

## RESEARCH ARTICLE

# Lifestyle and Sporadic Colorectal Cancer in India

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### Abstract

**Background:** The study evaluated the patient, lifestyle and tumor profile in patients undergoing upfront surgery for sporadic colorectal cancer (CRC) in Indian population. **Materials and Methods:** One hundred consecutive patients were included. Details related to their demographic profile, habits, signs and symptoms, tumor profile, further treatment and follow up were recorded. **Results:** The majority of the patients had colonic cancer (68%), advanced tumor stage 3 & 4 (46%), moderately differentiated tumors (70%) with absence of lymphatic invasion (60%) and metastasis (90%). Correlations between tumor location and abdominal pain (p-value 0.002), bleeding per rectum (p-value <0.001), difficulty in micturition (p-value 0.012) and constipation (p-value 0.007) were found to be statistically significant. Abdominal pain was more frequently reported in patients with metastasis (p-value 0.031). Loss of weight statistically correlated with absence of lymphatic invasion (p-value 0.047). Associations between tumor stage and alcohol intake (p-value 0.050) and non vegetarian diet (p-value 0.006); lymphatic invasion and intake of spicy food (p-value 0.040) and non vegetarian diet (p-value 0.001) and metastasis and alcohol intake (p-value 0.041) were also observed. Age and tumor grade were also correlated (p-value 0.020). **Conclusions:** Minimizing the adverse lifestyle factors can help in reducing the overall incidence of CRC in the Indian population.

**Keywords:** Signs and symptoms - tumor profile - lifestyle factors - sporadic colorectal cancer

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### Introduction

Colorectal cancer (CRC) is the third commonest cancer worldwide and designated as the leading cause of cancer deaths with incidence rates about 2 to 5 times higher in the developed countries in comparison to the developing countries (Notani PN, 2001). In India, the estimated incidence and mortality from CRC is 36476 cases and 25690 cases, respectively (Ferlay et al., 2010). It is a heterogeneous disease with complex etiology and its pathogenesis may be attributed to a variety of predisposing factors including physical inactivity, overweight and obesity, red and processed meat consumption, smoking and excessive alcohol consumption (Notani PN, 2001). These attributable factors may either singly or in combination synergistically may help in the rapid progression and multistep development of this disease. Different set of patients may present with variable symptoms depending upon the nature and aggressiveness of the disease. Delay in the presentation of symptoms remains a critical challenge in the early and timely diagnosis of CRC (MacArthur et al., 1984).

Genetic and epigenetic influences have also been shown to affect the disease progression in CRC and a host of genes may act synergistically and transform the

epithelial cells into adenocarcinomas (Sinha et al., 2013). Patients need to be managed differently depending upon a range of factors including the tumor profile, general physical condition, performance status, etc. Numerous studies have found the risk factors to be more evident and significantly associated in men (Giovannucci et al., 1994). Also, age wise classification of patients in terms of the risk factors may help in categorizing whether the younger or elderly patients are more affected with the disease and strengthening the approach towards managing this disease.

Identifying the risk factors associated with the causation and subsequent development of the disease may help in gaining a better understanding of the disease to assist in screening and assessing the prognosis of the patients suffering with this diverse group of cancers. The present study was thus aimed to evaluate the patient, lifestyle and tumor profile of patients undergoing upfront surgery for sporadic CRC in Indian population.

### Materials and Methods

A total of 100 consecutive patients who underwent upfront surgery for sporadic CRC in the Department of Surgical Oncology at Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India were included in the study.

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None of these patients had received any pre-operative treatment in the form of radiation or chemotherapy. Histopathological grades and clinical staging were evaluated according to the standard criteria (Edge et al., 2010) by two independent pathologists. Only histopathologically confirmed cases were included in this study. Details of each patient related to their demographic profile, habits, signs and symptoms, personal history, tumor profile including metastasis and histopathology reports, further treatment and follow up information was also recorded. The study was granted waiver by the Institutional Review Board and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

### Statistical analysis

All statistical analyses were performed by the standard methods using IBM SPSS Statistics (Version 22, IBM Corp, USA). Fischer's Exact Test or Chi Square Test was used as applicable. The findings were considered statistically significant at p values of < 0.05. Overall survival (OS) was calculated by the Kaplan Meier survival method (Kaplan and Meier, 1958).

