RESEARCH COMMUNICATION

A Case-control Study of Roles of Diet in Colorectal Carcinoma in a South Indian Population

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Abstract

Introduction: The worldwide incidence of colorectal cancer has increased rapidly in the past few decades and dietary habits have been implicated in the cause. Though the Indian diet varies substantially from western diet, there has not been detailed studies on any association. Materials and Methods: This is hospital based case control study enrolling 108 cases and 324 controls, all hailing from the Malabar region of Kerala, India. The subjects were interviewed using food frequency questionnaires for commonly consumed dietary items in the region. Results: A strong association was found between colorectal cancer and tapioca (OR=2.7 p=0.001), beef (OR=4.25, p=0.000) and pungent spices (OR=9.62, p=0.018). Fruits and vegetables a showed strong inverse association (OR= 0.15 p=0.002). Fish consumption on a daily basis showed a 25% reduction in risk on univariate analysis. Heavy consumption of sugar (OR=2.80) and tobacco use (OR=8.79) showed significant high risk. Conclusions: There is strong evidence from our study that intake of beef, refined carbohydrates and tobacco can promote colorectal cancer. Our study has also thrown light on some of the other commonly consumed items, like tapioca and spices which have positive associations. These are commonly consumed in Malabar region of Kerala. A cohort study is now needed to confirm our findings.

Key Words: Colorectal cancer - risk factors - red meat - smoking - prevention - vegetables - tea

Asian Pacific J Cancer Prev, **10**, 565-568

Introduction

Colorectal carcinoma (CRC) is the third most common malignancy in the world. The reported incidence of CRC in developing countries, including India, is 2 to 8 per 100,000 population (Notani, 2001). However, the population based cancer data available from the developing countries are not reliable. The worldwide incidence of CRC has shown a 49% increase between 1975 and 1990 among men (Notani, 2001). CRC which was the 4th most common malignancy among women in 1975 reached the second position in 1990. Though the reported incidences do not speak of the increasing burden of disease in India, surgeons in India have noticed a significant rise in the incidence of CRC in the past decades.

Colorectal cancer is a multifactorial disease. Research has identified many associated factors, including genetic disorders like familial adenomatous polyposis syndrome to acquired diseases like inflammatory bowel disease (Cirigliano and Lichtenstein, 1996). Diet is also considered one of the major factors and many studies have analyzed the association in great detail implicating a number of micro- and macro-nutrients (Graham et al., 1988; Benito et al., 1991; Slattery et al., 2004). Identifying specific dietary factors that are linked with the development of CRC has been difficult because of the complex composition of food and the fact that dietary changes affect multiple nutrients simultaneously.

Though the incidence of CRC has been increasing in India, not much research has gone into the factors involved in its causation in this region. This study is important as India is unique in her food habits in many ways. This is a pilot case-control study designed to identify the dietary predispositions of the indigenous population of Malabar region of the state of Kerala, India.

Materials and Methods

Accrual of subjects:

This is a hospital based case-control study. The subjects were identified from the Medical College Hospital, Calicut, Kerala which is one of the largest teaching hospitals in India. All the subjects were consented and interviewed by the authors during their admission to the institution for treatment between April 2003 and February 2006. The study population included the indigenous population of Malabar region of northern Kerala (India). The cases with known predispositions or prior malignancy were excluded. Subjects between 18 to 85 years of age were included. All the cases had histological diagnosis of adenocarcinoma of colon. The controls were subjects residing from the same geographic area, who were

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admitted for acute, non-neoplastic conditions, unrelated to long-term modification of diet. They were all admitted for a wide range of acute conditions, including trauma (45%) or other surgical conditions (55%, acute appendicitis, renal colic, etc.) The controls were accrued at a ratio of 1:3 and were age matched (± 5 years) and sex matched.

