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Diagnostics and Epidemiology of Colorectal Cancer

Frank T. Kolligs

Department of Internal Medicine and Gastroenterology, HELIOS Klinikum Berlin-Buch, Berlin, Germany

Keywords

Colorectal cancer · Colon cancer · Screening · Diagnostics · Colonoscopy · Staging

Summary

Colorectal cancer is one of the leading causes of cancer-related morbidity and mortality. Main risk factors include advanced age, family history, male sex, and lifestyle factors. Screening can reduce incidence and death from colorectal cancer. Therefore, prevention and early detection are crucial in order to detect and remove pre-neoplastic adenomas and to detect cancers at early stages. Colonoscopy, flexible sigmoidoscopy, and fecal occult blood tests are established tools for screening. Newer fecal immunochemical tests reveal higher sensitivities for advanced adenoma and cancer than guaiac-based hemoccult tests. Molecular stool and blood tests as well as virtual colonoscopy and colon capsule endoscopy are promising new developments so far not established as routine instruments for the prevention and early detection of colorectal cancer. Colonoscopy is the method of choice for the diagnosis of colorectal cancer and for adenoma removal. Prognosis is essentially dependent on the tumor stage at the time of the initial diagnosis. Proper staging based on imaging prior to therapy is a prerequisite. In rectal cancer, local staging is an essential requirement for the identification of appropriate candidates for neoadjuvant therapy.

Introduction

Colorectal cancer is the most frequent malignant disease of the gastrointestinal tract, the third most common cancer in men (746,000 cases, 10% of all cancers), the second most common cancer in women (614,000 cases, 9.2% of all cancers), and responsible for 600,000 deaths annually worldwide [1].

More than 50% of all cases occur in more developed regions with wide geographic variation in incidence across the world. Incidence rates vary ten-fold in both sexes worldwide, the highest estimated rates are found in Oceania (age-standardized rates of 44.8 and 32.2 per 100,000 in men and women, respectively), and the lowest in Western Africa (4.5 and 3.8 per 100,000) (fig. 1). For 2012, 345,000 new cases and 152,000 deaths were reported in the European Union [1]. In some regions with previously low incidence rates, e.g. Eastern Europe and East Asia, significantly increasing numbers of colorectal cancer cases have been noted and attributed to changes in risk factors and diet towards a lifestyle common to Western countries [2, 3].

In Germany, the lifetime risk of developing colorectal cancer is 6.9% in men and 5.7% in women. This corresponds to 1 in 14 men and 1 in 18 women being diagnosed with colorectal cancer within their lifetime, and 1 in 32 men and 1 in 39 women die from colorectal cancer [3]. The risk increases continuously with age. The mean age at diagnosis is 72 years in men and 75 years in women. Age-standardized incidence and mortality rates as well as absolute numbers of new diagnoses have recently been decreasing in Germany. The relative 5-year survival rate is 63% in both sexes.

Risk Factors and Inherited Forms

The individual risk of colorectal cancer is essentially dependent on non-modifiable dispositional factors such as age, sex, and family history as well as the in principle modifiable exposure to risk factors. It is estimated that 30–50% of the colorectal cancer risk is attributable to lifestyle factors such as smoking, high consumption of red and processed meat, obesity, diabetes, and excessive consumption of alcohol [4].

Age as a risk factor is equally relevant in women and men. More than 50% of colorectal cancers are diagnosed after age 70, and only 10% are diagnosed before age 55 [2]. However, the risk of men developing advanced adenoma or cancer is roughly double that of women [5, 6]. Furthermore, men develop advanced adenoma and colorectal cancer earlier in their lives than women

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Prof. Dr. med. Frank T. Kolligs
Klinik für Allgemeine Innere Medizin und Gastroenterologie
HELIOS Klinikum Berlin-Buch
Schwanebecker Chaussee 50, 13125 Berlin, Germany
frank.kolligs@helios-kliniken.de

