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Research Article

A STUDY LIFESTYLE ASSOCIATED RISK FACTORS IN ETIOLOGY OF COLORECTAL MALIGNANCIES

Handa A. K[1]., Arun Tyagi[2] and A.K. Srivastava[3]

[1]Consultant Gastroenterology
[2]Consultant Medicine, Command Hospital, Udhampur, India
[3]Advisor Medicine, Military Hospital, Jammu, India

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ABSTRACT

Introduction: Colorectal Cancer (CRC) is one of the commonest malignancies around the world. The incidence of this cancer is fast rising in developing countries owing to rapid urbanization and the adoption of 'Western lifestyle'. The rise in the incidence among the emigrants from low to high prevalence areas points to an environmental/lifestyle related factor in the etiology of this cancer. This study was undertaken to analyze lifestyle associated risk factors in etiology of CRC in north India.
Material and methods: This case-controlled study conducted at a tertiary care teaching hospital in North India. All consecutive consenting adult patients of either gender with histopathological diagnosis of CRC were enrolled in the study and interviewed within one month of diagnosis. Demographic variables, details of physical activity and personal habits like smoking and alcohol use were recorded.
Results: The study included ages and sex matched 85 cases and 109 controls. Males constituted 74% of cases. Ascending colon was the mainly involved site and adenocarcinoma was the most common histological category. The mean BMI and average energy expenditure was significantly lower among cases. The average duration and number of cigarettes/bidis smoked per day was higher among cases (17.54±6.4 vs 10.79±3.4, P =.002) and so was the mean duration of alcohol intake (21.25±6.2 vs 13.49±5.2 years).
Conclusion: The study revealed that obesity, alcohol use and smoking of either cigarettes or bidis was associated with increased risk of CRC. Physical activity, on the other hand was found to have protective effect on CRC.

INTRODUCTION

Colorectal Cancer (CRC) is one of the commonest malignancies around the world. According to GLOBOCAN 2018 data, CRC is the third most deadly and fourth mostdiagnosed cancer in the world.[1]CRCwas encountered generally less frequently in developing nations as compared to the developed nations, but with increasing urbanization and the adoption of 'Western lifestyle' developing countries are fast catching up in the increasing incidence of this preventable cancer[2,3]. The prevalence of this malignancy in India is relatively low. However, five-year survival rate of CRC in India is one of the lowest in the world at less than 40%.[4] The incidence rate of colorectal cancer in India (4.3 and 3.4/100,000) is comparably lower than the other Asian countries. Overall lifetime risk of developing colon cancer among Indians was found ranging from 1/167-1/500 for females to 1/167-1/250 for males. The lifetime risk of developing rectal cancer ranged from 1/200-1/500 for females to 1/100-1/353 for males.[5]The epidemiological disparity in the incidence of CRC between developed and developing countries has been one of the thrust areas of research in the Western world specifically concerning likely risk factors etiologically related to its development.[6]

Lifestyle has gradually assumed importance in a variety of diseases, CRC being no exception. The role of obesity and sedentary lifestyle has been postulated to give rise to a hyperinsulinemic state, providing a greater risk in the causation of this cancer. In addition, alcohol and tobacco use are known risk factors in its causation. Calcium, vitamin D, folate, and low dose aspirin are being evaluated as chemopreventive agents in CRC.[7,] [8]With increasing urbanization and the adoption of a 'Western-lifestyle', Asian countries are fast catching up in the growing incidence of this preventable cancer.[9]The rise in the incidence of CRC among the emigrants from a low prevalence areas to one of the high endemicity regions again points to an environmental factor/lifestyle related factor in the etiology of this cancer.[10]This is a matter of concern in our part of the world, already burdened by other communicable and degenerative diseases. Despite ongoing research on likely risk factors, the

Corresponding author:* **Handa A. K
Consultant Gastroenterology

etiopathogenesis of CRC remains uncertain. The role of alcohol use and smoking in causation of colorectal malignancies is far from clear. More specific answers to these questions would go a long way in alleviating this largely preventable disease.

AIMS AND OBJECTIVES

To study lifestyle associated risk factors in etiology of colorectal cancers.

