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Comparative study of tumor markers in patients with colorectal carcinoma and role of fibre in diet

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Abstract
Community around the world does not eat the sufficient amount of fibre required to prevent key life-threatening illnesses, new research suggests. A nutritional review, which includes 285 studies and 50 clinical trials conducted over nearly 30 years, found that eating at least 25g to 29g of fibre per day was linked to a 15 to 30 per cent reduction in rates of life-threatening cancers. But most of people consume less than 20g of fibre in a day. This has risen a healthy trend that not less than 25 gram fibre and not less than 10% fibre should comprise diet. In the US rates of consumption are even worse, with the average adult eating just 15g of fibre a day. It is clarified that for every 8g increase in colorectal cancer plummeted by 8-32 per cent. This is because consuming much of it could have bad effects for people with decreased iron or mineral levels. Whole grains, definitely high in fibre, can further reduce iron levels. It is reiterated time again that their results mainly related to fibre rich foods than manufactured fibers. But carbohydrates in diet were ignored to count the fibre content in diet. So increasingly intake of carbohydrates should consider the opportunity cost of missing out on fibre from whole grains. This proves that both carbohydrates and high fiber intakes are clearly important for longer term health." Green vegetables along with nutritive fruits have high fibre. one should never take intensely baked foods. There's also a need to remove the sugar from products made from grains. Findings from two studies published this week in *The Lancet* add to the body of evidence suggesting that a high-fibre diet can reduce the risk of developing colon cancer (2003;361:1491 and 1496). There are opposing results, with some suggesting that no such protective effect exists. Recently a study compared fibre intake among people who had tested negative for any type of tumor. This also applies to high intake of fibre intake for people having at least one tumor or adenoma once upon a while. Fibre in diet reduces the 26 per cent lower risk for adenoma than those whose diets contained the least fibre. The fibers can be ingested from grains, cereals and fruits. Fibre intake from vegetables doesn't reduce the risk of tumor. Another investigation examined the link between dietary fibre intake and colorectal cancer. The researchers almost finalized that tripling the intake of dietary fibre will reduce the incident by more than 42%.

Objective: To screen out serum tumor markers that has the best effects on the diagnosis, conditions monitoring and therapeutic evaluation in colorectal cancer patients and thus to provide the optimal model of simple, sensitive and noninvasive with serum markers in early auxiliary diagnosis and monitor of colorectal cancer patients.

Methods: Literatures used in early supervision of colorectal cancer and published publicly during 1990-2013 were retrieved and Meta-analysis was performed to screen serum markers that were of high detection value. Then 100 colorectal cancer patients and 50 patients with benign colorectal disease were recruited to test the level of serum markers which were screened out via Meta-analysis with ELISA, and Logistic regression analysis, ROC curve and Bhattacharyya-SVM analysis were used to screen the optimal combination of serum markers of colorectal cancer.

Results: The result of Meta-analysis showed that 12 serum markers had certain correlation with colorectal cancer. At the same time, analysis of clinical data indicated that the area under the ROC curve (AUC) of CEA, CA19-9 and HSP60 when they were tested individually and jointly were 0.762, 0.752, 0.825 and 0.906. Their accuracy was 82.67%; sensitivity was 96.90%; and specificity was 90.57%. Bhattacharyya-SVM respectively adopted 12 indicators, 4 indicators (whose Bhattacharyya distance was more than 3) and 7 indicators (Bhattacharyya distance more than 2) to establish three SVM models. The classification accuracy rates of them were respectively 76.7%, 83.3% and 90.0%, sensitivity 80.0%, 85.0% and 90.0%, specificity 70.0%, 80.0% and 90.0%. The SVM prediction model established by CEA, CA50, CYFRA21-1, CA199, CA724, CA125 and UGT1A8 had the highest classification accuracy. Conclusion: The 12 serum markers such as CEA, CA242, and HSP60 are of high value for diagnosis of colorectal cancer. And the SVM models established in this study on basis of clinical validation results of these serum markers possess good predictive efficacy, which should be widely applied to clinical practice. Keywords: Colorectal cancer, serum marker, optimized model, logistic regression, Bhattacharyya-SVM

Background: Epidemiological studies have suggested that intake of dietary fiber is associated with decreased risk of colon cancer, however, these findings are inconsistent in that dietary fiber intake is differentially associated with risks of proximal colon and distal colon cancers.