## Results

A total of 100 patients with sporadic CRC were included in the study. The mean age at diagnosis of these patients was 52 years with a higher preponderance of male patients (77%). Altogether, 26% patients had presented with co-morbidities including hypertension, diabetes, heart disease and tuberculosis. Also, 12% patients had a family history of cancer. The details of demographic profile and follow up information is given in Table 1. Computed tomography scan performed in 77% patients was the most common mode of diagnosis. Post surgery, chemotherapy was administered in 39% patients. The overall survival of these cases was 99% at 49 months while the median follow up was 8.5 months.

Majority of the patients had colonic cancer (68/100), advanced tumor stage 3 and 4 (46/100), moderately differentiated tumors (70/100) with absence of lymphatic invasion (60/100) and metastasis (90/100). The correlation between signs and symptoms and the tumor profile of the patients is shown in Table 2. The most commonly observed signs and symptoms included abdominal pain (58%) and loss of weight (53%) followed by bleeding per rectum (48%). Abdominal pain was seen more frequently in colonic tumors (69.1%) and stage 4 disease (80%) with undifferentiated tumor (100%), presence of lymphatic invasion (60%) and metastasis (90%). Loss of weight was more commonly observed in rectosigmoid tumors (70%) and stage 4 disease (80%) with undifferentiated tissue (100%), presence of lymphatic invasion (55%) and metastasis (60%). Bleeding per rectum was predominant in rectal tumors (86.4%) and stage 4 disease (60%) with undifferentiated tissue (100%) and presence of lymphatic invasion (57.5%) and absence of metastasis (48.9%). The correlation between tumor location and abdominal pain (p-value 0.002), bleeding per rectum (p-value <0.001), difficulty in micturition (p-value 0.012) and constipation

(p-value 0.007) was found to be statistically significant. Also, abdominal pain was more frequently reported in patients with metastasis (p-value 0.031). Loss of weight statistically correlated with the absence of lymphatic invasion (p-value 0.047)

The correlation between lifestyle factors and the tumor profile of the patients is given in Table 3. Among the lifestyle factors, intake of fatty food (60%), spicy food (45%) and non vegetarian diet (43%) were more frequently witnessed. Intake of fatty food was more commonly observed in colonic tumors (67.6%) and stage 3 disease (63.4%) with undifferentiated tissue (100%) and presence of lymphatic invasion (62.5%). Spicy food intake was more frequent in patients with colonic tumors (48.5%), stage 3 disease (61%) with undifferentiated tissue (100%), presence of lymphatic invasion (57.5%) and presence of metastasis (50%). Non vegetarian diet was associated with rectosigmoid tumors (50%) and

**Table 1. Demographic profile and follow up of 100 patients with sporadic CRC**

Characteristic	N (%)
Mean age at diagnosis	52.6+14.2 years
Males : Females	77 (77%) : 23 (23%)
Co morbidities*	26 (26%)
Family history of cancer	12 (12%)
Signs & Symptoms	
Abdominal pain	58 (58%)
Loss of weight	53 (53%)
Bleeding per rectum	48 (48%)
Fatigue	44 (44%)
Constipation	43 (43%)
Loss of appetite	42 (42%)
Obstruction features	29 (29%)
Back pain	22 (22%)
Diarrhea	21 (21%)
Nausea & Vomiting	13 (13%)
Difficulty in micturition	8 (8%)
Lifestyle factors	
Fatty diet	60 (60%)
Spicy food	45 (45%)
Non-vegetarian diet	43 (43%)
Alcohol intake	40 (40%)
Smoking	39 (39%)
Irregular intake of fruits	27 (27%)
Lack of physical exercise	25 (25%)
Tobacco chewing	15 (15%)
Mode of diagnosis	
Computed tomography scan	77 (77%)
Biopsy	57 (57%)
Colonoscopy	52 (52%)
Treatment received	
Surgery only	50 (50%)
Surgery + CT** only	39 (39%)
Surgery + RT** only	2 (2%)
Surgery + CT** + RT**	9 (9%)
Follow up	
Overall survival	99% at 49 months
Status - Dead	1 (1%)
Median follow up	8.5 months (1-49 months)

