Benefits and Risks of Colorectal Cancer Screening

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Colorectal Cancer Screening: Pro

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In the Western world, colorectal cancer (CRC) is responsible for one of the most common metastatic tumors. In Germany in 2010, 33,800 men and 28,620 women newly developed CRC, and 13,489 men and 12,510 women died from this disease [1]. Despite an observed reduction in incidence and mortality of more than 20% in the last 10 years in both sexes, adjusted to age (fig. 1), CRC still is the third most commonly diagnosed cancer and the second most common cause of death.

There is a clear correlation with age: Beginning at age 50 years, the risk for men increases significantly; for women of 55 years or older, the risk increases but is slightly lower. The prognosis of this tumor is dependent on disease stage. Thus, the chances for cure are much higher in earlier compared to later stages. The relative 5-year survival rates range between 90% in early T1 stages and 15% in the case of distant metastasis [2].

According to our current level of knowledge, 75% of newly diagnosed CRC are sporadic. However, there are certain risk groups characterized by familial CRC accumulation as well as genetic disorders. In persons with familial exposure, the cancer risk is moved up by 10 years in contrast to the general population; familial risk accounts for 15–20% of CRC. 40- to 45-year-old persons with a familial risk have a comparable cancer risk as 55- to 59-year-old persons in the general population [3]. The classic genetic cancer, Lynch syndrome (4–5%), and familial intestinal polyposis (FAP, 1%) account for 5–6% of CRC. The S3 guideline of the German Society of Digestive Diseases and Metabolism describes and specifies the neces-

sary diagnostic and therapeutic steps of all examination modalities, the indications for general CRC screening, risk situations, as well as the necessary follow-up intervals after diagnosis and resection [4].

In most cases, CRC develops via precursor lesions, so-called polyps or adenomas, the progression of which through accumulation of genetic changes is well known (adenoma-cancer sequence). An important fact is that these tumors grow slowly over 10–15 years, and because of this time frame and due to the process of growth into the lumen of the gut, they can be easily detected via fecal analysis (occult blood test) or by endoscopy (colonoscopy) with the possibility of immediate resection of precursor lesions or early cancers. Recent investigations have demonstrated that especially in the right-sided colon there are subgroups of polyps, so-called serrated adenomas, which grow faster [5]. Since 2002 in Germany, an enhanced but still opportunistic prevention and early detection program exists for both sexes, which includes the guaiac-based fecal occult blood test (gFOBT) beginning with the 50th year of age as well as screening colonoscopy beginning with the 55th year of age. The stool test is offered annually up to the 55th year, and in the case of refusal of colonoscopy every 2 years beginning with the 56th year. Screening colonoscopy can be repeated 10 years after an inconspicuous initial colonoscopy.

The basis for the implementation and validation of the gFOBT was formed by a number of large randomized studies with a long-term follow-up and the highest evidence level of 1A. According to these studies, it is accepted that with annual or biennial use of the test a significant reduction in CRC incidence of approximately 20% can be achieved [6–8].

Fig. 1. Incidence and mortality of CRC in Germany (modified from [1]).

The basis for screening colonoscopy was provided amongst others by the American National Polyp Study which showed that following consequent polypectomy a reduction in CRC incidence of up to 90% may be achieved [9]. In a recently published survey of patients approximately 20 years after the initial study, it was in fact demonstrated that after polypectomy patients were 50% less likely to die of CRC compared to the control group [10].

Some randomized studies using once-only flexible sigmoidoscopy screening, a method which is common in Great Britain but not in Germany, have shown that with this technique also a significant reduction in CRC incidence and mortality can be achieved [11–14]. In the German CRC S3 guidelines, these data have led to a recommendation grade B and a level of evidence 2B (de novo) [4]. Results of epidemiologic studies allow the conclusion that with screening colonoscopy presumably an ever greater effect might be achieved [15, 16]. For screening colonoscopy, prospective randomized studies are under way [17].

It would be unethical and unjustifiable to wait for the results of these studies and withhold the possibility of a colonoscopy from insured people in the meantime, especially against the background of the results of another recent American study which showed a reduction in incidence after more than 20 years and especially a reduction in mortality of proximal colon cancer achieved by colonoscopy [18].