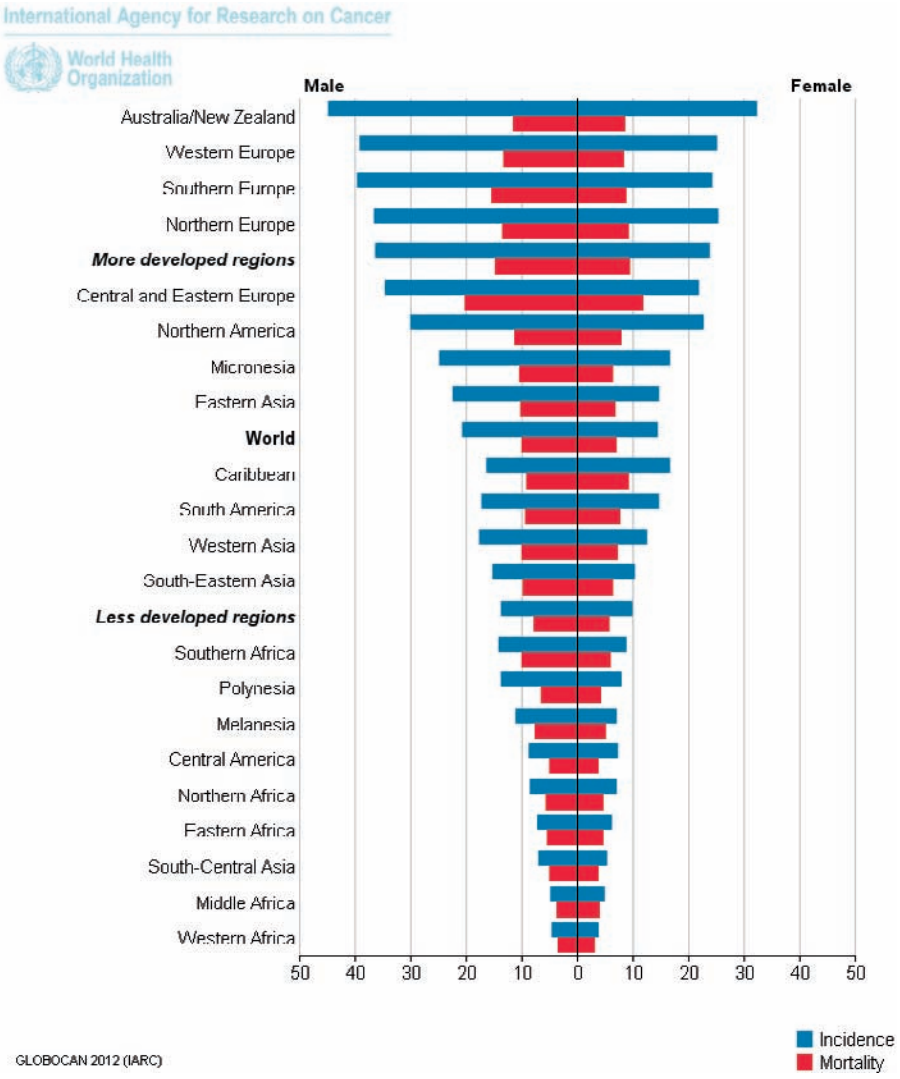

Fig. 1. Estimated age-standardized rates of colorectal cancer worldwide per 100,000 persons [1].

[6, 7]. A recent study demonstrated that male sex increases the risk to a similar extent as a positive family history of colorectal cancer [8].

