Faecal levels of Tumour M2-PK: sensitivity, specificity and correlation with tumour staging in colorectal cancer

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Introduction

According to Cancer Research UK colorectal cancer is the third most common cancer in the UK. In 2001 34,539 people in the UK were diagnosed with CRC, and 16,220 patients died from CRC in 2002 [1].

The development of CRCs takes place over several years. Early stages can easily be treated by endoscopic polypectomy or endoscopic resection of the mucosa. In this context effective screening strategies are of the utmost importance. Although colonoscopy is the most sensitive and specific diagnostic tool, most patients will decline this investigation as an initial screening procedure because of its invasiveness and inconvenience. Cost constraints and lack of suitably trained and experienced colonoscopists are practical obstacles to increased uptake. Therefore, more acceptable alternative markers are needed in order to detect patients at high risk.

One common alteration found during carcinogenesis is the isoenzyme shift of the glycolytic enzyme pyruvate kinase. The tissue specific isoenzymes, which have different metabolic tasks, are pyruvate kinase type L in the liver and kidney, type M1 in muscle and brain and type R in erythrocytes. All proliferating cells express the pyruvate kinase isoenzyme type M2 (Figure 1) [http://www.metabolic-database.com].

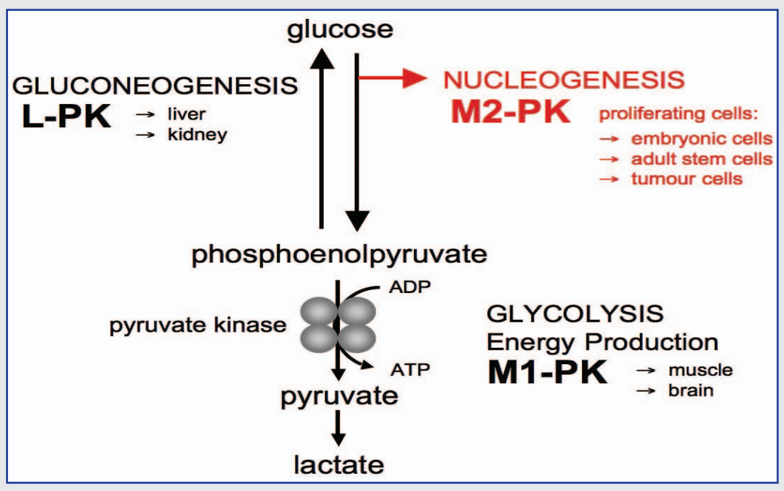

Figure 1: Different isoforms of pyruvate kinase

In healthy tissues all isoenzymes of pyruvate kinase consist of four subunits. In all tumours investigated so far, including gastrointestinal tumours, only the type M2 is detectable and pyruvate kinase is mainly in the dimeric form (Figure 2) [2]. Therefore, the dimeric form of M2-PK has been termed Tumour M2-PK.

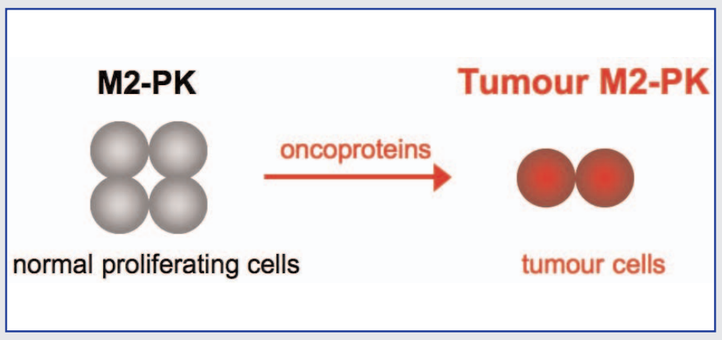

Figure 2: Shift to the dimeric form of M2-PK in cancer

In GI cancers Tumour M2-PK is elevated in EDTA-plasma samples of patients with colonic, rectal, gastric, oesophageal and pancreatic carcinomas [2, 3, 4, 5, 6].