Screening colonoscopies in the United States (U.S.) confirm that in an asymptomatic population without any risk after age 50 years cancer can be detected in 1% and advanced adenomas in 8–9%; in up to 20% smaller adenomas can be detected [19]. With today's high-definition endoscopy also very small, flat lesions can be evaluated accurately, at least with regard to their dignity, and can be completely resected with the use of latest techniques. In Germany, screening colonoscopy is scientifically governed by the Zentralinstitut für die

Kassenärztliche Versorgung (ZI). In a 10-year survey, it was demonstrated that in Germany similar results (1% cancers, 6–7% advanced adenomas) can be achieved [20]. Of importance is the fact that cancers detected by screening colonoscopy exhibit a significant stage shift to the prognostically favorable stages; 69% of cancers were detected in International Union Against Cancer (UICC) stages I and II with a very good to good prognosis.

Intermediate results of 2,821,392 German screening colonoscopies carried out between 2003 and 2008 have been published in top-ranking journals and represent the largest ever cohort of patients receiving screening colonoscopy described in a national or international publication [21]. The authors of this study report an age-dependent number needed to screen (NNS) for the detection of advanced neoplasia (large adenomas, cancers) – an important figure for judging the benefits of a procedure. In the age group of 55–59 years, this figure is approximately 14 for men and 26 for women; in the age group of 70–75 years, it is 9 and 14, respectively. If a benefit for the general population with a CRC risk of 6% can be clearly seen, it can be expected that in risk persons this benefit is even higher, despite the fact that large prospective and randomized studies are missing (which may be generally justifiable on ethical grounds?).

On the basis of these data, in 2010, it was shown that more than 100,000 cancers could be avoided and over 50,000 detected early with the chance of curative treatment. The avoided cases of resection of an advanced adenoma would have become clinically manifest in a median time of 10 years after screening colonoscopy. In analogy to the U.S. American data [10], it can be anticipated that even with the existing opportunistic screening model (colonoscopy after positive gFOBT, polypectomy), in the next years, an additional significant reduction in mortality and incidence can be seen. An invitation program following European recommendations has the potential to clearly improve these figures.

The total complication rate in 2012 was with 2.1 events per 1,000 colonoscopies on the same level as in previous years (bleedings 1.3/1,000, cardiopulmonary problems 0.4/1,000, perforations 0.2/1,000). This shows that colonoscopy is a nearly safe procedure [21]. The participation rate for screening colonoscopy up to now has been adequate: in 10 years approximately 20% of women and 18% of men have had a colonoscopy [22].

It is important to know that especially men have an increased risk for CRC, which not only the ZI data show [20] but which is also verified by other studies. Hence, the NNS to detect an adenoma in men is 5.4, in women 9.3. There is also a gender-specific age shift: 55- to 59-year-old men get the disease as frequently as women being a decade older [23, 24]. The conclusion is that the offered start of screening examinations should be differentiated and handled with more flexibility.

The existing opportunistic CRC screening is quite adequate in comparison to other European countries; however, within the National Cancer Plan a working group for the further development of CRC screening in Germany has recommended the introduction of a nationwide organized invitation program: every eligible person from the age of 50 years should be invited to a counseling session in which further prevention and early detection procedures can be discussed [25, 26]. Meanwhile, the lower house of the German parliament (Bundestag) and the Federal Assembly (Bundesrat) have decided on a cancer early detection and registry law (Krebsfrüherkennungs- und -registriergesetz, KFRG), which follows the recommendation of the working group and provides a personal invitation for men and women to participate in CRC screening comparable to the invitation program for breast cancer screening which still exists for women. Additional progress has been made due to the flexibilization of the age limits, which allows an earlier start of CRC screening especially for risk persons. The Federal Joint Committee (G-BA) is to implement the KFRG by 2017.