Interviews:

An interviewer-administered Food Frequency Questionnaire (FFQ) developed by the authors was used to assess the subject's habitual diet. The structured questionnaire, apart from dietary data, included problem oriented medical history, socio-demographic characteristics and lifestyle habits (e.g. smoking and alcohol consumption etc.). Information was elicited on average frequency of consumption of the food items commonly consumed in the geographic area during 2 years prior to diagnosis of CRC or hospital admission. However, if there was a history of change in the food habit in the period 3yrs preceding the diagnosis or admission, the habits prior to the change were considered for the study.

Statistical analysis:

Initially the data was scanned using the standard descriptive statistics. The Odds Ratios (OR) and 95% Confidence Intervals (CI) were estimated by univariate analysis. The factors with significant results were further subjected to multivariate analysis. Odds Ratio of 1 was taken as standard for comparison. Data analysis was done together as well as for males and females separately. As most of the results were similar for males and females, they will be presented together unless there is significant difference.

Table 1. Distribution of Cases of Colorectal Cancer by Location

Location	Number	(%)
Caecum	20	(18.5%)
Ascending colon	4	(3.7%)
Hepatic flexure	4	(3.7%)
Transverse Colon	4	(3.7%)
Splenic Flexure	4	(3.7%)
Descending Colon	12	(11.1%)
Sigmoid Colon	40	(37.0%)
Rectum	20	(18.5%)

Results

There were 119 cases of CRC enrolled in the study period, of which 11 could not be interviewed for various reasons. The authors interviewed 108 cases (76 males and 32 females) and 324 controls (228 males and 96 females). The mean age of the cases was 55.6 ± 0.98 years (male 55.8±1.20 years and female 55.1±1.69 years). The mean age of the controls was 55.8±0.56 years (male 55.9±0.68 years, female 55.5±0.98 years). The age of the subjects ranged from 36 to 85 with median being 56. The pattern of distribution of the disease in the large bowel in the cases is given in Table 1. A predominance of left colonic disease is seen with more than 60% of cases afflicting this part of the colon which is in line with the world statistics.

The dietary data collected using FFQ was subjected to univariate analysis. These food items have been listed in table 2 along with their OR and 95% CI. The statistically significant associations were further analyzed by logistic regression. The OR, 95% CI and p values of the food items that were found statistically significant are listed in table 3.

There is a strong positive association between the consumption of beef and CRC (comparing OR of the highest quartile with the lowest quartile). The difference in risk was significant on univariate analysis. On logistic regression a strong positive association was present for those consuming beef more than once a week; OR= 4.25 (2.02, 8.94) for more than once a week verses OR=0.07 (0.03, 0.38) for those who do not consume beef (p=0.000). Men consuming beef once a week had relatively higher risk of 6.43 (2.77, 15.09) when compared to women consuming same amount of beef, who had a risk of 4.03 (0.76, 27.43) though the values were not statistically

Table 2. Odds Ratios (OR) and 95% Confidence Intervals for Colorectal Carcinoma Risk Associated with Individual Dietary Items on Univariate Analysis

Dietary item	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Tapioca	1.00	0.08 (0.04, 0.18)	1.35 (0.34, 4.96)	3.86 (1.85, 8.09)
Fishes	1.00	0.44 (0.13, 0.98)	0.36 (0.18, 0.73)	0.32 (0.18, 0.56)
Beef	1.00	0.14 (0.08, 0.26)	1.77 (1.65, 4.71)	5.89 (2.80, 12.5)
Fruits & Vegetable	1.00	0.46 (0.19, 1.06)	0.51 (0.21, 1.18)	0.21 (0.13, 0.35)
Sugar	1.00	0.58 (0.35, 0.96)	2.38 (1.45, 3.91)	2.80 (1.52, 5.21)
Spices	1.00	0.22 (0.13, 0.37)	0.81 (0.49, 1.34)	9.45 (5.32, 16.9)
Tea	1.00	0.22 (0.13, 0.37)	1.33 (0.84, 2.11)	1.03 (0.62, 1.71)

Table 3. List of Items showing Significant Risk on Multivariate Analysis with their Odds Ratios (OR), 95% Confidence Intervals (CI) and p Values