Hereditary Colorectal Cancer Syndromes

Up to one-third of the colorectal cancer risk may be attributable to hereditary factors. Individuals who have biological relatives with a history of colorectal cancer or colorectal adenoma are at increased risk of developing colorectal cancer. The level of risk depends on the degree of kinship, the age at which the index person was diagnosed with colorectal cancer, and the number of relatives affected [9]. Besides familial risk, 3–5% of colorectal cancer cases are attributable to hereditary syndromes (table 1) [10]. The two most common forms of hereditary colorectal cancer are hereditary nonpolyposis colon cancer (HNPCC, Lynch syndrome) and familial adenomatous polyposis coli (FAP). Both syndromes are autosomal dominant disorders where in HNPCC one allele of a DNA repair gene and in FAP one allele of the tumor suppressor gene *adenomatous polyposis coli* (*APC*) are inactivated in the germline. Tumor formation occurs when the function of the remaining gene allele is abrogated by a somatic event. However, only approximately 80% of individuals with FAP have an affected parent, around 20% of cases are de novo mutations. Beginning at a mean age of 16 years (range 7–36 years), hundreds and even thousands of colonic adenomas develop [11]. By age 35, 95% of individuals with FAP have adenomas. Without colectomy, colon cancer is inevitable. Colectomy is usually recommended when more than 20–30 adenomas or multiple adenomas with advanced histology have developed. In contrast, attenuated FAP is characterized by a significant but lower risk for colon cancer than in classical FAP with fewer colonic adenomas which are more proximally located. Cancer occurs later in life. In individuals with attenuated FAP, colectomy may be necessary, but in individuals with a limited number of adenomas, colonoscopy surveillance and polypectomy may be sufficient [12].

Lynch syndrome is attributable to pathogenic variants of the genes *MLH1* (50% of cases), *MSH2* (40%), *MSH6* (7–10%), *PMS2* (<5%), and *EPCAM* (1–3%), and is characterized by an increased risk for colorectal cancer (lifetime risk 52–82%, mean age at diagnosis 44–61 years) and cancers of the endometrium (25–60%, 48–62 years), ovaries (4–12%, 42.5 years), stomach (6–13%, 56

Table 1. Hereditary colorectal cancer syndromes

Syndrome	Precursor lesions	Genetic defect	Disease specifics
HNPCC	development of up to 30 adenomas; typical molecular pathogenesis of colorectal cancer	mismatch repair deficiency; inactivation of DNA repair genes (*MLH1*, *MSH2*, *MSH6*, *PSM2*) or the gene *EPCAM*; autosomal dominant inheritance; allele frequency 1:350–1:1,700	mean age at cancer diagnosis is 40 years; lifetime risk of developing colorectal cancer 50–80%; frequent development of syn- and metachronous cancers, e.g. endometrial, ovarian, gastric, and small intestinal cancers
FAP	development of hundreds to over a thousand adenomatous polyps, classical adenoma-to-carcinoma sequence	mutation of the *APC* gene; autosomal dominant inheritance; allele frequency 1:10,000	start of adenoma formation at the age of 10, development of colorectal cancer from age 20 onwards; obligate precancerous condition; duodenal and periampullary adenoma in 45–90%
Attenuated FAP	development of 10–100 adenomatous polyps	mutation of the *APC* gene; autosomal dominant inheritance	lifetime risk of developing colorectal cancer >80%
MAP	development of 20 to >100 adenomatous polyps	mutation of the *MUTYH* gene; autosomal recessive inheritance	lifetime risk of developing colorectal cancer >80%
PJS	development of up to 20 mostly hamartomatous polyps	mutation of the *STK11* gene; autosomal dominant inheritance	lifetime risk of developing colorectal cancer approximately 40%; hyperpigmented macules on lips and oral mucosa
JPS	development of up to 5 to >100 hamartomatous polyps	mutation of the *SMAD4* or the *BMPR1A* gene; autosomal dominant inheritance	lifetime risk of developing colorectal cancer 40–70%
Cowden syndrome	mixed polyposis including hamartomas	*PTEN* mutation in 80% of cases; autosomal dominant inheritance	lifetime risk of developing colorectal cancer approximately 15%; increased risk of developing several types of cancer, including cancers of the breast, thyroid, and uterus; cumulative risk of developing any cancer by age 70 is approximately 90%

HNPCC = Hereditary non-polyposis colon cancer (Lynch syndrome); FAP = familial adenomatous polyposis coli; MAP = MUTYH-associated polyposis; PJS = Peutz-Jeghers syndrome; JPS = juvenile polyposis syndrome; APC = adenomatous polyposis coli.

years), small intestine, hepatobiliary tract, urinary tract, brain, and skin [8]. Regular colonoscopy with removal of precancerous polyps reduces the incidence of colorectal cancer. Therefore, the current recommendation is to perform colonoscopy every 1–2 years beginning at ages between 20 and 25 years or 2–5 years before the earliest diagnosis in the family, whichever is earlier [13].