In the 1990s, new immunologic tests to detect occult blood in feces (fecal immunochemical tests, FITs) were developed, which in numerous studies have shown better results than the commonly used gFOBT [27–29]. FITs are heavily used in quite a few neighboring European countries [30]. The tests generally show significantly better sensitivity with equal specificity compared to the gFOBT [31, 32]. With FITs, no diet restrictions are necessary because only human hemoglobin is measured. The tests are easier to handle; in general only one probe is necessary. Another advantage is better acceptance compared to interventional procedures like colonoscopy [33]. FITs fulfill the necessary preconditions to qualify as an advanced low-threshold option for CRC detection besides colonoscopy. Currently, an intense debate is ongoing as to the quality requirements FITs ought to fulfil in order to be accepted by general insurance funds. The new S3 guidelines for CRC have included this test as a so-called ‘is able’ recommendation [4], and the German National Cancer Plan has recom-

mended that the gFOBT in the regular early cancer detection program should be replaced or at least complemented by the better FITs [25, 26].

The experience in Germany with the opportunistic CRC screening program implemented in 2002 and the currently planned adjustment to an organized invitation program reinforces the pro arguments for CRC screening: i) CRC in Germany, with approximately 62,400 new cases and 26,000 deaths per year despite an observed slow reduction over the last years, remains a relevant disease; ii) Efficient methods (gFOBT, colonoscopy) for CRC screening and prevention are at hand; iii) Evidence-based as well as long-term follow-up studies show a significant reduction in the incidence and mortality of CRC; iv) Endoscopic resection of advanced adenomas prevents the development of CRC; v) Cancers detected by screening colonoscopy are in 2/3 of the cases in the early UICC stages I and II and have a very good prognosis; vi) With the FITs, a further improvement of low-threshold screening options can be achieved (implementation in the general insurance in Germany is awaited); vii) Colonoscopy as gold standard has a low complication rate (2.1 events/1,000 examinations) and is therefore very safe; viii) The 10-year follow-up data of the ZI show that especially through screening colonoscopy more than 100,000 CRC cases have been prevented and over 50,000 were detected in the early UICC stages I and II; ix) Persons at increased risk of CRC benefit from risk-adapted early detection.

The legal decision to follow the recommendations of the working group for the further development of CRC screening within the framework of the National Cancer Plan to implement a nationwide organized invitation program was a forceful step in the right direction.

Colorectal Cancer Screening: Benefits and Harms

Carsten Schröder (Bremen); Maria Kallenbach (Bremen); Klaus Giersiepen (Bremen)

In 2010, there were 33,800 new cases of CRC in men and 28,620 in women in Germany, which makes CRC the second most frequent type of cancer in men and the third most frequent in women. In the same year, 13,489 men and 12,510 women died of CRC [1]. German cancer registry data show a decreasing age-adjusted incidence in both men and women since the year 2000.

Screening by stool tests or flexible endoscopy allows not only the detection of prevalent CRC. Screening is mainly geared towards benign intestinal adenomas as precursor lesions which can be removed during the endoscopy session. CRC screening thus has the potential to reduce CRC incidence and mortality.

The present CRC screening strategy in Germany for those insured under statutory health insurance (70 million, total population 80.6 million [34, 35]) comprises [36]: i) Opportunistic

gFOBT (Hemoccult®, POCT Ltd., London, UK) offered annually and free of charge to the asymptomatic population aged 50–54 years; for individuals aged 55 years and older, gFOBT is offered biennially with no upper age limit. ii) Opportunistic colonoscopy screening, provided free of charge by internists, gastroenterologists, or surgeons with pertinent certified specializations, as an alternative to gFOBT, for those aged 55 years and older, to be repeated after 10 years. Reimbursement guidelines require endoscopic imaging and photographic documentation of the cecum for a full reimbursement, while partial colonoscopy without documentation of the cecum carries a lower fee. Polyps and adenomas may be removed during the endoscopic procedure and are reimbursed and documented separately as well as biopsies. In these cases, screening, diagnosis, and therapy take place during the same session.

Flexible sigmoidoscopies may not be reimbursed under the German statutory health system, neither for screening of asymptomatic individuals nor for the diagnostic workup of symptomatic patients: as a consequence, sigmoidoscopes are almost unavailable and sigmoidoscopies are rarely carried out.

FITs, designed as a qualitative point-of-care (POC) test to be interpreted by the person examined or by practice personnel, are not yet available in the context of statutory health insurance (i.e., free of charge). POC-FITs are offered by many general practitioners and gastroenterologists and have to be paid for individually by the patient (Individuelle Gesundheitsleistungen; IGeL). Quantitative FITs designed for mass screening and requiring specific laboratory equipment for reading, interpretation, and centralized documentation are not commonly used in Germany.