Meta-analysis methods: Database was searched to identify relevant cohort studies up to December 2018 to examine the association between dietary fiber and risks of proximal colon and distal colon cancers, respectively. A random-effects model was used to compute summary risk estimates.

Results: 11 prospective cohort studies were identified and included in the analysis. We observed that the risk of proximal colon cancer was 14% lower among the highest dietary fiber intake compared with the lowest intake (RR = 0.86, 95% confidence interval [CI] = 0.78 to 0.95). A similar result was also found for distal colon cancer (RR = 0.79, 95% CI = 0.71 to 0.87).

Conclusions: In current analysis, we show that dietary fiber intake is associated inversely with risks of both proximal and distal colon cancers.

Keywords: community, database, inversely, life-threatening

Introduction
Colorectal cancer is the third most common type of cancer, with 1.2 million new cases diagnosed in 2008 worldwide, accounting for about 9.7% of all cases of cancer [1]. Evidence from ecological studies, migrant studies, and secular trend studies suggest that environmental risk factors are of major importance in the cause of colorectal cancer. Dietary factors have been suspected as important, but only intakes of red and processed meat and alcohol are considered to be convincing dietary risk factors for colorectal cancer [5]. In the 1970s, Burkitt proposed the hypothesis that dietary fibre reduces the risk of colorectal cancer, based on the observation of low rates of such cancer among rural Africans who ate a diet with a high fibre content [6]. Several plausible mechanisms have

been proposed to explain the hypothesis, including increased stool bulk and dilution of carcinogens in the colonic lumen, reduced transit time, and bacterial fermentation of fibre to short chain fatty acids [7]. However, although many epidemiological studies have investigated the association between fibre intake and risk of colorectal cancer, the results have not been consistent and the possibility of residual confounding by folate intake remains a controversial issue. Case-control studies have generally shown a protective association, whereas the results from cohort studies have been mixed. In addition, it is not clear whether only specific types or sources of fibre are associated with the risk. Although initial cohort studies generally reported no significant association between fibre intake and risk of colorectal cancer, the hypothesis regained interest when the European Prospective Investigation into Cancer and Nutrition (EPIC) study reported a linear decrease in the risk of colorectal cancer with increasing fibre intake.[19] A subsequent pooled analysis of 13 North American and European cohort studies (not including the EPIC study) reported an 18% increased risk of colorectal cancer with low fibre intake (<10 g/day *v* 10-15 g/day), but no further reductions in risk were observed with higher intake. More recently, results from additional large cohort studies have been published and, together with the EPIC study, included more than 1.7 million participants and 12 000 cases and included several studies from Asian populations. With such a large number of additional studies we had sufficient statistical power to clarify the dose-response relation between fibre intake and risk of colorectal cancer. In addition we examined whether specific types of fibre are associated with risk. Whole grains are a major source of dietary fibre and contain germ, endosperm, and bran, in contrast with refined grains that contain only the endosperm. The germ and bran contain numerous nutrients, which are removed during the refining process. In addition, whole grains are a major source of several vitamins, minerals, and phytochemicals, which have anticancer properties and could plausibly influence the risk of colorectal cancer by several potential mechanisms. An earlier review and meta-analysis of case-control studies of whole grain intake and colorectal cancer and polyps reported a summary odds ratio of 0.79 for the highest versus the lowest intake. However, the interpretation of case-control studies is hampered by possible recall and selection biases, which make it difficult to draw firm conclusions. Over the past decade results from several cohort studies have been published on whole grain intake and risk of colorectal cancer, with mixed results. Some studies suggested no association, whereas others reported an inverse association with higher whole grain intake. To clarifies the association between dietary fibre and whole grain intake and risk of colorectal cancer we carried out a systematic review and meta-analysis of published prospective studies. We also did meta-regression and sensitivity analyses to evaluate potential sources of heterogeneity in the analyses