\* Co morbidities include hypertension, diabetes, heart diseases and tuberculosis;\*\* CT, chemotherapy; RT, radiotherapy: both given adjuvantly

stage 4 disease (80%) with poorly differentiated tissue (56.5%) and presence of lymphatic invasion (62.5%) and metastasis (70%). The correlation between tumor stage and alcohol intake (p-value 0.050) and non vegetarian diet (p-value 0.006); lymphatic invasion and intake of spicy food (p-value 0.040) and non vegetarian diet (p-value

**Table 2. Correlation between Signs & Symptoms and tumor profile of 100 patients with sporadic CRC**

Characteristic	N	Loss of weight n (%)	Vomiting n (%)	Abdominal pain n (%)	Diarrhea n (%)	Bleeding per rectum n (%)	Difficulty in micturition n (%)	Constipation n (%)	Fatigue n (%)	Obstruction features n (%)	Loss of appetite n (%)	Back pain n (%)
<b>Tumor location</b>												
Colon	68	37 (54.4)	11 (16.2)	47 (69.1)	15 (22.1)	22 (32.4)	2 (2.9)	22 (32.4)	33 (48.5)	16 (23.5)	34 (50)	14 (20.6)
Rectum	22	9 (40.9)	2 (9.1)	6 (27.3)	5 (22.7)	19 (86.4)	5 (22.7)	15 (68.2)	9 (40.9)	10 (45.5)	5 (22.7)	6 (27.3)
Rectosigmoid	10	7 (70)	0 (0)	5 (50)	1 (10)	7 (70)	1 (10)	6 (60)	2 (20)	3 (30)	3 (10)	2 (20)
p-value		0.286	0.301	0.002	0.665	<0.001	0.012	0.007	0.224	0.143	0.057	0.795
<b>Tumor stage</b>												
1	11	6 (54.5)	0 (0)	3 (27.3)	5 (45.5)	5 (45.5)	0 (0)	5 (45.5)	5 (45.5)	4 (36.4)	3 (27.3)	3 (27.3)
2	43	21 (48.8)	5 (11.6)	27 (62.8)	5 (11.6)	20 (46.5)	4 (9.3)	15 (34.9)	19 (44.2)	11 (25.6)	23 (53.5)	9 (20.9)
3	41	22 (53.7)	7 (17.1)	24 (58.5)	10 (24.4)	20 (48.8)	3 (7.3)	20 (48.8)	17 (41.5)	11 (26.8)	14 (34.1)	8 (19.5)
4	5	4 (80)	1 (20)	4 (80)	1 (20)	3 (60)	1 (20)	3 (60)	3 (60)	3 (60)	2 (40)	2 (40)
p-value		0.619	0.469	0.129	0.089	0.947	0.56	0.507	0.888	0.398	0.226	0.729
<b>Tumor grade*</b>												
WD	6	4 (66.7)	1 (16.7)	3 (50)	2 (33.3)	3 (50)	0 (0)	1 (16.7)	2 (33.3)	2 (33.3)	4 (66.7)	1 (16.7)
MD	70	33 (47.1)	11 (15.7)	42 (60)	11 (15.7)	34 (48.6)	7 (10)	36 (51.4)	29 (41.4)	20 (28.6)	28 (40)	15 (21.4)
PD	23	15 (65.2)	1 (4.3)	12 (52.2)	8 (34.8)	10 (43.5)	1 (4.3)	6 (26.1)	12 (52.2)	7 (30.4)	10 (43.5)	5 (21.7)
U	1	1(100)	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)
p-value		0.298	0.532	0.725	0.201	0.731	0.704	0.067	0.501	0.921	0.501	0.301
<b>Lymphatic invasion</b>												
Absent	60	31 (51.7)	8 (13.3)	34 (56.7)	11 (18.3)	25 (41.7)	3 (5)	22 (36.7)	26 (43.3)	16 (26.7)	30 (50)	13 (21.7)
Present	40	22 (55)	5 (12.5)	24 (60)	10 (25)	23 (57.5)	5 (12.5)	21 (52.5)	18 (45)	13 (32.5)	12 (30)	12 (30)
p-value		0.744	0.903	0.741	0.423	0.121	0.176	0.117	0.869	0.529	0.047	0.921
<b>Metastasis</b>												
Absent	90	47 (52.2)	10 (11.1)	49 (54.4)	19 (21.1)	44 (48.9)	7 (7.8)	39 (43.3)	38 (42.2)	26 (28.9)	39 (43.3)	18 (20)
Present	10	6 (60)	3 (30)	9 (90)	2 (20)	4 (40)	1 (10)	4 (40)	6 (60)	3 (30)	3 (30)	4 (40)
p-value		0.64	0.092	0.031	0.935	0.594	0.806	0.84	0.283	0.941	0.418	0.148