M2-PK tests, which are based on the fecal pyruvate kinase isoenzyme, are widely used by company physicians offering screening to the workforce they are in charge of. M2-PK tests may also be offered by gastroenterologists and general practitioners, and also have to be paid for individually (IGeL) as they are not covered by statutory health insurance.

Neither computed tomography colonography, video capsule colonoscopy, nor stool DNA tests are covered by German statutory health care. They may be purchased as individually paid health tests. There is no evidence of any beneficial effect from randomized trials on CRC incidence or mortality.

Benefits and Harms of Tests for CRC

The benefits of gFOBT screening in terms of reduced mortality from CRC have been shown decades ago by large randomized controlled trials (RCTs), some of them population-based [37]. However, as yet, no trial has proven the benefits of gFOBT in terms of total mortality [8]. The Cochrane Review in 2011 stated a possible reduction in cancer incidence through the detection and removal of colorectal adenomas.

Harms of gFOBT may be caused by false-positive or false-negative test results or by overdiagnosis relating to cancers

that would never have caused any symptoms if not detected by screening. At the time of diagnosis, overdiagnosed cancers cannot be distinguished from cancers with a poor prognosis and are thus subjected to the same therapy and associated beneficial and adverse effects. In the case of overdiagnosis, therapy is unnecessary and has to be judged by its adverse effects only. A French population-based study with a study population aged between 50 and 74 years calculated the NNS to avoid one case of CRC death by gFOBT to be 239 [38].

While colonoscopy is the gold standard diagnostic test in symptomatic patients and serves as verification test after a positive fecal test or sigmoidoscopy, there are still doubts about its use as a primary screening tool in asymptomatic individuals. Contrary to the requirements defined by the WHO screening criteria, colonoscopy is not a simple test widely accepted by the population. 8 years after the introduction of the German colonoscopy program, the cumulative proportion of participants was estimated to be 18% [22, 39, 40]. These figures are based on case data and may thus be an overestimate, as repeated examinations of the same individual cannot be identified.

There is moderate evidence for reduced CRC incidence and mortality from case-control and cohort studies [10, 41], while RCTs testing the effect of colonoscopy on CRC incidence and mortality or total mortality are still lacking. A study by Brenner et al. [42, 43] used Markov models to estimate the reduction in incident cancers since the commencement of the CRC screening program in 2002 in Germany (follow-up until 2010), and calculated that about 100,000 CRC were prevented by the program during that period. These calculations were based on prevalence data on advanced adenomas stemming from the program, and transition rates were used from advanced adenomas to preclinical CRC and from preclinical cancer to clinically manifest cancer, assuming that 85% of CRC arise from advanced adenomas. The concept of the adenoma-cancer sequence was first described by Morson in 1975, but there is hardly any longitudinal data supporting this idea [18, 44]. A 30-year follow-up within the Nurses' Health Study (NHS) showed multivariate hazard ratios for death from CRC of 0.59 (95% confidence interval (CI) 0.45–0.76) after screening sigmoidoscopy and 0.32 (95% CI 0.24–0.45) after screening colonoscopy. Reduced mortality from proximal colon cancer was observed after colonoscopy (0.47; 95% CI 0.29–0.76) but not after sigmoidoscopy. These data show a stronger protective effect of colonoscopy compared to sigmoidoscopy. The NHS, however, did not use random allocation of screening tests, so selection bias may have played a role (as was the case with the apparent benefit found for hormone replacement therapy on cardiovascular risk [45], which could not be confirmed in a large RCT following the NHS [46]).

Guidelines support the idea of colonoscopy surveillance after detection and removal of adenomas [30, 47]. Taking into account several studies designed to define the most appropriate interval after the removal of polyps or adenomas (e.g. U.S.

