Abstract. Background: Colorectal cancer (CRC) is a disease with major impact on public health and public health costs. Colonoscopy is purportedly the best screening tool for CRC. However, the acceptance by the general population is very poor. Therefore evaluation of additional screening tools is of great interest. Patients and Methods: The use of M2-PK measurement in the feces has been reported in 6 studies to date. The data of these studies were analysed and critically reviewed. Additionally, 1,906 persons undergoing routine health care check-up provided stool samples for M2-PK measurement. Results: The overall sensitivity of M2-PK is 77.9% for CRC. Specificity ranges from 74.3 to 83.3%. Of the 1,906 screened persons, 90.4% had results within the normal range, while 9.6% had elevated results. Conclusion: Measurement of tumor M2-PK in feces seems to be the most promising tool for CRC screening at the present time. In combination with colonoscopy, this test should hence be recommended for CRC screening programs.

Colorectal cancer is a disease with major impact on both public health and public health costs. The incidence of CRC has doubled from 1960-1980 (1). Because of the rather long process of carcinogenesis in colorectal cancer (adenoma-carcinoma sequence), appropriate screening tools provide a good opportunity to prevent carcinomas or to diagnose and treat them (e.g. by endoscopic techniques) at a very early stage.

Colonoscopy is currently purportedly the best screening tool for CRC. However, the acceptance of this method by the general population is very poor. Although it has been included in screening programs in the German health system since 2002, only about 1.7% of the population could be enrolled (2). Thus, in order to prevent and detect CRC sufficiently, the evaluation of additional screening tools is of great interest.

Recently, testing for fecal occult blood (FOBT), genetic alterations (tumor-suppressorgenes, oncogenes) and alterations of tumor metabolism (e.g. tumor M2-PK) have been under investigation. FOBT has been included in screening programs around the world and has proven a certain benefit, however the performance of this marker is fairly poor (3-7). Testing for genetic alterations (such as \( K-ras \) and \( p53 \)) is a very interesting approach, yet DNA isolation requires very fresh stool samples and, to date, the tests are still very limited in their clinical and economic usefulness.

It has been shown that the measurement of M2-PK concentrations in the feces may be a very useful screening tool with promising prospects (8-10).

Here we give an overview of the characteristics and performance of M2-PK in the feces for CRC screening and supply new data on this screening tool obtained in a health care check-up setting.

Patients and Methods

Review. Performance of M2-PK screening (sensitivity, specificity) and characteristics of all present available and published studies (6 studies) on the use of M2-PK in the feces were critically reviewed. A meta-analysis of the available studies was conducted.

Health care check-up program. After informed consent, 1,906 individuals (age 45-65 years) undergoing routine health care check-up examination provided stool samples for the measurement of fecal M2-PK concentrations. Measurements were performed using a commercially available ELISA kit (ScheBo Biotech AG, Germany) (10, 11). All subjects were considered to be healthy. If clinical findings or symptoms were present, they were recorded using standard forms.

Results

Review. The overall sensitivity of M2-PK measurement in the feces was 77.9% with regard to CRC. Specificity ranged from 74.3% for persons undergoing colonoscopy to 83.3% for...
persons considered to be healthy according to a health survey. Overall sensitivity for adenomas was 45.9%, increasing to 61.1% for adenomas larger than 1 cm. A high percentage of positive results (90.4%) was also observed in patients with chronic inflammatory bowel disease (Tables I and II).

**Health care check-up program.** In 1,906 individuals participating in the health care check-up program, the mean M2-PK level was 1.63 U/ml (SEM±0.08 U/ml), the median being 0.29 U/ml (SEM±3.68 U/ml). Of these, 1,431 had levels <2.0 U/ml, while another 292 had levels <4.0 U/ml. Using 4.0 U/ml as a cut-off level, which has been suggested in recent studies, 90.4% of the total had results within the normal range, while 9.6% had elevated results (Figure 1).

The results of colonoscopies of those who tested positive on check-up will be available shortly.

**Discussion**

Considering all the available data and the new data provided here, measurement of tumor M2-PK in the feces appears to be a good and reliable screening tool for...
colorectal carcinoma, with a sensitivity of 77.9% and a specificity ranging from 74.3% to 83.3%. The specificity appears to be even higher according to the data of the health care check-up study presented here. Taking into consideration that several of the persons screened in the health care check up are suspected of having CRC and/or adenomas according to age and risk, the specificity appears to be higher than 90%. The lower specificity in persons undergoing colonoscopy might be due to the reason that they all had specific symptoms or complaints (reason for colonoscopy) and therefore diseases of the upper gastrointestinal tract do not seem to be unlikely in this collective. Elevated M2-PK levels in patients with acute and/or chronic inflammatory bowel diseases are probably due to proliferation of epithelial cells and leukocytes in the inflammatory area. Yet this is no limitation for the use of this screening parameter for large-scale population screening, since chronic inflammatory bowel disease patients are usually diagnosed at an early age and are subject to endoscopic surveillance anyway.

Compared to the fecal occult blood test (FOBT), the M2-PK-test seems to be superior for CRC screening since the reported sensitivity of the FOBT is only about 40% (15,16). Specificity of the FOBT ranges between 20-98% (17), yet false-positive results are reported in up to 80% of asymptomatic patients (18). A major reason for the limitations of the FOBT is that many carcinomas and adenomas do not bleed (19) or bleed only intermittently (20).

Another promising screening tool is testing for genetic alterations. The most interesting candidates for this seem to be K-ras (reported sensitivity: 60%) (21), p53 (reported sensitivity: 28%) (22), APC (reported sensitivity: 57%) (23) and MSI (reported sensitivity: 40%) (24) or a combination in multigene test assays with a reported sensitivity of 63% to 100% (18). Yet, the limitations of this screening tool are its high costs and the very limited handling and shipping time of the feces (18).

Thus in comparison to the FOBT or genetic testing, measurement of M2-PK in the feces seems to be a very promising screening tool for CRC. With regard to handling, effectiveness and analysis, M2-PK would appear to have good prospects for large-scale screening for colorectal carcinoma. It might even be used to detect larger adenomas.

In combination with colonoscopy, we believe this test should hence be recommended for large scale CRC screening programs.

References


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