\*WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; U, undifferentiated; p value < 0.05 was taken as significant

**Table 3. Correlation between lifestyle factors and tumor profile of 100 patients with sporadic CRC**

Characteristic	N	Alcohol intake n (%)	Tobacco chewing n (%)	Smoking n (%)	Fatty diet n (%)	Irregular intake of fruits n (%)	Spicy food n (%)	Non vegetarian diet n (%)	Lack of physical exercise n (%)
<b>Tumor location</b>									
Colon	68	30 (44.1)	10 (14.7)	28 (41.2)	46 (67.6)	14 (20.6)	33 (48.5)	31 (45.6)	13 (19.1)
Rectum	22	6 (27.3)	3 (13.6)	8 (36.4)	10 (45.5)	8 (36.4)	8 (36.4)	7 (31.8)	8 (36.4)
Rectosigmoid	10	4 (40)	2 (20)	3 (30)	4 (40)	5 (50)	4 (40)	5 (50)	4 (40)
p-value		0.374	0.89	0.763	0.072	0.079	0.575	0.471	0.137
<b>Tumor stage</b>									
1	11	1 (9.1)	1 (9.1)	2 (18.2)	5 (45.5)	4 (36.4)	4 (36.4)	2 (18.2)	5 (45.5)
2	43	18 (41.9)	7 (16.3)	14 (32.6)	27 (62.8)	11 (25.6)	14 (32.6)	13 (30.2)	6 (14)
3	41	17 (41.5)	7 (17.1)	19 (46.3)	26 (63.4)	12 (29.3)	25 (61)	24 (58.5)	13 (31.7)
4	5	4 (80)	0 (0)	4 (80)	2 (40)	0 (0)	2 (40)	4 (80)	1 (20)
p-value		0.05	0.711	0.065	0.544	0.477	0.063	0.006	0.098
<b>Tumor grade*</b>									
WD	6	4 (66.7)	1 (16.7)	2 (33.3)	3 (50)	1 (16.7)	4 (66.7)	2 (33.3)	2 (33.3)
MD	70	27 (38.6)	10 (70)	29 (41.4)	43 (61.4)	20 (28.6)	31 (44.3)	28 (40)	15 (21.4)
PD	23	8 (34.8)	4 (17.4)	8 (34.8)	13 (56.5)	6 (26.1)	9 (39.1)	13 (56.5)	8 (34.8)
U	1	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)
p-value		0.308	0.956	0.785	0.779	0.851	0.441	0.398	0.531
<b>Lymphatic invasion</b>									
Absent	60	22 (36.7)	11 (18.3)	21 (35)	35 (58.3)	18 (30)	22 (36.7)	18 (30)	14 (23.3)
Present	40	18 (45)	4 (10)	18 (45)	25 (62.5)	9 (22.5)	23 (57.5)	25 (62.5)	11 (27.5)
p-value		0.405	0.253	0.315	0.677	0.408	0.04	0.001	0.637
<b>Metastasis</b>									
Absent	90	33 (36.7)	13 (14.4)	34 (37.8)	54 (60)	25 (27.8)	40 (44.4)	36 (40)	22 (24.4)
Present	10	7 (70)	2 (20)	5 (50)	6 (60)	2 (20)	5 (50)	7 (70)	3 (30)
p-value		0.041	0.641	0.452	1	0.599	0.738	0.069	0.7

\*WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; U, undifferentiated; p value < 0.05 was taken as significant