Table 1. Relative risks (RR) and 95% confidence intervals (CI) for invitation to sigmoidoscopy versus no invitation: results of intention-to-treat and per protocol analysis from Norway, the United Kingdom, Italy, and the USA

	RR (95% CI; p)			
	Norway [53]	UK [11]	Italy [12]	USA [13]
CRC incidence (intention-to-treat)	134.5 vs. 131.9 cases per 100,000 person years	0.77 (0.70–0.84; p < 0.0001)	0.82 (0.69–0.96)	0.79 (0.72–0.85; p < 0.001)
CRC incidence (per protocol)	not assessed	0.67 (0.60–0.76)	0.69 (0.56–0.86)	not assessed
CRC mortality (intention-to-treat)	0.73 (0.47–1.13; p = 0.16)	0.69 (0.59–0.82; p < 0.0001)	0.78 (0.56–1.08)	0.74 (0.63–0.87; p < 0.001)
CRC mortality (per protocol)	colorectal: 0.41 (0.21–0.82; p = 0.011) rectosigmoidal: 0.24 (0.08–0.76; p = 0.016)	0.57 (0.45–0.72)	0.62 (0.40–0.96)	not assessed

National Polyp Study [48], Funen Adenoma Follow-up Study [49]), the European guideline suggests that the first follow-up colonoscopy should be at least 3 years after baseline polypectomy for most patients with adenomas [30]. The German guideline makes more detailed recommendations on the interval of follow-up colonoscopies. Depending on size, quantity, and histology of the removed adenomas, the recommendations vary between a first follow-up colonoscopy after 2–6 months and no follow-up examination at all [47]. The evaluation concept presently used in Germany only provides process outcomes (e.g. participation, detection, and biopsy rates), but does not provide any information on CRC incidence and mortality as endpoints [50].

In the German documentation system, complications occurring during colonoscopy, e.g. hemorrhage or perforation, have to be recorded by the endoscopist. As adverse effects of colonoscopy may occur after the patient has left the screening facility, underreporting of adverse effects is likely. Follow-up studies based on health insurance data, however, have shown that hospital stays due to gastrointestinal hemorrhage or perforation are rare in the aftermath of a colonoscopy in both symptomatic and asymptomatic cases [51, 52]. However, these studies were not designed to detect effects in those patients who received sedation (propofol in most cases) for colonoscopy but did not undergo the procedure due to adverse effects of the sedation or of bowel cleansing/laxatives in preparation of the examination. In such cases, a colonoscopy is not recorded in the reimbursement data and will be missed in subsequent analyses of adverse effects.

While flexible sigmoidoscopy is practically unknown in Germany and cannot be reimbursed by statutory health insurance, there is strong evidence of a benefit from 3 large RCTs from the United Kingdom [11], Italy [12], and the USA [13]. In populations aged between 55 and 64 years (USA 55–74 years), a reduction in CRC incidence of more than 20% after a follow-up of at least 10 years was recorded (table 1). A Norwegian study, however, could only detect a benefit of the intervention in the per-protocol analysis after a follow-up of 7 years [53]. The British and the American study also showed a reduction in CRC mortality in the intervention arm. These

protective effects on CRC incidence and mortality are most likely the results of the removal of adenomas and polyps during sigmoidoscopy or a subsequent colonoscopy. Removal of adenomas or polyps were part of the intervention test in the British, Norwegian and Italian studies, but not in the American study where sigmoidoscopy-positive patients were referred to ‘usual care’.

A recent meta-analysis confirmed the preventive effects of sigmoidoscopy-based screening on the incidence and mortality of CRC. The calculated NNS to prevent 1 case of CRC was 361, and the NNS to prevent 1 death from CRC was 850 [14]. Similar conclusions were drawn in another meta-analysis of 14 trials. Flexible sigmoidoscopy was more effective at detecting advanced adenoma and carcinoma than stool-based tests [54]. The European guideline recommends sigmoidoscopy as a screening tool [55]. The German guideline published more recently (June 2013) mentions the British study only and recommends sigmoidoscopy only for those refusing a colonoscopy [47].

Individuals scheduled for sigmoidoscopy are required to consume nothing but clear fluids the day before the test, and to either take an enema on the morning of the procedure at home or have an enema administered at the screening center. In contrast, persons undergoing colonoscopy take oral laxatives only, usually requiring no more than 1 day of sick leave.