The quantification of Tumour M2-PK in faeces provides a new, sensitive screening tool for colorectal tumours [7, 8] by direct detection of a tumour-derived enzyme that is released into the intestinal lumen.

Material and Methods

This study includes 303 patients who underwent complete colonoscopy after providing a sample for the determination of Tumour M2-PK. Stool samples were tested from patients with CRC and patients with no pathological findings. Histology was obtained from the routine biopsies and/or from surgery for all patients. Tumour M2-PK in stool extracts was determined immunologically with a quantitative ELISA which is based on two monoclonal antibodies (ScheBo® • Biotech AG, Germany).

	N	Mean [U/ml]	Median [U/ml]	Range [U/ml]
Colorectal CA	130	51.3 ± 8.9	17.0	0.11 – 800.0
Colon CA	78	60.2 ± 13.8	26.2	0.11 – 800.0
Rectal CA	52	37.9 ± 7.8	12.1	0.11 – 270.4
Controls	173	3.3 ± 0.4	1.6	0.16 – 34.3

Table 1: Tumour M2-PK in Colorectal Carcinoma (CA) and Controls

Results

Data from 173 controls with no pathological findings upon colonoscopy and 130 patients with CRC have been evaluated to date (Table 1 and Figure 3). There is a highly significant difference ($p < 0.001$) between tumour patients and controls. At a cut-off point of 4 U/ml, the calculated sensitivity is 83% for colon cancer and 73% for rectal cancer and the specificity is 82%. Faecal Tumour M2-PK levels of CRC patients were correlated with tumour staging according to TNM (Figure 4) and Dukes' classifications (Figure 5). There is a significant difference ($p = 0.007$) between controls and tumour stage T2, and a highly significant difference ($p < 0.001$) between controls and tumour stages T3 and T4. Sensitivity for T1, T2, T3 and T4 is 56%, 57%, 80%, and 83%, respectively (Figure 4). Staging according to Dukes' classification revealed a significant difference ($p < 0.0087$) between controls and Dukes A, and a highly significant difference ($p < 0.001$) between controls and Dukes B to Dukes D. Sensitivity is 55% for Dukes A, 80% for Dukes B, 80% for Dukes C and 86% for Dukes D (Figure 5).