Discussion

CEA is has been an oncofetal antigens that is produced by the normal fetal cells and can be produced in appreciable amounts by some malignant, but not normal adult cells. The positivity is thought to be associated with behavior common to both fetal and malignant cells, enabling them to grow rapidly, spread, and escape destruction by the response of host tissue. Since its discovery, CEA has been evaluated in a wide range of malignancies, including breast cancer, and historically, it has been considered the standard to which new serum markers are compared. Several studies have reported that positive serum CEA levels at the time of primary breast cancer diagnosis may represent a negative prognostic parameter. There are multiple serum-based tumor markers that have been described for breast cancer, such as CA 15-3, CA 27.29, tissue polypeptide antigen CEA, tissue polypeptide specific antigen, and HER2, the most widely used markers are CA 15-3 and CEA.

Four observations

First, there was a very much significant difference in the levels of serum CEA before (11.71 ± 2.79 ng/ml) and after (9.63 ± 2.76 ng/ml) resection, and a further significant decline after a course of chemo-radiotherapy (7.30 ± 2.79 ng/ml). Second, there was no significant difference in the levels of serum CEA between different histological types of breast cancer (ductal 10.23±2.58ng/ml and lobular carcinoma 9.45 ± 3.44 ng/ml). Third, there was a significant difference in the levels of serum CEA between axillary lymphnode-positive (11.73 ± 2.67 ng/ml) and axillary lymphnode-negative patients (8.41 ± 1.99 ng/ml). Fourth, there was no significant difference in the levels of serum CEA between premenopausal (10.14±2.54 ng/ml) and postmenopausal patients (10.05±3.35ng/ml). This endevour resembles Ebeling *et al*. reported in their study a decline in the level of serum CEA after removal of tumor in breast cancer patients. Behrami *et al*. have followed decrease in the level of serum CEA after surgery and a further decline after chemo-radiotherapy. They was seen by them rise in CEA levels in case of recurrence of the disease and metastases. Pathak *et al*. observed that following successful treatment, serum CEA levels fell significantly below pre-treatment level. Duffy *et al*. found potential use of serum CEA in early diagnosis of breast cancer, determining its prognosis, prospectively predicting response and resistance to specific therapies, surveillance after primary surgery, and monitoring therapy in patients with primary disease. Kiang *et al*. studied the tumor markers CEA and CA 15-3. All the investigations of markers levels in blood observed after starting chemotherapy and rise in amount was found due to tumor proliferation and a fall in levels due to tumor cytolysis. This was confirmed that tumor markers in shortening the rise in level of disease and in early hope of therapeutic response. Van Dalen *et al*. found veiled in some patients, increase in the level of CEA at the time of tumor resolution and fall in the level at the time of tumor proliferation. This elucidates the fact that dead cells release a large amount of marker in the blood and the chemotherapeutic drugs that inhibits the flow of CEA from the cell, though there is no fall in it's Synthesis.