Patients with long-standing inflammatory bowel disease also have an increased risk of developing colorectal cancer [14]. The risk is essentially determined by the extent and duration of the inflammation in the colon. Risk is further increased in the case of coexistence of primary sclerosing cholangitis.

Early Detection and Prevention

Lifestyle modification, identification of individuals at risk, and removal of pre-neoplastic lesions are the most important measures for the prevention of colorectal cancer. Evidence from randomized trials shows a protective effect of several drugs including aspirin and hormone replacement therapy. A meta-analysis demonstrated a reduction in colorectal cancer-associated mortality among aspirin users with a latency of 10 years [15]. However, adverse effects including gastrointestinal bleeding preclude the use of aspirin for the primary prevention of colorectal cancer among the general population.

Screening for Occult Blood

Colorectal cancer commonly develops slowly over many years. The disease can be prevented if adenomas are detected and removed before they progress to cancer. Moreover, colorectal cancer is mostly curable if detected at early stages. Therefore, in contrast to the majority of other cancers, screening and early detection are excellent measures for the secondary prevention of colorectal cancer and associated death. Colorectal cancer-related morbidity and mortality can be reduced by screening programs. This has been demonstrated for stool tests detecting occult blood and flexible sigmoidoscopy. Non-invasive stool tests include gFOBTs (guaiac fecal occult blood tests) and FITs (fecal immunochemical tests for hemoglobin). These tests detect microscopic amounts of blood by targeting either heme (gFOBTs) or human globin (FITs). A meta-analysis of 4 large randomized controlled trials demonstrated that

annual or biennial gFOBT screening led to an average 16% reduction in colorectal cancer-related mortality [16]. However, in 3 of the 4 studies, there was no effect on the incidence of colorectal cancer. The limited impact of gFOBT testing is due to its limited sensitivity for advanced adenoma with 10–15% and cancer with 30–35%. In contrast to gFOBTs, FITs are specific for human globin and have a higher sensitivity for advanced adenoma and cancer.

Qualitative FITs use an immunochromatographic approach similar to other point-of-care tests, e.g. home pregnancy tests. Quantitative tests are usually analyzed automatically using immunoturbidimetric methods. Some tests reach sensitivities of up to 25% for advanced adenoma and of 70% for cancer while maintaining a high specificity of 95% and higher [17, 18]. To date, there are no randomized controlled trials available that demonstrate superiority of FITs over gFOBTs in terms of reducing colorectal cancer-related mortality. However, considering the facts that both FIT and gFOBT identify components of erythrocytes, gFOBT has been demonstrated to reduce mortality, and performance of several FITs in terms of sensitivity and specificity is superior to gFOBT, it is very likely that fecal immunochemical testing has a superior effect on colorectal cancer incidence and mortality [19].

Endoscopy

Four randomized controlled trials have demonstrated that a single round of screening by flexible sigmoidoscopy resulted in a reduction in incidence (18–23%) and mortality (22–31%) of colorectal cancer [20–23]. Colonoscopy is the gold standard as a diagnostic tool for the colon and serves as the method of choice for the further work-up of positive stool tests and sigmoidoscopies, both in studies and in clinical routine. Cohort studies have demonstrated that colonoscopy in combination with polypectomy is able to reduce the incidence and mortality of colorectal cancer [24, 25]. A recent study demonstrated that colonoscopy was able to reduce the risk of dying from colorectal cancer by 68% [26]. Randomized controlled trials demonstrating a reduction in incidence and mortality through colonoscopy screening are not yet available but are underway: NordICC (NCT00883792), COLONPREV (NCT00906997), SCREESCO (NCT02078804), and CONFIRM (NCT01239082). Results are expected between the years 2025 and 2034.