One of the disadvantages of flexible sigmoidoscopy is that only the distal colon can be reached by the instrument, and more proximal tumors may thus be missed. Autopsy studies in various populations have shown 57–67% of rectal cancers growing in the distal colon, which may thus not be visible during sigmoidoscopy. Only 26–35% of all tumors develop proximal to the left colonic flexure [56]. As these proximally located tumors are missed by sigmoidoscopy, this strategy has been likened to performing mammography on 1 breast only [57]. Empirical data challenge this apparently plausible reasoning; however, several studies have shown that the preventive effect of colonoscopy on incidence and mortality from CRC is mostly limited to the left side of the colon, which can also be examined via sigmoidoscopy [58–60].

An additional argument for a sigmoidoscopy-based screening program is the axiom of starting with a simple, sensitive

test that is widely accepted by the population, rather than immediately implementing the most sophisticated and expensive one. This reasoning led to a decision against mass screening by endoscopy in the Netherlands for instance. In this context, the possibility of an additional benefit from colonoscopy must be weighed against additional harm and costs to individuals and society [61]. However, any positive stool test or positive sigmoidoscopy will trigger subsequent colonoscopy with biopsies taken for verification or exclusion of cancer. This step will again reduce the number of false-negative screening tests.

Laboratory-based semiquantitative FITs have shown better test parameters than the currently used gFOBT. Compliance with FITs is superior, as a gFOBT requires samples from 3 successive defecations while for a FIT it is sufficient to take only 1 sample from different parts of the surface of a single defecation [31, 62–64]. A Dutch study found FITs to be more cost-effective than gFOBT in spite of a higher price per FIT [63]. Due to superior test characteristics of FITs compared to gFOBT, the European guideline recommends quantitative immunochemical tests as the test of choice for new population screening programs. In contrast to quantitative FITs, POC-FITs are not advised for population-based screenings because their individual interpretation by the users themselves or by medical staff complicates standardized assessment and evaluation. However, centralized laboratory processing of FITs and participation in laboratory external quality assurance schemes are essential [49, 65].

Overdiagnosis

Every screening program will detect cancers that would not have appeared clinically during the individual's lifetime. Overdiagnosis is likely when incidence continues to rise after the prevalence round of a screening program with repeated invitations while mortality remains unchanged. As the main objective of CRC screening is to detect precursor lesions, and only a fraction of those removed during screening would have turned into manifest cancer, there is a large potential for overdiagnosis and overtreatment of adenomas. In the present German program, for each patient detected with manifest CRC there are 7 participants who have their adenomas or polyps removed during the screening session, not counting follow-up colonoscopies [43]. This issue deserves further attention as patients with once detected adenomas are monitored more often than the average population, and this has to be considered when judging benefits and harms.

Outlook for the German CRC Screening Program

Starting in autumn 2015, the German CRC screening strategy will be expanded by an invitation scheme intended to raise the participation rate. The National Cancer Plan suggests that

every German citizen above a not yet determined age limit will receive a letter of invitation to attend a scheduled colonoscopy [26]. We believe there is no scientific reason to restrict the invitation to colonoscopy only. Instead, we suggest a study that includes an equal ratio of colonoscopy, sigmoidoscopy, and quantitative FIT. A positive FIT or sigmoidoscopy test result would lead to subsequent colonoscopy. The 3 tests should be offered in a randomized fashion to asymptomatic persons between 55 and 70 years of age. In Germany, this would currently apply to approximately 14 million people. We suggest randomizing by month of birth, so all 3 groups would have a comparable age distribution [66]. If all 3 tests are labelled by unique billing codes in health services data, an evaluation scheme can be set up either by intention to screen or per protocol. Such a design would help to find the best test and the one with the highest cost-benefit ratio. It would also save money, as iFOBT and sigmoidoscopies are cheaper than colonoscopies for all. Scientifically, this approach would go beyond the statement by Inadomi in 2012 [67]: 'patient preferences for screening tests should be identified and respected – in this case, the best test is the one that gets done'. The 'any test will be beneficial' approach would maximize the use of tests among the population, but would also leave the following questions unanswered: 'Which is the best test?' and 'What are the harms caused by each test?'

As the target population of 14 million people in Germany cannot be served all at once, we should learn from Finland while establishing the invitation program, where new screening programs are set up in a randomized fashion [68]. In Finland, intervention and reference group are distinguished by year of birth. As soon as 50% of the population have been invited to take part in screening, the reference group is invited and joins the intervention group. The time lag between the first 50% served and the second 50% can then be used for detecting potential benefits and harms of the program. We believe that following the Finnish model will not cause any delay in serving the population or lead to extra costs in Germany, but will provide answers as to the benefits and harms of FITs, sigmoidoscopies, and colonoscopies offered to the asymptomatic population.