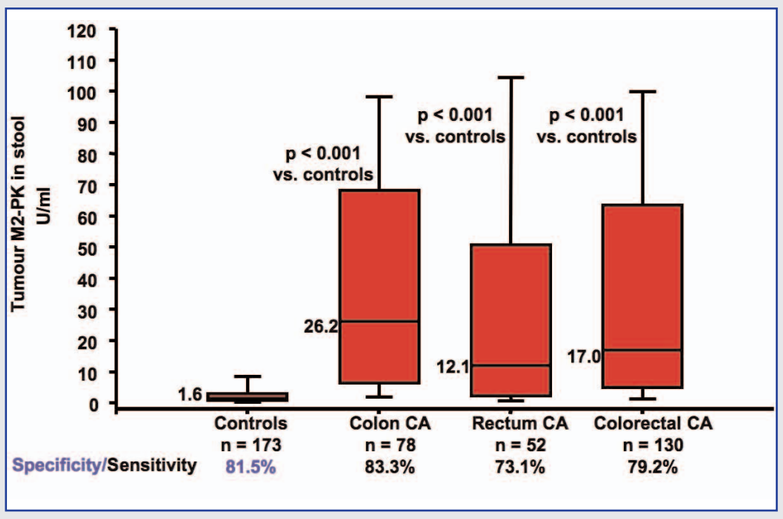

Figure 3: Faecal Tumour M2-PK in Colorectal Carcinoma (CA) and Controls

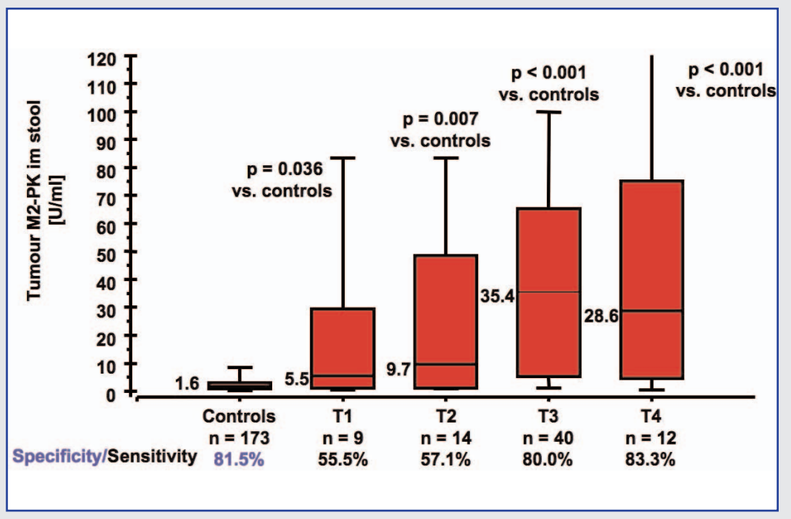

Figure 4: Correlation of faecal Tumour M2-PK levels and TNM staging in Colorectal Carcinoma patients (n = 76)

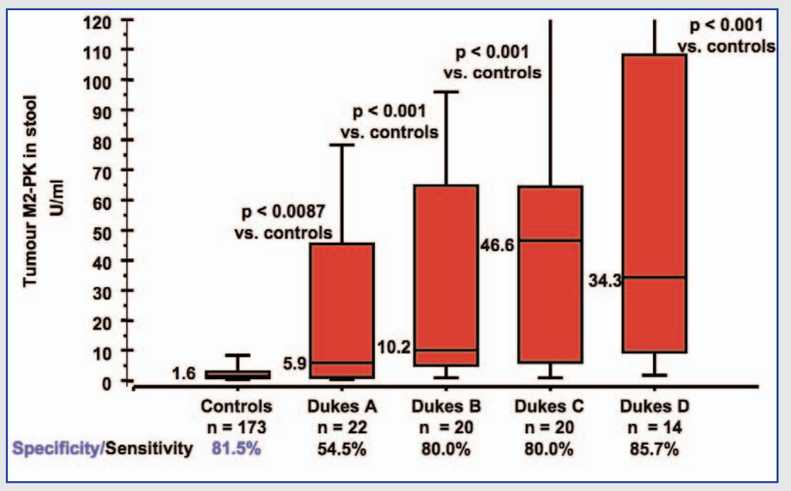

Figure 5: Correlation of faecal Tumour M2-PK levels and staging according to Dukes' classification (n = 75)

Conclusions and Discussion

This study shows that the determination of Tumour M2-PK in the stool is a valuable tool for the early detection of colorectal cancer. Tumour M2-PK levels are significantly higher in CRC patients than in the control group ($p < 0.001$) and correlate with tumour staging according to Dukes' and TNM classifications. Overall sensitivity is 79% and specificity is 82%. In comparison to FOBT (sensitivity < 30% [9]), Tumour M2-PK has a much higher sensitivity using a single spot stool sample. Since genetic testing (e.g. APC mutations) is much more expensive and did not provide better results in the clinical setting, we suggest the use of faecal Tumour M2-PK testing in combination with endoscopy of patients with positive results as a practical approach to reducing mortality from colorectal cancer.

References:

1. Cancer Research UK, www.cancerresearchuk.org
2. Hardt et al. Anticancer Res 2000; 20: 4965-4968
3. Schulze et al. Anticancer Res 2000; 20: 4961-4964
4. Mazurek et al. in: Tumor Markers: Physiology, Technology, and Clinical Applications, Diamandis et al. (Eds.) AACC Press 2002: 471-475, 2002
5. Zhang et al. World J Gastroenterol 2004; 10: 1643-1646
6. Ventrucci et al. Dig Dis Sci. 2004; 49:1149-1155
7. Hardt et al. Anticancer Res. 2003; 23: 851-854
8. Hardt et al. Brit J Cancer 2004; 91: 980–984
9. Lieberman et al. N Engl J Med 2001; 345: 555-560