complementary must be less. If data are applied to these formulae, the result is that a patient can be sick and healthy concurrently.

In response to Birindelli and associates' analysis of Table 1: Case 1 is not positive since

$$RR_{SCM} = \frac{0.200}{0.205} = 0.98$$

which represents a change in IFFP of less than 5%. We would define this as "no decision" (and run it again); case 2 is positive since $RR_{SCM} > 1$ and IFFP decreased by at least 5% in response to TAE; in case 3,

$$RR_{SCM} = \frac{0.231}{0.215} = 1.074$$

and the change in IFFP due to TAE is less than 5%, suggesting a negative result; case 4 is false positive by our criteria; case 5 is positive since $RR_{SCM} = 1.028$ is in the no decision range, but the decrease in IFFP in response to TAE is greater than 5%; case 6 is negative since $RR_{SCM} = 1.15$.

Finally Birindelli and associates' results show a ratio of less than 2 between positive findings, among patients and those among healthy controls (50%/27%). Since these results are based mainly on $IFFP_{basal}$ and $IFFP_{BrAg}$ measurements, a serious doubt is cast as to the validity of the antigens they used, and their ability to differentiate between healthy controls and cancer patients. Birindelli and associates did not use our own TAE preparations. Based on our experience, purification and calibration procedures should be carried out with great care since these influence the performance of TAE which is greatly affected by its molecular characteristics and concentration. Therefore, when a new TAE is introduced, calculating the sensitivity and specificity per antigen or even per time period, defined according to the overall system performance, is recommended.

In conclusion, considering problems stemming from cell heterogeneity, we are now exploiting the Cellscan to analyse individual and subpopulations of cells in order to optimise measurement of the SCM phenomenon. Special software and hardware tools have been developed in our laboratory for this purpose. These tools are now in use.


1. Rahmani H, Deutsch M, Ron I, *et al.* Adaptation of the Cellscan technique for the SCM test in breast cancer. *Eur J Cancer* 1996, **32A**(10), 1758–1765.
2. Cercek L, Cercek B. Application of the phenomenon of changes in the structuredness of cytoplasmic matrix (SCM) in the diagnosis of malignant disorders: a review. *Eur J Cancer* 1977, **13**, 903–915.
3. See references [3-7] and [9-16] of reference [1] .
4. Pritchard JAV, Seaman JE, Davis BH, *et al.* Cancer specific identity in lymphocytes after stimulation with phytohaemagglutinin. *Lancet* 1978, **2**, 1275–1277.
5. Wiltschke Ch, Krainer M, Budinsky AC, *et al.* Reduced mitogenic stimulation of peripheral blood mononuclear cells as a prognostic parameter for the course of breast cancer. A prospective longitudinal study. *Br J Cancer* 1995, **71**, 1292–1296.


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# Non-steroidal Anti-inflammatory Drugs in the Treatment of Colorectal Cancer

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GOOD EVIDENCE indicates that the regular consumption of non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin reduces the risk of fatal colorectal cancer [1]. The potential of NSAIDs in the treatment of colorectal cancer has received little attention. The purpose of this letter is to highlight this important possibility.

Pharmacologically, NSAIDs inhibit the cyclo-oxygenase (COX) enzyme leading to the reduced synthesis of prostaglandins (PGs). PGs such as $PGE_2$ are produced in excessive amounts by colorectal cancers and appear to contribute to a number of deleterious pathological effects [2]. These include maintenance of cancer blood flow, immunosuppression, cachexia and metastatic potential. Given these properties, the use of NSAIDs in the treatment of colorectal cancer is logical. Two clinical studies have addressed this possibility.

In 1982, Lipton and associates [3] reported a randomised trial with 66 colorectal cancer patients. Aspirin was given to reduce platelet aggregation in an attempt to prevent haematogenous cancer spread. For patients randomised to receive aspirin, 600 mg twice daily for 2 years did not prevent metastatic spread. Despite this rationale, however, this study is seriously flawed since the dose of aspirin given was too high for platelet inhibition. Furthermore, the degree of PG inhibition that can be achieved with this dose of aspirin is, at best, modest. More positively, in 1995 Preston and associates [4] noted that ibuprofen (400 mg three times daily for 3 days) attenuated accelerated whole-body protein kinetics in 7 colorectal cancer patients. Although this study implicates PGs as mediators of cachexia, it remains to be seen whether the long-term administration of ibuprofen alters the survival rate in patients with malignant disease.

More recently, an inducible isoform of COX, COX-2, has been implicated as producing excessive $PGE_2$ in colorectal cancers [5]. Additionally, NSAIDs have been shown to induce apoptosis (programmed cell death) in colorectal cancer cell lines [6]. Further clinical studies with NSAIDs in

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colorectal cancer are, therefore, warranted. Selective COX-2 inhibitors are attractive agents since they may inhibit cancer-derived $PGE_2$ without risk of adverse gastric or renal effects. By reversing the deleterious $PGE_2$ effects described above, COX-2 inhibitors could promote cancer regression and relief from other systemic manifestations such as pain, fever and hypercalcaemia [7, 8]. In addition, selective COX-2 inhibitors may be usefully combined to existing chemotherapies, surgery and radiotherapy [9]. Their value could also be addressed in combination with other approaches such as immunotherapy and genetic therapy. Such approaches would be particularly justified in patients with terminal disease.

In summary, NSAIDs have potential in the treatment of colorectal cancer. These possibilities also apply to oesophageal cancer [10]. Further studies are warranted and $PGE_2$ blood levels may help to identify patients eligible for NSAID therapy. This approach could be supported by further studies addressing COX-1 and COX-2 activities in normal and cancer tissue.

1. Morgan GP. NSAIDs and the chemoprevention of colorectal and oesophageal cancer. *Gut* 1996, **38**, 646–648.
2. Bennet A, Del Tacca M, Stamford IF, Zebro T. Prostaglandins from tumours of human large bowel. *Br J Surg* 1977, **35**, 882–884.
3. Lipton A, Scialla S, Harvey H. Adjuvant antiplatelet therapy with aspirin in colorectal cancer. *J Med* 1982, **13**(5/6), 419–429.
4. Preston T, Fearon KCH, McMillan DC. Effect of ibuprofen on the acute-phase response and protein metabolism in patients with cancer and weight loss. *Br J Surg* 1995, **82**, 229–234.
5. Eberhart CE, Coffey RJ, Radhika A, Giardiello FM, Ferrenbach S, DuBois RN. Up-regulation of cyclo-oxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas. *Gastroenterology* 1994, **107**, 1183–1188.
6. Elder DJE, Hague A, Hicks DJ, Paraskeva C. Differential growth inhibition by the aspirin metabolite salicylate in human colorectal tumour cell lines: Enhanced apoptosis in carcinoma and *in vitro* transformed adenoma. *Cancer Res* 1996, **56**, 2273–2276.
7. Johnson M. Neoplastic fever. *Palliative Med* 1996, **10**, 217–224.
8. Pace V. Use of nonsteroidal anti-inflammatory drugs in cancer. *Palliative Med* 1995, **9**, 273–286.
9. Morgan GP. The potential of NSAIDs in the prevention and treatment of colorectal carcinoma. *Eur J Surg Oncol* 1996, **22**, 560.
10. Morgan GP. The potential of NSAIDs in the treatment of oesophageal carcinoma. *Eur J Surg Oncol* 1996, **22**, 217–219.