**Table 4. Correlation between Age, Gender and Tumor Profile of 100 Patients with Sporadic CRC**

Characteristic	N	Age			Gender		
		<30 years n (%)	>30 years n (%)	p-value	Male n (%)	Female n (%)	p-value
Tumor location							
Colon	68	5 (7.4)	63 (92.6)	0.176	54 (79.4)	14 (20.6)	0.395
Rectum	22	4 (18.2)	18 (81.8)		17 (77.3)	5 (22.7)	
Rectosigmoid	10	0 (0)	10 (100)		6 (60)	4 (40)	
Tumor stage							
1 & 2	54	4 (7.4)	50 (92.6)	0.547	41 (75.9)	13 (24.1)	0.863
3 & 4	46	5 (10.9)	41 (89.1)		36 (78.3)	10 (21.7)	
Tumor grade*							
WD & MD	76	4 (5.3)	72 (94.7)	0.02	56 (73.7)	20 (26.3)	0.161
PD & U	24	5 (20.8)	19 (79.2)		21 (87.5)	3 (12.5)	
Lymphatic invasion							
Absent	60	3 (5)	57 (95)	0.087	45 (75)	15 (25)	0.561
Present	40	6 (15)	34 (85)		32 (80)	8 (20)	
Metastasis							
Absent	90	8 (8.9)	82 (91.1)	0.907	69 (76.7)	21 (23.3)	0.812
Present	10	1 (10)	9 (90)		8 (80)	2 (20)	

\*WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; U, undifferentiated; p value < 0.05 was taken as significant

0.001) and metastasis and alcohol intake (p-value 0.041) were found to be statistically significant.

Correlation between age and tumor profile is presented in Table 4. A total of 9 patients were in the age group of <30 years whereas 91 patients belonged to the age group of >30 years. The younger patients showed the presence of rectal tumors (18.2%), stage 3 and 4 disease (10.9%) with poorly differentiated and undifferentiated tumors (20.8%), presence of lymphatic invasion (15%) and metastasis (10%). On the other hand, the older patients showed a preponderance of rectosigmoid tumors (100%) and stage 1 and 2 disease (92.6%) with well to moderately differentiated tumor (94.7%), absence of lymphatic invasion (95%) and absence of metastasis (91.1%). Correlation between age and tumor grade was found to be statistically significant (p-value 0.020). Furthermore, majority of the male patients had colonic tumors (79.4%), stage 3 and 4 disease (78.3%), poorly and undifferentiated tumors (87.5%), presence of lymphatic invasion (80%) and presence of metastasis (80%) whereas the female patients mostly had rectosigmoid tumors (40%), stage 1 and 2 disease (24.1%), well to moderately differentiated tumors (26.3%), absence of lymphatic invasion (25%) and metastasis (23.3%).

## Discussion`

CRC is a multistep and multifactorial disease and an excellent example for gaining the deepest insights into the process of carcinogenesis (Lao and Grady, 2011; Hibi and Nakao, 2006). At the molecular level, studies have clearly shown that genetic/ epigenetic changes may greatly affect the development of the disease transforming the epithelial cells into adenocarcinomas (Frank et al., 2010; Carvalho et al., 2012; Sinha et al., 2013; Farkas et al., 2014). Numerous signs and symptoms have been reported in patients presenting with CRC and a host of attributable factors have been found to play a significant role in the development of this disease. Minimizing the

adverse and unhealthy factors and adopting a healthier lifestyle can help in reducing the overall incidence of this disease. Further, if the symptoms are dealt with in a stricter fashion, it might greatly help in picking up the disease at an early stage. To the best of our knowledge, this is the first study to simultaneously explore the roles of various presenting symptoms and the lifestyle factors and their effect on the detailed profile of tumor in CRC patients undergoing upfront surgery for this disease in the Indian population.