Materials and Methods

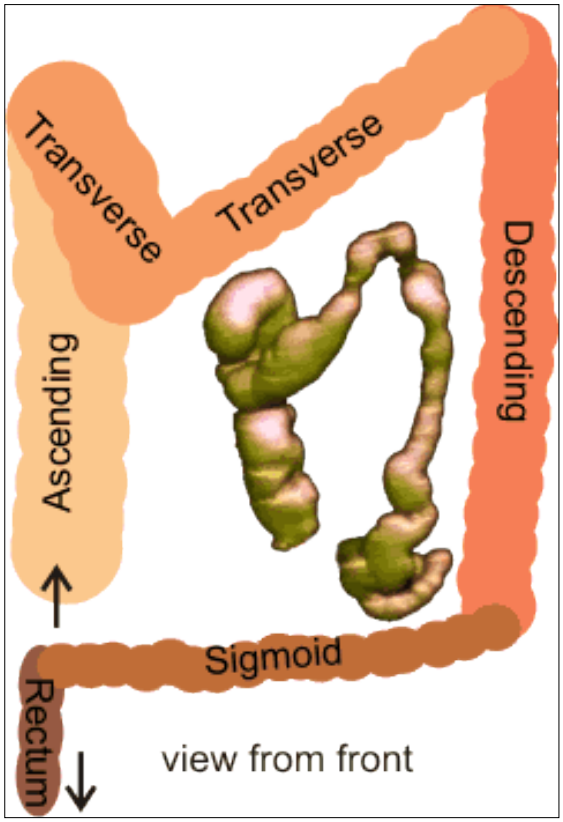

Fig 1: Introduction aetiology and pathology

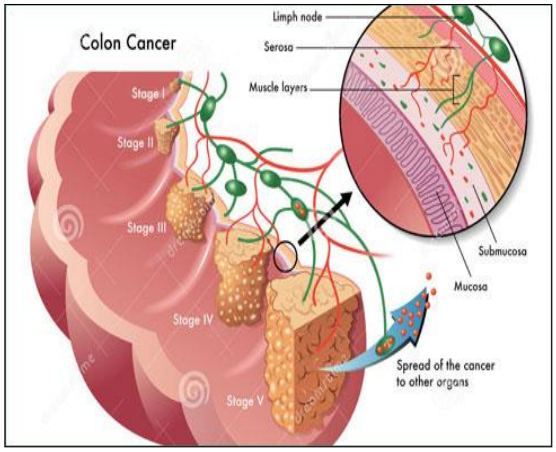

Fig 2: Dietary fibre and health

High fibre diet sources

Table 1

Fruits	Serving size	Total fiber (grams)*
Raspberries	1 cup	8.0
Pear	1 medium	5.5
Apple, with skin	1 medium	4.5
Banana	1 medium	3.0
Orange	1 medium	3.0
Strawberries	1 cup	3.0

Table 2

Vegetables	Serving size	Total fiber (grams)*
Barley, pearled, cooked	1 cup	6.0
Bran flakes	3/4 cup	5.5
Quinoa, cooked	1 cup	5.0
Oat bran muffin	1 medium	5.0
Oatmeal, instant, cooked	1 cup	5.0
Popcorn, air-popped	3 cups	3.5
Brown rice, cooked	1 cup	3.5
Bread, whole-wheat	1 slice	2.0
Bread, rye	1 slice	2.0

Table 3

Legumes, nuts and seeds	Serving size	Total fiber (grams)*
Split peas, boiled	1 cup	16.0
Lentils, boiled	1 cup	15.5
Black beans, boiled	1 cup	15.0
Baked beans, canned	1 cup	10.0
Chia seeds	1 ounce	10.0
Almonds	1 ounce (23 nuts)	3.5
Pistachios	1 ounce (49 nuts)	3.0
Sunflower kernels	1 ounce	3.0

Chart of high-fiber foods

Dietary fibre

Twenty one prospective studies were identified and included in the analysis of the highest versus the lowest intake of dietary fibre and risk of colorectal cancer, 18 of which were included in the dose-response analyses. Twelve of the studies were from the United States, five from Europe, and four from Asia. Table 4 summarizes the characteristics of the included studies. The ranges of intake varied: 6.3-21.4 g/day for total dietary fibre, 1.8-15.5 g/day for fruit fibre, 1.9-16.8 g/day for vegetable fibre, 3.0-16.9 g/day for cereal fibre, and 1.3-3.8 g/day for legume fibre (results not shown).