Dietary item	Tertile 1	Tertile 2	Tertile 3	p value
Tapioca	1.00	0.02 (0.01, 0.07)	2.70 (1.32, 3.31)	0.001
Fishes	1.00	0.10 (0.03, 0.38)	0.09 (0.03, 0.28)	0.001
Beef	1.00	0.07 (0.03, 0.19)	4.25 (2.02, 8.94)	0.000
Fruits & vegetable	1.00	8.26 (2.20, 16.9)	0.15 (0.05, 0.46)	0.002
Spices	1.00	0.28 (0.09, 0.80)	9.62 (3.62, 22.0)	0.018

significant. Men who did not consume beef had a 30% lower risk compared to women.

Tapioca showed strong positive association with CRC on univariate and multivariate analysis. On logistic regression OR was 0.02 (0.01, 0.07) for occasional consumption and OR was 2.70 (1.32, 3.31) for consumption 2 to 3 times a week (p=0.000).

Consumption of fish with every meal showed 20% lower risk [OR=0.32 (0.18, 0.73)] compared to people who rarely consumed fish [OR=0.44 (0.13, 0.98)]. On multivariate analysis the difference in the risk was not significant; OR=0.09 (CI=0.03, 0.28) for daily consumption verses OR=0.10 (0.03, 0.38) for occasional consumption (p=0.000).

There was a strong inverse association for consumption of fruits and vegetables with more than 50% lower risk for daily consumption on univariate analysis. On logistic regression there is a very strong inverse association between daily consumption of fruits and vegetables, and CRC; OR= 8.26 (2.20, 16.90) for rare consumption and OR= 0.15 (0.05, 0.46) for daily consumption (p=0.002).

The consumption of spices, mainly pungent spices like chilies and pepper showed strong positive association on both univariate and multivariate analysis (p=0.018). In high quantities it showed 9.62 fold increase in risk (3.62, 21.98) when compared to the subjects consuming less spiced food; OR=0.28 (0.09, 0.80). Also men consuming very spicy food had 11.56 (CI=5.77, 23.35) fold increase in risk compared to women consuming same amount who had a 5.80 fold increase (CI=1.93, 17.78).

Consumption of sugar or sucrose was assessed by the subject's interest in sweetmeat. A strong positive association was noted for those who consumed sweets daily (OR=2.38 CI=1.45, 3.91); when compared to those who did not have a liking for sweetmeat (OR= 0.58 CI=0.35, 0.96). Tea consumption did not show an increase in risk when consumed upto 2 cups a day; OR=0.22 (0.13, 0.37). Among men, very frequent consumption of tea (more than 12 cups in a day) showed a significantly higher risk: OR=1.99 (1.11, 3.56). Tea and sugar did not show statistically significant results on logistic regression.

Apart from dietary factors the history of use of tobacco and alcohol was analyzed. Tobacco use for a period of 6 months continuously or more at any time during life was found to produce 8.79 fold increase in risk (CI=5.18, 14.96). Alcohol showed a risk of 1.60 (0.89, 2.88) though statistically not significant.

Discussion

Strong direct associations between various food items and CRC have been described in studies conducted on different populations. Tapioca or cassava is a cheap source of carbohydrate and it is known to contain toxins like linamarin and cyanide derivatives (Carlsson et al., 1999; Oluwole et al., 2002). It needs to be processed in order to rid the toxins. In Kerala unprocessed boiled tapioca is consumed on regular basis. There have been conflicting reports of tapioca causing ataxic polyneuropathy, amblyopia and tropical pancreatitis (Mori et al., 1999; Oluwole et al., 2002). There is also one case-control study from Kerala which has implicated tapioca in pancreatic cancer (Mori et al., 1999). The role of tapioca in CRC is unknown. In our study on daily consumption there is nearly a 4 fold increase in the risk. The toxins in unprocessed tapioca could be directly acting on the bowel mucosa to cause CRC.