Numerous studies have reported the common signs and symptoms observed in patients with CRC. In our study, it was observed that abdominal pain (58%), loss of weight (53%) and bleeding per rectum (48%) were the most commonly reported signs and symptoms. Majumdar et al observed the most common symptoms of CRC to be rectal bleeding (58%), abdominal pain (52%) and change in bowel habits (51%) (Majumdar et al., 1999). The authors clearly stated that the physicians should continue to rely on the clinical findings for detecting this cancer. Studies have reported the presence of rectal bleeding as a single symptom or it may also present in conjunction with other symptoms (Astin et al., 2011). Most of the symptoms present more rampantly in higher stage tumors as an indicator of the aggressive nature of this disease, however, this may not always be true. Often, the symptoms initially may not even be identifiable and often go undiagnosed. It may not be correlated with cancer per se and hence is confused with other medical conditions. These symptoms, especially if appearing in conjunction with others should be addressed with a more focused approach to rule out the possibilities of misinterpretation and to come down to the specific disease diagnosis for initiating treatment as soon as possible, given the gravity of this disease.

Environmental factors including lifestyle modifications rampant in various countries are important but modifiable predictors of the disease (Gingras et al., 2011; Jemal et al., 2011). Risk factors including red and processed meat consumption, obesity, physical inactivity, excessive

smoking and alcohol consumption may significantly manipulate the causation of CRC (Giovannucci et al., 1995; Boyle et al., 2011; Jemal et al., 2011; Kim et al., 2011; Sinha et al., 2013). In our study, intake of fatty diet (60%), spicy food (45%) and non vegetarian diet (43%) were the most commonly observed lifestyle factors. The lifestyle factors were found to greatly affect the disease and directly correlated with higher stage and tumor grade. Also, the presence of these factors was more commonly witnessed in tumors with presence of lymphatic invasion and metastasis highlighting the fact that all these factors contribute towards the development of more aggressive tumors. Identifying the early symptoms and the lifestyle factors may be greatly helpful in identifying the disease at an early treatable stage. Lifestyle in the Indian population is witnessing a dramatic shift towards that observed in the western population. Intake of fruits and vegetables which have increased amounts of salicylic acid and shown to have an anticancer effect by sensitizing the normal cells to evade tumor formation is dramatically being replaced by ready to eat foods. Alcohol has also been observed to play a role in the development of CRC (Seitz et al., 1990). Alcohol may increase the risk for CRC indirectly through immune suppression, delay of DNA repair, activation of liver procarcinogens by induction of cytochrome P-450 enzymes, or changes in bile acid composition (Kune et al., 1992). Risk of colon cancer was increased with high intake of red and processed meat chiefly due to the formation of heterocyclic aromatic amines due to high temperature cooking of meat proteins (Magalhaes et al., 2012). Increased risk of CRC has been observed upon cigarette smoking due to the carcinogenic action of polynuclear aromatic hydrocarbons, nitrosamines and aromatic amines, either present in, or produced by, burning tobacco (Giovannucci et al., 1996). By lifestyle modifications and adopting a healthier routine, the overall risk of developing disease including cancer can greatly be reduced thereby increasing the life span of most individuals.

CRC is a disease affecting the individuals in the later stages of their lives. Very few patients (approximately 1% of CRCs) present in the early stages of their lives (Recio and Bussey, 1965; Rodriguez-Bigas et al., 1996; Miller and Liechty, 1967). A total of 9% patients were in the age group < 30 years in the present study and found to have higher stage (10.9%) and higher grade (20.8%) tumors with the presence of lymphatic invasion (15%) and metastasis (10%). Different studies have investigated the incidence rates and the underlying causes of the development of the disease in the younger patients (Recio and Bussey, 1965; Mills and Shannon Allen, 1979; Gardner et al., 1981; Elliot and Steven, 1984; Rao et al., 1985; Palmer et al., 1991; Cozart et al., 1993; McGaharen et al., 1995). CRC has been found to have a worse prognosis among the younger patients which may be due to the advanced stage of the tumor at the time of diagnosis of this disease. However, why these patients present with advanced tumors is a matter of grave concern and a futuristic area of research. In a study by Minardi et al, the younger patients presented with an increased incidence of advanced disease and 37% of the lesions were Duke's C and 22% were Duke's D (Minardi et al., 1998). Also, in the present study, the male

patients showed a preponderance of higher stage (78.3%) and higher grade (87.5%) with the presence of lymphatic invasion (80%) and metastasis (80%).

Identifying the symptoms at an early stage and modifying the lifestyle factors may greatly help in reducing the overall burden of this disease. Also, it becomes absolutely imperative for the managing physician to have a more stringent approach towards this disease in the younger patients and male patients.

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