The emergence of interval cancers after initially negative screening colonoscopy is an important issue. Interval cancers are colorectal cancers that are diagnosed within 5 years of the last colonoscopy with either a negative result or followed by removal of all adenomas. There are three major reasons for the occurrence of interval cancers of the colon: i) colonoscopy missed advanced adenomas or cancer; ii) incomplete polypectomy; and iii) rapid de novo carcinogenesis. Prerequisites for avoiding interval cancers are a clean lavage of the colon, examination by an experienced colonoscopist, and total endoscopy reaching the cecum. A colonoscopist adenoma detection rate of ≥20 has been demonstrated to be associated with the lowest number of interval colorectal cancers [27]. Complete polypectomy is essential to avoid adenoma recurrence [28]. After polypectomy, a surveillance endoscopy is recommended after 3–5 years depending on the size, number, and histology of the polyps removed. In the case of a piecemeal resection of an adenoma, the follow-up colonoscopy should be performed within 2–6 months.

New Kids on the Block

Several new tools for colorectal cancer screening have been developed and are currently being tested. These include computed tomographic colonography (CTC), magnetic resonance colonography (MRC), colon capsule endoscopy (CCE), and molecular stool and blood tests. CTC reaches sensitivities of 90% and more for adenomas ≥10 mm [29–31] and is therefore the second most sensitive tool for evaluating the colon. In contrast to CTC, MRC is not based on ionizing radiation but on magnetic resonance. In one study, sensitivities of MRC for adenomas ≥6 mm and advanced adenoma were 78.4 and 75%, respectively [32]. CCE is a procedure that uses an ingestible capsule with a camera at both ends that produces images of the colon during transit. Second-generation CCE reaches a sensitivity of 88% for polyps ≥10 mm [33]. CTC, MRC, and CCE are first-round screening tests. While their sensitivities for significant findings are superior to stool tests, they all have two major drawbacks: i) one prerequisite similar to colonoscopy is colon lavage, and in the case of significant findings, a colonoscopy possibly preceded by a second lavage needs to be carried out; and ii) depending on the cut-off size of lesions for referral to colonoscopy, cost-efficiency might be a major issue.

Highly sensitive and specific, easily applicable, and broadly accepted first-round screening tests able to reliably select screenees with significant findings for colonoscopy would be ideal. Unfortunately, no such test is in sight yet. Newer stool and blood tests are based on the detection of DNA, RNA, or protein biomarkers derived from the tumors, either released into the circulation or shed into the stool. Based on the detection of circulating methylated Septin 9 DNA, the SEPT9 test has been demonstrated to have a sensitivity of 48% for colorectal cancer and of 11% for advanced adenoma which is not beyond that achievable with gFOBT and FIT [34]. A large study recruited 9,989 participants who provided a stool sample before colonoscopy that was analyzed using a panel of 4 DNA methylation markers and a FIT. This study demonstrated a sensitivity of 92.3% for colorectal cancer and of 42.4% for advanced adenoma for the DNA stool test plus FIT versus 72 and 23% for the FIT alone [35]. However, taking into account the lower specificity of the DNA test, there is no clear advantage of the DNA test over the FIT [36].

Diagnosis and Staging

Stage at diagnosis is the most important prognostic factor. The 5-year relative survival of patients diagnosed with colorectal cancer is 90% for patients with localized disease, 69% for patients with regional spread, and below 12% for patients with metastatic disease

Table 2. Classification of colorectal cancers according to local invasion depth (T stage), lymph node involvement (N stage), and presence of distant metastases (M stage) [38]