Cooked red meat has been consistently implicated in the causation of CRC due to N-nitroso compounds, polycyclic aromatic hydrocarbons and heterocyclic amines (HCA) content (Lee et al., 1989; Peters et al., 1992; Sandhu et al., 2001). Dry heat or barbecuing has been shown to increase the HCA content in red meat (Augustsson et al., 1999; Steele, 2002). However, the level of consumption above 1900 ng daily which is carcinogenic is rarely reached even on western diet (Augustsson et al., 1999). The same study also found that beef promotes CRC irrespective of its HCA content (Augustsson et al., 1999). Meat is also known to increase bile acid release into the gut which is a known to promote mitosis (Steele, 2002). It is important to note that Kerala has a significantly larger beef consuming population compared to other states of India (Sankaranarayanan et al., 1994). In Kerala beef usually not barbecued, but consumed prepared as curry. Also, the curry forms a small part of a meal as an accompaniment with parboiled rice. Our study shows that beef consumed even in small quantities can promote CRC.

The local population consumes fish in the form of curry along with rice as a part of their staple diet. Commonly consumed fishes in Kerala are sardines and mackerel which are sea fishes rich in vitamin D and selenium. Studies have shown that consumption of even small amounts of fish is protective against CRC (Giovannucci et al., 1994; Fernandez et al., 1999). However, fish meat also forms HCA on cooking in dry heat and thus can be carcinogenic (Augustsson et al., 1999). Though fish consumption is safe, it does not appear to significantly reduce the risk of CRC in our study population.

In the studies on dietary associations of CRC, consumption of fruits and vegetables have consistently been found to lower the risk (Giovannucci et al., 1994; Willett, 1995). This reduction in risk has been linked to factors like vegetable fiber content, antioxidants and various vitamins and minerals in fruits and vegetables (Giovannucci et al., 1994; Willett, 1995). Though the exact reason is unknown, it appears that some factors in fruits and vegetables are protective against CRC with significant reduction in risk when consumed on daily basis.

Refined sources of carbohydrate like polished cereals have been linked to CRC (Willett, 1995; Chatenoud, 1999). We studied the association of consumption of sucrose and found it to increase the risk significantly. From the studies, including ours, it appears that more refined the meal is, more is the risk.

Average Indian food is very rich in pungent spices like chilies. The effect of capsaicin which gives the pungency to chilies, has not been studied in humans so far (Verschoyle et al., 2007). Capsaicin is one of the alkaloids that is being studied for anticancer properties (Aggarwal et al., 2008). Studies have also reported

capsaicin to be carcinogenic (Verschoyle et al., 2007). Even in our study we found that consumption of very pungent food on regular basis can promote carcinogenesis.

Tea is consumed ubiquitously in Kerala. Unlike many other cultures, in India tea is prepared with cream as well as sugar. The results have been conflicting regarding the association of tea with CRC (Dray et al., 2003). A recent study conducted in USA has shown significant reduction in risk especially among men when more than 1.5 cups per day was consumed (Su and Arab, 2001). We found that up to 2 cups of tea per day may be safe. The higher risk when more than 12 cups of tea were consumed in a day could be associated with the added sugar and cream.

This being a pilot study has been conducted on a small sample size. This sample is grossly inadequate to extrapolate the results on the entire population. The results could be skewed due to small size of individual groups. Many of the recent studies on diet and CRC have tried to assess the role of micronutrients and macronutrients. Dynamic nature of diet makes it difficult to estimate the dietary composition accurately. Authors are of the opinion that it would be better to study the commonly consumed dietary items in a given population in order to identify and modify the consumption of disease promoting items. A well planned cohort study is now needed to estimate the associated risk for individual dietary items for a given population.

References

Aggarwal BB, Kunnumakkara AB, Harikumar KB, et al (2008). Potential of spice-derived phytochemicals for cancer prevention. *Planta Med*, **74**, 1560-9.

Augustsson K, Skog K, Jägerstad M, et al (1999). Dietary heterocyclic amines and cancer of the colon, rectum, bladder and kidney: a population-based study. *Lancet*, **353**, 703-10.

