one of the criteria of the revised Bethesda guidelines for MSI testing, and patients treated in the public sector were more likely to fulfil these criteria than those from the private sector (65/160 (41%) v. 10/46 (22%),  $p=0.03$ ).

**Conclusion**

We found colorectal cancer to be relatively rare in the Northern Cape province of South Africa. The annual incidence was 3.7/100 000 population, with the ASR calculated to be 4.2/100 000. This is considerably lower than the incidences reported in First-World countries, which range from 45 to 61 cases per 100 000 per year,<sup>15,16</sup> but in keeping with previous studies conducted in Africa, where annual incidences from 2 to 11/100 000 have been reported.<sup>17-19</sup>

The low incidence of colorectal cancer in this study may be due to under-reporting. It is not known how many patients living in the Northern Cape may have sought medical care outside that province, and these patients would not have been identified in this study. Also, the disease may be under-diagnosed. Access to health care in the Northern Cape is limited, with a predominantly rural population who live in often very remote areas, and there is only one trained colonoscopist in practice in the public sector in the entire province. This is, however, unlikely to explain the tenfold reduction in incidence compared with Western countries.

The median age of diagnosis of CRC was 59 years, and 54/205 patients (26%) were under the age of 50 years. This is in keeping with other studies in South Africa, Nigeria, Kenya and Ethiopia,<sup>7, 20-22</sup> in which the median ages of diagnosis were between 47 and 59 years, and is in contrast to reports from America (71 years)<sup>16</sup> and the UK (73 years).<sup>23</sup> A shorter life expectancy in African countries and different demographics (with more young people in the population overall) may partly explain the median age at diagnosis, or it may reflect different tumour biology. Similarly, we found that patients who were treated in the public sector were diagnosed with CRC at a younger age than those in the private health system (57 v. 63 years). In South Africa, access to private health care may be seen as a marker of affluence and a Western lifestyle. Because of the entrenched inequalities in our society, it

**TABLE III. PATHOLOGICAL STAGE DISTRIBUTION OF COLORECTAL CANCER ACCORDING TO HEALTH CARE SYSTEM**

Duke's stage	Public (N (%))*	Private (N (%))*	Total (N (%))*	p-value
<b>A</b>	<b>11 (11.3)</b>	<b>2 (7.1)</b>	<b>13 (10.4)</b>	<b>0.73</b>
<b>B</b>	<b>43 (44.3)</b>	<b>18 (64.3)</b>	<b>61 (48.8)</b>	<b>0.086</b>
<b>C</b>	<b>31 (32.0)</b>	<b>8 (28.6)</b>	<b>39 (31.2)</b>	<b>0.91</b>
<b>D</b>	<b>12 (12.4)</b>	<b>0 (0.0)</b>	<b>12 (9.6)</b>	<b>0.067</b>
<b>Total</b>	<b>97</b>	<b>28</b>	<b>125</b>	

\*Percentage of cases in which staging was adequately documented.

**TABLE IV. FEATURES SUGGESTIVE OF MICROSATELLITE INSTABILITY (MSI)**

Feature*	Count	% of total colorectal cancers
<b>Age &lt;50 yrs</b>	<b>54</b>	<b>26.3</b>
<b>Synchronous/metachronous colorectal cancer</b>	<b>10</b>	<b>4.9</b>
<b>Other HNPCC-related tumours</b>	<b>4</b>	<b>1.9</b>
<b>MSI-H histology<sup>†</sup></b>		
<b>Mucinous/signet-ring differentiation</b>	<b>18</b>	<b>8.7</b>
<b>Presence of tumour infiltrating lymphocytes</b>	<b>14</b>	<b>6.8</b>

\*Features comprise the revised Bethesda guidelines,6 with the exception of criteria 4 and 5 (concerning family history).

<sup>†</sup>Crohn's-like lymphocytic reaction and medullary growth pattern were not mentioned specifically in any of the pathology reports.

may also be a marker for racial and therefore genetic difference between these groups. The patients' racial groupings were not recorded on the pathology reports, and we made no attempt to obtain that information as we felt that that would be a breach of the patients' privacy.

Patients under the age of 50 years were more likely to have right-sided and mucinous tumours, suggesting that MSI-h-type tumours were more prevalent in the younger patients. In this study, 36% of patients overall fulfilled at least one of the revised Bethesda guidelines for MSI testing, even without any family history being known. These patients will be further investigated for possible HNPCC (by taking their family histories, and by further immunohistochemical and genetic studies). This may allow families with HNPCC (who would benefit from colonoscopic surveillance<sup>24</sup>) to be identified.

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