Colorectal Cancer Screening: Comment

Hans-Joachim Schmoll (Halle/Saale)

Screening for CRC and Precursor Lesions: An Unanimous 'Yes' – But by Which Means?

Early detection of a manifest cancer at an early stage and – even more relevant with respect to cure – detection and elimination of clearly defined potential precursor lesions is without any doubt the best approach to strongly reduce cancer mortality and morbidity. This is even more relevant for those tumors which have a high prevalence as CRC which is the most frequent tumor type across Europe if males and fe-

males are taken together. Screening for early and almost always curable stages, and in particular precursor lesions, is a dream which is reality for only a very limited amount of cancer types, mostly minority diseases. Besides CRC, only cervical cancer, melanoma visible on the skin, and at least in part breast cancer (however, in contrast to CRC, metastasis may occur even at very early local stages) are to some degree suited to early diagnosis and prevention by eliminating precursor lesions. The colon and rectum, which can be repeatedly explored by endoscopy, have an almost unique position in the fight against cancer, in particular since effective means for primary prevention are not available.

The introduction of mass screening for early CRC and potential precursor lesions, including their resection, must be regarded as a major achievement and has without any doubt saved an enormous amount of lives over time, with even more to be achieved in the future. Those countries which have implemented free endoscopic screening for persons over 50–55 years of age have introduced a highly effective measure and reaped the benefits of this procedure in terms of considerably reduced mortality – an effect that will become more and more pronounced in the future due to the lead time of more than 10 years from diagnosis of adenoma and polyps to death from CRC.

Accordingly, both author groups, the ‘pro’ and ‘cons’, are clearly in favor of the screening and early detection approach as performed in Germany for over 10 years. The question, however, is raised by the ‘con’ party, whether colonoscopy is an adequate screening tool, as besides being a more expensive procedure it may cause harm to a degree that could reduce the benefit of this in principle excellent approach. Indeed, with 14 million people to be screened in Germany, even a small benefit results in high success rates; accordingly, even a low risk of complications can add up to a relatively high number. This is the main argument of the ‘con’ authors who propose a prospective evaluation of the available methods within the current screening program in order to identify the best method with respect to efficacy, morbidity, and costs. In particular, their criticism of the reporting of acute side effects as part of the screening program in Germany, indicating a low complication rate of 1 in 5,000, is supported by the fact that only acute problems are registered and later occurring events are not reported within this program. There is an unclear number of more severe side effects of mass screening colonoscopy, despite the fact that in Germany gastroenterologists and endoscopists are well trained, with a documented low acute complication rate.

Clearly, sigmoidoscopy is less invasive, less expensive, and much easier on the patient with regard to the preparation required for this investigation; however, at least 1/3 of the lesions – located in the right and median part of the colon – are not detected. With the addition of the FIT stool test, at least some of these lesions may be picked up; however, only early- or later-stage cancers but not adenomas/polyps can be de-

tected this way, resulting in a clinically relevant lesser reduction in CRC incidence in the screened group. It is, however, debatable whether this would result in higher cancer mortality or only in higher morbidity due to otherwise unnecessary treatment measures; at least this is an obvious risk.

There is total agreement that the stool test, if done, must not be FOBT but FIT due to its higher accuracy (although more expensive), and this will be used in most countries including the U.S. and Germany from next year on. Furthermore, in the U.S., a probably even more exact FIT test combined with the molecular marker ‘K-ras mutation’ was recently accepted by the FDA, paving the way for a highly sensitive and specific molecular screening methodology [69]. It can be expected that in the near future even more precise and sensitive molecular methods will be established based on DNA fragments in the stool or – even more interesting – circulating in the blood. However, before this can be routinely implemented, a long road is ahead, in particular with regard to comparative testing and development of ‘easy-to-use’ methodology for this mass investigation. Such a blood test would revolutionize cancer screening per se and also screening for CRC; however, this does not currently enter into the discussion here. Furthermore, it is still unclear whether those methods based on circulating DNA will be able to safely identify the presence of adenomas and polyps. It is very likely that these new, ‘non-toxic’ methods would strongly enhance the participation rate in mass screening for CRC (and most other tumors) – a clear drawback of the current set-up with ‘only’ 20% of the target population having been investigated within a 10-year period in Germany. Because of the current low acceptance rate despite strong efforts (including the important activities of the Felix Burda Foundation), from 2015 a thorough invitation system will be implemented, which is a promising measure.