Benito E, Stiggelbout A, Bosch FX, et al (1991). Nutritional factors in colorectal cancer risk: A case-control study in Majorca. *Int J Cancer*, **49**, 161.

Carlsson L, Mlingi N, Juma A, Ronquist G, Rosling H (1999). Metabolic fates in humans of linamarin in cassava flour ingested as stiff porridge *Food Chem Toxicol*, **37**, 307-12.

Chatenoud L, LaVecchia C, Franceschi S, et al (1999). Refined-cereal intake and risk of selected cancers in Italy. *Am J Clin Nutr*, **70**, 1107-10.

Cheng AL, Hsu CH, Lin JK, et al (2001). Phase I clinical trial of Curcumin, a chemopreventive agent, in patients with high-risk or premalignant lesions. *Anticancer Res*, **21**, 2895-900.

Cirigliano M, Lichtenstein GR (1996). Colorectal cancer prevention: What to tell patients. *Hospital Physician*, **32**, 40-8.

Dray X, Boutron-Ruault MC, Bertrais S, et al (2003). Influence of dietary factors on colorectal cancer survival. *Gut*, **52**, 868-73.

Fernandez E, Chatenoud L, La Vecchia C, Negri E, Franceschi S (1999). Fish consumption and cancer risk. *Am J Clin Nutr*, **70**, 85-90.

Ghadirian P, Lacroix A, Maisonneuve P, et al (1997). Nutritional factors and colon carcinoma: A case-control study involving French Canadians in Montreal, Quebec, Canada. *Cancer*, **80**, 858-64.

Giovannucci E, Rimm EB, Stampfer MJ, et al (1994). Intake of fat, meat, and fiber in relation to risk of colon cancer in men. *Cancer Res*, **54**, 2390-7.

Graham S, Marshall J, Haughey B, et al (1988). Dietary epidemiology of cancer of the colon in western New York. *Am J Epidemiol*, **128**, 490-503.

Lee HP, Gourley L, Duffy SW, et al (1989). Colorectal cancer and diet in an Asian population-a case-control study among Singapore Chinese. *Int J Cancer*, **43**, 1007-16.

Mori M, Hariharan M, Anandakumar M, et al (1999). A case-control study on risk factors for pancreatic diseases in Kerala, India. *Hepatogastroenterology*, **46**, 25-30.

Notani PN (2001). Global variation in cancer incidence and mortality. *Current Science*, **81**, 465-74.

Oluwole OS, Onabolu AO, Sowunmi A (2002). Exposure to cyanide following a meal of cassava food. Toxicol Lett. 135, 19-23.

Peters R K, Pike M C, Garabrant D, Mack T (1992). Diet and colon cancer in Los Angeles County, California. *Cancer Causes Control*, **3**, 457-473.

Sandhu M S, White I R, McPherson K (2001). Systematic review of the prospective cohort studies on meat consumption and colorectal cancer risk: a meta-analytical approach. *Cancer Epidemiol Biomarkers Prev*, **10**, 439-46.

Sankaranarayanan R, Varghese C, Duffy SW, et al (1994). A case-control study of diet and lung cancer in Kerala, south India. *Int J Cancer*, **58**, 644-9.

Slattery ML, Curtin KP, Edwards SL, Schaffer DM (2004). Plant foods, fiber, and rectal cancer. *Am J Clin Nutr*, **79**, 274-81.

Steele RJC (2002). Disorders of the colon and rectum. Essential Surgical Practice, 4th ed: Arnold pub, 569-626.

Su LJ, Arab L (2001). Tea consumption and the reduced risk of colon cancer - results from a national prospective cohort study. *Public Health Nutrition*, **5**, 419–425.

Verschoyle RD, Steward WP, Gescher AJ (2007). Putative cancer chemopreventive agents of dietary origin - how safe are they? *Nutr Cancer*, **59**, 152-62.

Willett WC (1995). Diet, nutrition, and avoidable cancer. *Environ Health Perspect*, **103**, 165-70.