High versus low intake

Nineteen prospective studies (18 publications) were included in the analysis of high versus low intake of total dietary fibre and risk of colorectal cancer (table 4). The summary relative risk was 0.88 (95% confidence interval 0.82 to 0.94), with no evidence of heterogeneity (I^2=0%, P=0.48, see web extra figure 1a).

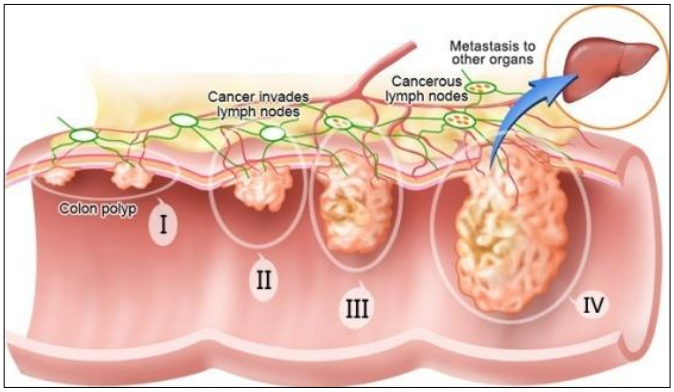

Fig 3: Use of dead bacteria to kill colorectal carcinoma

Dose-response analysis

Sixteen prospective studies (15 publications) were included in the dose-response analysis, with 14 514 cases among 1 985 552 participants. The summary relative risk was 0.90 (0.86 to 0.94) for each 10 g/day intake, with no significant heterogeneity (I^2=0%, P=0.48, fig 22). A statistically significant inverse association was seen for colon cancer (13 studies, summary relative risk 0.89, 0.81 to 0.97, I^2=35%, P=0.11) but not for rectal cancer (10 studies, 0.91, 0.83 to 1.03, I^2=15%, P=0.31), although evidence was lacking for heterogeneity between subsides (P=0.86, see table 6). Publication bias was not evident with either Egger's test (P=0.62) or Begg's test (P=0.56). In a sensitivity analysis excluding one study at a time, the summary relative risk for colorectal cancer ranged from 0.89 (0.85 to 0.93) when the National Institutes of Health-American Association for Retired Persons (NIH-AARP) Diet and Health Study was excluded to 0.91 (0.88 to 0.96) when the EPIC study was excluded. A non-linear association was not evident between intake of total dietary fibre and risk of colorectal cancer (P=0.32 for non-linearity. Many potential markers, including biochemical markers, have been studied in an attempt to identify the presence of early colorectal neoplasia or risk of neoplasia, particularly in those families with hereditary colonic neoplasia syndromes. Unfortunately, most of these markers are useless in screening or diagnosis. Nevertheless, such markers as carcinoembryonic antigen (CEA) and CA 19-9 may have a role in pretherapeutic and posttherapeutic monitoring of disease or recurrence. The newer tumor markers, including the carbohydrate markers, ornithine decarboxylase (ODC) and the polyamines, are of great interest as potential tumor markers; ODC and the polyamines may also have a future potential as therapeutic targets. However, further studies are needed to determine their true sensitivity and specificity in hereditary colonic neoplasia syndromes, as well as in patients without genetic syndromes who are at risk for colorectal cancer.