Subjects and Methods

Study Design It was acase control study conducted at a tertiary care teaching hospital in North Indiafrom July 2010 till October 2011. All consecutive patients of either gender between 18-80 years of age, with histopathological diagnosis of CRC were enrolled in the study. Informed consent was taken from all the patients as per Helsinki and ICMR guidelines. The cases were interviewed within a month of diagnosis being established. Pregnant females, patients on hormone replacement therapy or contraceptive pills and those with history of cholecystectomy were excluded from the study.

Controls Population controls were taken from healthy and asymptomatic relatives accompanying patients in the various outpatient and indoor departments of the hospital. All controls were free from any cancer or gastrointestinal problems. Controls were matched by sex 5-year age groups.

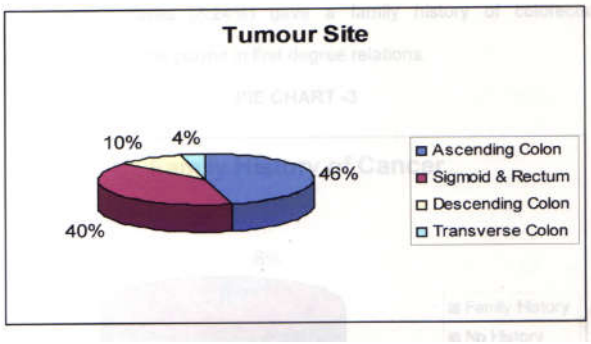
Protocol Demographic variables namely height, weight, and body mass index (BMI) were obtained. A BMI of 19 to 25 was considered normal, 25 to 30 overweight and more than 30 kg/m^2 obese. Details of physical activity either structured, occupational, or recreational were recorded. This was used to arrive at average weekly energy expenditure using standard tables. Personal habits like alcohol intake and smoking were recorded. Cigarette/bidi smoking was quantified in terms of numbers smoked per day and for number of years. Similarly, alcohol consumption was quantified in terms of daily, weekly, and occasional use. Also, source of water supply viz tap water, pond or well was confirmed and any industry near the source was verified. Daily intake of prescription drugs or vitamin supplements was scrutinized. A family history of cancer was explored. The site of the cancer as also its morphological and histological type was recorded.

Statistical analysis

All data was analysed using SPSS version 10 software. Unconditional logistic regression was used to estimate the odds ratio (OR) confidence interval (Cl) and significance levels. The cases and controls were compared for various risk factors and multivariate logistic regression analysis was performed for the entire data set using parameters which were found to be significant in univariate analysis (value of < 0.05). The effect of increasing dose response for various risk factors was assessed by considering the least value as reference odds ratio equivalent to 1.

RESULTS

The study included 85 cases and 109 controls, matched by sex and 5-years age groups. Generally, the patients and controls belonged to north India (37%). Males constituted 74% of cases as against 26% females and amongst controls males constituted 73%, against females forming 27%. Mean age was comparable for cases and controls. Majority of the patients and controls belonged to the Indian state of Punjab (cases 34%, controls 30%).Farmers (cases 16.4%, controls 5.5%), office workers (cases 28.24%, controls 21.1%),factory workers (cases 16.4%, control 20.2%), businesspersons (cases 4.7%, controls 8.2%), and homemakers (cases 24.7%, controls 21.1%) was the breakup of the occupation.



Pie Diagram Frequency of Involvement of Various Sites IN CRC

Site of Tumour Ascending colon was the main involved site of colonic cancer; followed by sigmoid colon, and descending colon. Transverse colon was the site of malignancy in only 4% of cases (Pie Diagram). Histologically, 94% of the patients had adenocarcinoma, 5% mucinous and only 1% had signet cell carcinoma. A family history of colorectal carcinoma or colonic polyps was available in only 7 (8.24%) out of 85 patients, constituting the group with hereditary syndromes.

Body Mass Index (BMI) The meanBMI among cases was 22 + 3.9 kg/m^{2}which was significantly lower that average BMI of controls (25.2 + 3.12kg/m2). The difference was significant (*P*=.001) and is expected as any malignant disease leads to malaise, anorexia and weight loss.