It is very much acceptable that the ‘con’ authors ask for a prospective investigation of the 3 available screening methods (FIT, sigmoidoscopy, colonoscopy) within the German national screening plan. This is an attractive proposal since – by using the ongoing screening system and already allocated financial and human resources – the at least scientifically open question of the ‘best’ method in terms of efficacy and cost could be answered. This ‘trial’ would require hardly any additional financial resources and would provide important data to add to those currently generated in Finland. This would be a great effort and in principle feasible; however, after the introduction of colonoscopy as the method for early detection and prevention to the German population, a change in this policy with randomization into these 3 groups would potentially have a strong negative effect on the perception of CRC screening among the German population. This would counteract all the years invested in educating and informing the public and thus the benefit achieved so far. A possible more feasible alternative could be a limited trial with a small but representative group of potential participants who agree to such a

randomization or are financially compensated for participation in the trial. The proposal of the ‘con’ authors for a large trial incorporating all participants seems, although scientifically very attractive, unrealistic and counterproductive in the current German situation. It is also questionable whether it is really necessary to comparatively test the 3 options: it is obvious that colonoscopy can identify 30% more precursor and definitive lesions which cannot be easily identified by FITs, as these tests detect only blood; both precursor lesions and early cancers are not very likely to bleed. Do we really need a large trial to demonstrate what is ‘logical’ and known at least in principle? For me this is somewhat questionable indeed.

However, there are other important questions which ought to be addressed in the near future, e.g. the frequency and interval of follow-up colonoscopy after resection of adenomas or polyps; in Germany, these intervals seem to be very short with 2–3 months, in contrast to other countries where up to 2 years are recommended. There seems to be ample room for improvement for the guidelines in Germany. Recent data showed that the adenoma detection rate, depending on the screening interval, is inversely associated with the risk of interval colorectal cancer and advanced stage or fatal interval cancer [70].

Another question is raised by the ‘con’ party relating to ‘overdiagnosis’ of CRC by identification of a cancer which may never create problems and will never lead to the death of the patient. There is some truth to this argument; however, we have no way of knowing which lesion will grow further and which will not. Therefore, this ‘overdiagnosis’ seems to be a more hypothetical side effect of CRC screening, which has no relevant impact on the discussion and decision-making process.

The same authors very rightly also question the quality of the FIT evaluation, and propose a centralized expert evaluation for a reliable reading of the test results. This is indeed an important request which needs to be openly discussed and addressed in the guidelines.

The two author groups disagree somewhat on the dimension of the NNS to detect 1 polyp or adenoma which then will

be resected, or 1 cancer. However, the range of available data, mostly based on population analyses and evaluations of accumulated data, suggests the best ratio currently achievable in cancer prevention and early diagnosis. There is obviously still uncertainty about the rate at which adenomas/polyps develop into overt malignant tumors, limiting the accuracy of those figures. However, it does seem to be clear that with the FOBT test the NNS is 239 to detect 1 cancer. Meta-analysis data indicate that 361 sigmoidoscopies are necessary to prevent 1 case of CRC and 850 to prevent 1 death from CRC. Furthermore, with 7 resected adenomas, 1 early CRC is identified and cured. This range of outcome data is comparable only to that seen with cervix screening. Both tumor types are frequent, and any approach to reduce incidence and prevalence and ultimately death should be strongly supported.

The benefit of this screening program seems to be substantial, and the long-term reduction in incidence and death from CRC will probably be more than 50% over time. Although several details must be improved and guidelines and methods adjusted, the screening program as planned from next year is very meaningful and will be effective in the long term. It should not be hampered by restrictions or the investigation of basic scientific questions, but rather strongly pushed forward. Having said that, in the future, the program may also benefit from accompanying scientific studies using the enormous amount of real-life data in order to obtain more precise information on cost and benefit.

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