Conclusion

Diet and lifestyle are critical factors for the synthesis of the gut microbiota. Their interactions with bacterial metabolism also affect host metabolism and also purchasable bacteria metabolism in the gut lumen. Many microbial metabolites formed from dietary compounds, such as acetaldehyde from ethanol or ammonia, polyamines and hydrogen sulfide from protein, rise or fall of this carcinoma, while SCFAs formed from dietary fiber could exert mainly anti-carcinogenic properties. These interactions would influence immunity, and it is a well acknowledged that chronic inflammation is a risk factor for CRC. Raised amount of fiber diet, reduced softened red meat intake and decrease in frequency of intake of alcohol regress CRC, through inciting the gut microbiota. However, there are many frequent variations in microbes, and it is difficult to define whether those states of the community are beneficial or bad for one's long-term health. A better theoretical understanding of the influences of diet or lifestyle on the microbial metabolome of individuals is needed. As an easily modifiable environmental factor, it may be possible that applying dietary or lifestyle intervention combined with therapeutic microbiota transplantation could effectively protect against the development of CRC in the future. The population included in this study consists of patients with a diagnosis of CRC who underwent surgery in the period from January 1, 2005, to January 1, 2010, in the Braga Hospital (BH). This endevour, the following inclusion criteria were: patients with histological confirmed CRC who underwent surgical resection with curative intent. Exclusion criteria were: patients with inflammatory bowel disease (IBD), namely Crohn's disease and ulcerative colitis; patients with hereditary syndromes such as familial adenomatous polyposis (FAP) and hereditary colorectal cancer not associated with polyposis (HCCNP); patients with no primary disease of the colon or rectum; patients diagnosed with CRC but who did not undergo surgery, and patients with CRC undergoing non-curative surgical treatment. The exclusion of patients with hereditary syndromes was performed after confirmed by genetic studies in patients for whom there was a clinical suspicion. To collect information, a prospective database of CRC was surveyed, and the following data were collected:

Table 1: Comparison of select tumor markers between cases and controls

Parameters studied	Mean	Controls	P Value
CEA	5.94±7.98	2.3±0.78	0.005
PRL	29.09+14.87	16.87±12.65	<0.000
AFP	29.98±12.65	15.34+4.09+1.87	0.0001
TOTAL HCG	3.54±3.87	3.76±2.4	0.54
CA-125	39.98+21.87	30.76±+8.76	0.071
TESTOSTERONE	243.98±41.51	287.98±56.87	0.10
PSA	2.12+1.98	1.87±1.01	0.19
FERRITIN	172±38.98	176.87+54.98	0.65

Table 2: Comparison of select biomarkers between pre-chemotherapy and post-chemotherapy

Comparison of select biochemical parameters			
Parameter	**Prechemotherapy (Mean±+SD)**	**Postchemotherapy (Mean ±SD)**	**P Value**
CEA	6.32±9.87	4.98±2.98	0.003
PRL	31.98±12.54	26.87±11.98	0.076
AFP	11.98±6.09	11.98±+12+43	<0.0001
CA-125	38.34±22.87	32.98±564	0.54

CEA, (Carcinogenic Antigen), PRL (Prolactiin), AFP (alfafetiprotein): CA-125, cancer antigen

Table 3: Comparison of significant tumor markers

Comparison of select tumor markers across four stages of colorectal carcinoma					
Vegetables	**Serving size**	**Total fiber (grams)***	**Vegetables**	**Serving size**	**P Vaue**
AgeINYears	43.70±10.8	50.87±12.08	46.98±12.60	50.65±11.87	0.765
CEA	6.5±5.9	7.98±11.76	7.98±9.38	4.65±1.98	0.98
PRA	26±9.09	23.87±15.42	32.87±12.76	32.11+13.98	0.67
AFP	6.7±3.1	7.98±6.90	14.87±7.06	18.65±3.76	0.121
CA 125	19±8.9	32.98±14.98	34.87±12.09	69.12±+12.76	0.001
Testosterone	231±36.32	321.09±65.09	223.65±54.09	234.98±12.43	0.001

Post-HOC Bonferroni Test: *Stage 1 *VS.* Stage 4: P<0.001 And Stage 2 *VS.* Stage 4: P<0.001; **Stage 1 *VS.* STAGE 4: P<0.001; Stage 2 *VS.* Stage 4: P<0.001 AND Stage 3 *VS.* Stage 4: P<0.001. CRC, COLORECTAL carcinoma; CEA, Carcinoembryonic Antigen; PRL, Prolactin; AFP, ALFA Feto Protein; CA-125, Cancer Antigen-125

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