Physical Activity Energy expenditure per week (a reflection of physical activity) was seen to be higher in controls in the 16000-19000, OR 0.205, 90% Cl 0.071 - 0.593, P=.006 (19000-22000 Cal), OR 0.286, 95% CI 0.117 - 0.698, P=.003 and in the >22000 Calgroup, OR 0.313, 95% CI 0.118 - 0.834, *P* =.002.Energy expenditure per week was seen to be significantly higher among controls compare to the cases (Table 1).

Table 1 Average Weekly Energy Expenditure

Energy Expenditure (Cal/week)	Cases	Controls	OR	Cl		P
				Lower	Upper	value
Sedentary (< 16000)	21(24.71%)	9 (8.2%)	1			
Low (16000-19000)	11(12.94%)	23 (21.1%)	.205	0.071	.593	.006
Moderate (> 19000-22000)	34(40.0%)	51(46.7%)	.286	0.117	.698	.003
High (> 22000)	19(22.3%)	26 (23.8%)	.313	0.118	.834	.002

Smoking The number of smokers and non-smokers was comparable in the two groups. However, the average number of cigarettes/bidis smoked per day was higher among cases (17.54±6.4 vs 10.79±3.4, *P* =.002) as also was the duration of smoking among cases (21.25±6.29 vs 15.79±3.82 years, *P* =.002).

Alcohol The number of alcohol-users and teetotalers was comparable among cases and controls. The type of alcohol or the frequency of alcohol intake was also comparable between the two groups and was not statistically significant. However, the mean duration of alcohol intake was higher amongst cases (21.25±6.2 vs 13.49±5.2 years) and this was statistically significant (*P* =.03).

Univariate Analysis

Lifestyle risk factors that were significantly associated with risk of CRC are presented in Table 2.

Table 2 Univariate Analysis of Lifestyle Factors Associated With Risk of Colorectal Carcinoma

Risk Factors	Cases	Controls	*P* values
Smoking Duration (in years)	24	19	< 0.002
Smoking Number (per day)	24	19	< 0.002
Alcohol Duration (in years)	30	43	< 0.03
Physical Activity	85	109	0.002

Multivariate Analysis

Multivariate Analysis was carried out for factors which had significant association with colorectal carcinoma on univariate analysis. On multivariate analysis, the duration of smoking, number of cigarettes/bidis smoked, and duration of alcohol consumptiondid not carry a significant association with risk of CRC. On the hand, physical activity was found to be protective (*P*=.002).

DISCUSSION

Colorectal carcinomais one of the most diagnosed cancers in the western world. International correlation studies have shown that the highest incidence of colorectal cancer occurs in North America, Great Britain, and parts of Europe and that the lowest incidences of colon cancer occur in Asia, Latin America and Africa.[11,12,13]Migrant studiesshow an elevation in risk of colon cancer in populations that have moved from low incidence areas like Japan, China, and South Asia to high incidence areas like United States, and Great Britain.[8] These findings suggest that the variation in colon cancer incidence is strongly influenced by environmental factors. Recent reports suggest that lifestyle factors like physical activity, obesity, cigarette smoking, alcohol use, and certain vitamins and medications may contribute to the variation in colon cancer risk.[14,15]

Body Mass Index and Physical Activity

Obesity especially abdominal obesity has been found to have strong association with increased risk of CRC. About 11% of CRC cases in Europe have been attributed to increased BMI and obesity.[16,17]For every 2kg/m^2 risein BMI the risk of CRC increases by 7%.[18]Obesity is associated with alteration of the adipocytokines. Low levels of adiponectin and leptin have been found in the patients of CRC.[19,20]However, in the current study, we found a statistically lower BMI among cases compared to controls (22+ 3.9 vs 25.2 ± 3.12 kg/m^2*P* =.001). This may reflectanorexia and loss of weight induced because of the malignant process. The low BMI has been implicated as one of the poor predictors of long-term outcome in the patients of CRC.[21]The body weight four to five years prior to the detection of the malignant process could have helpeddecide whether a low or high BMI was etiological on colorectal cancer risk. Unfortunately, weight record was not available in almost any of the patients, majority of them being from agrarian background. Therefore, BMI as an etiological factor in colorectal cancer cannot be commented upon in the current study.