	Definition
T stage	
Tx	no information about local tumor infiltration available
Tis	tumor restricted to mucosa, no infiltration of lamina muscularis mucosae
T1	infiltration through lamina muscularis mucosae into submucosa, no infiltration of lamina muscularis propria
T2	infiltration into, but not beyond, lamina muscularis propria
T3	infiltration into subserosa or non-peritonealized pericolic or perirectal tissue, or both; no infiltration of serosa or neighboring organs
T4a	infiltration of the serosa
T4b	infiltration of neighboring tissues or organs
N stage	
Nx	no information about lymph node involvement available
N0	no lymph node involvement
N1a	cancer cells detectable in 1 regional lymph node
N1b	cancer cells detectable in 2–3 regional lymph nodes
N1c	tumor satellites in subserosa or pericolic or perirectal fat tissue, regional lymph nodes not involved
N2a	cancer cells detectable in 4–6 regional lymph nodes
N2b	cancer cells detectable in 7 or greater regional lymph nodes
M stage	
Mx	no information about distant metastases available
M0	no distant metastases detectable
M1a	metastasis to 1 distant organ or distant lymph nodes
M1b	metastasis to more than 1 distant organ or set of distant lymph nodes or peritoneal metastasis

Table 3. Overall Union International Contre le Cancer stage classification of colorectal cancer [38]

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1–T2	N0	M0
Stage II	T3–T4	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
Stage III	any	N+	M0
IIIA	T1–T2	N1	M0
	T1	N2a	M0
IIIB	T3–T4a	N1	M0
	T2–T3	N2a	M0
	T1–T2	N2b	M0
IIIC	T4a	N2a	M0
	T3–T4a	N2b	M0
	T4b	N1–N2	M0
Stage IV	any	any	M+
IVA	any	any	M1a
IVB	any	any	M1b

[37]. Colorectal cancers are classified according to local invasion depth (T stage), lymph node involvement (N stage), and presence of distant metastases (M stage) (table 2) [38]. These TNM stages are combined into an overall Union Internationale Contre le Cancer (UICC) stage definition (table 3) which provides valuable prognostic information and basic therapeutic guidance. However, the individual patient's outcome and response to therapy are not predicted. Patients presenting with stenosing cancer who cannot be completely endoscopied prior to surgery can receive CTC, but should receive complete colonoscopy within 6 months after curative resection, because synchronous colorectal cancers occur in up to 4% of cases.

Two-thirds of all colorectal cancers are located in the colon and one-third in the rectum. Once the histological diagnosis of colorectal cancer is established, the local and distant extent of disease needs to be determined. About 20% of patients with newly diagnosed colorectal cancer have distant metastases. Basic examinations include an abdominal ultrasound and a chest X-ray. In the case of significant findings or limited informational value, a CT scan of the abdomen or thorax should be performed. It is standard practice in many institutions to perform standard abdominal, pelvic, and chest CTs prior to surgery in patients with stage II, III, and IV colorectal cancers. However, while this approach is debatable, certain findings such liver metastases not detected by ultrasound may alter the surgical approach. Sensitivity for liver metastases is highest for MRI followed by CT, and lowest for ultrasound [39].

CT imaging of the chest might be of more value in patients with rectal cancer since the liver is bypassed here and the venous drainage of the lower rectum is via the hemorrhoidal veins to the vena cava inferior. One major issue is the finding of indeterminate lesions in the lung in many patients, a minority of which finally turn out to be colorectal metastases. In a review of 12 studies including 5,873 patients who received a chest CT scan for staging, 9% were found to have indeterminate pulmonary nodules. Only 10.8% of these nodules finally turned out to be colorectal cancer metastases [40]. Positron emission tomography CT scanning is not a standard examination in preoperative staging but may be helpful in evaluating patients with metastatic disease for further surgery.

Accurate local staging is essential in patients with rectal cancer and a prerequisite for identifying patients who are candidates for chemoradiotherapy prior to surgery. The exact distance of the tumor from the anal verge is determined by rigid rectoscopy. Transrectal ultrasound (TRUS) and MRI are the most accurate imaging modalities for locoregional staging. Involvement of the circumferential resection margin (CRM) is an important independent prognostic factor in rectal cancer and can be most reliably determined preoperatively by MRI. Cancers that involve the CRM have a higher rate of pelvic recurrence after surgery alone [41]. If the mesorectal fascia is involved or if the tumor extends to a point that is within 1–2 mm of the mesorectal fascia, the CRM is threatened; these patients are appropriate candidates for neoadjuvant therapy.

Disclosure Statement

The author declares no competing interests.

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