Physical activity, however remained a factor after multivariate analysis. Increasing energy expenditure (therefore increased physical activity) was found to be highly protective, especially in the moderate (*P* =.003) and heavy (*P* =.002) categories. Though no specific trend was evident in mild physical activity, any type of physical activity, occupational, recreational, or structured, was found to be protective. To rule out the effect of malignant process on reduced physical activity seen among the cases, the routine activity one to two years prior to detection of CRC was recorded. However, the correctness and truthfulness of recall could still be a confounding factor.

A higher total calorie intake in absence of physical activity leads to obesity and is associate with increased risk of CRC.[22,23]But physical activity, in any form- occupational or structured, carries an independent protective association with incidence of CRC.[24,25]High BMI and low physical activity tend to induce a hyperinsulinemic state in addition to alteration of adipocytokine levels. Hyperinsulinemia, in turn, induces proliferation of colonocytes, resulting in the increased risk of CRC.[26]

Alcohol Mean duration of alcohol consumption was statistically higher amongst casescompared to controls (21.25 years vs13.49 years, *P* =.03). Forty percent of cases as against 16% for controls consumed alcohol daily. This indicates that increasing duration of alcohol consumption is a risk factor in etiology of CRC. However, this factor was seen only on univariate analysis in our study. Our study on the effect of alcohol is in consonance with those of Song-Yi Park *et al* and Tzu-Chiao Lin *et al*, who in their study on effect of alcohol, found that amount and duration of alcohol intake was directly related to increased risk of colon cancer.[27,28]Alcohol potentially adversely influences the folate and one-carbon metabolism in the large intestine mucosa, where the cell proliferation rate is high. Intestinal bacteria have high alcohol dehydrogenase (ADH) activity leading to a profound increase of the concentration of acetaldehyde. Acetaldehyde has a strong anti-folate effect. The combination of high alcohol-low folate and the MTHFR677TT genotype are related to markedly elevated serum levels of homocysteine and to DNA hypomethylation.[29]

Smoking

The average duration of smoking and the average number of cigarettes / bidis smoked among cases was significantly higher compared to controls in this study on univariate analysis (*P*= .002). Our study is in consonance with other studies on smoking and risk of CRC. Slattery ML *et al* observed approximately a 50% increase in colon cancer risk from smoking over a pack of cigarettes per day among both men and women. The risk among smokers increased even more if they also had elevated BMI. The study also found that those who quit smoking remained at increased risk, even after 10 years.[30]Cigarette smoking increases the risk of CRC in a dose-dependent manner with intensity and duration. Smoking is associated with rise in serum cotinine, O-cresol sulfate and hydroxycotinine. Cross AJ *et al* found that individuals with detectable levels of hydroxycotinine and cotinine had an increased CRC risk but not those with detectable level of O-cresol sulfate did not.[31]Smoking likely increases the risk of CRC through the microsatellite instability pathway, characterized by microsatellite instability, CpG island methylator phenotype positive, and BRAF mutation.[32]

CONCLUSION

This case control study was conducted to ascertain the lifestyle risk factors associated with the increased risk of colorectal cancer among north Indian population. The study revealed that obesity, alcohol use and smoking of either cigarettes or bidis

was associated with increased risk of CRC. Both, smoking duration and numbers smoked per day were the risk factors for development of CRC. Longer duration of alcohol use was found to be associated with CRC risk. Physical activity, on the other hand was found to have protective effect on CRC.

Limitatons of the Study: The findings in the study, except for BMI, are based on the subjective responses from the patients/relatives which could vary depending on recall, awareness, intelligence, and literacy level of the responder.

CONFLICT OF INTEREST Nil

Contribution of Authors

AK Handa- Concept, organization, conduct of study, and statistical analysis.
Arun Tyagi- Overall supervision, internet search, and preparation of manuscript.
A. K. Srivastava- Proof reading

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