# Signet Ring Cell Colorectal Cancers portend an aggressive biology: A 17-year analysis of operable colorectal cancers at a tertiary hospital in Pakistan

**Nifasat Farooqi**
Aga Khan University Hospital
**Sadaf Khan**
Aga Khan University Hospital
**Sabeeh Siddique**
Aga Khan University Hospital
**Uswa Jiwani**
Aga Khan University Hospital
**Amir Shariff**
Aga Khan University Hospital
**Ajia Syed**
Aga Khan University Hospital
**Safna Virji**
Aga Khan University Hospital
**Kulsoom Ghias**
Aga Khan University Hospital
**Munira Moosajee** ( munira.moosajee@aku.edu )
Aga Khan University Hospital

**Research Article**

**Keywords:** Colorectal cancer, histopathology, signet ring cell carcinoma, Pakistan, age, prognosis

**Posted Date:** June 21st, 2022

**DOI:** https://doi.org/10.21203/rs.3.rs-1721829/v1

# Abstract

**Introduction:** Primary signet ring cell carcinoma (SRCC) is a rare variant of colorectal cancer, reportedly comprising 0.1%-2.6% of all colorectal cancers. Due to manifestations occurring later in the course of the disease, the overall survival is reportedly poorer than that of colorectal adenocarcinoma. The Southeast Asian region has been observed to have a higher likelihood of having the signet ring cell carcinoma variant.

**Objective:** The following study determines the overall proportion and histopathological characteristics of colorectal cancer in a Pakistani population across a tertiary care hospital.

**Methods:** The histopathology reports of the colon and/or rectum specimens diagnosed as primary colorectal carcinoma were identified and reviewed at the Aga Khan University Hospital (AKUH). These included all the surgical specimens submitted to AKUH from January 2002 to December 2018. Biopsies and histopathological specimens with fragmented bowel, lack of orientation of tissue, and post chemotherapeutic complete resolution of the tumor were excluded.

**Results:** Of the 2,662 surgical specimens of colorectal carcinoma identified, 1,708 specimens met the inclusion criteria. The cohort consisted of 62.4% (n = 1065) males, with an overall mean age of 50.41 years (SD = 16.98). Among these patients, 29.5% (n = 504) were 40 years of age or younger, 19% (n = 325) were between the ages of 41 and 50, and 51.5% (n = 879) were older than 50 years ($p<0.001$). The frequency of signet ring cell cancer was found to be 5.4% (n = 92). The histopathological characteristics associated with worse prognosis were significantly associated with the type of tumor. Lymphovascular and perineural invasion, stage, and grade were all significantly higher in SRCC than the other types.

**Conclusion:** Pakistani population tends to present with colorectal cancer at a younger age and with poorer prognostic features including higher rates of signet ring cell cancer.


# Introduction

Colorectal cancer has traditionally been one of the most common malignant disorders in western populations, whereas cancers of the upper gastrointestinal tract (esophagus and stomach) and liver have predominated in the east. However, during the past few decades, there have been remarkable changes in the incidence of colorectal cancer in Asian countries, with colorectal cancer being the 3rd most common cancer in both males and females in Asia [1]. The age-standardized rate of colorectal cancer per 100 000 men is 49.3 in Japan, 24.7 in South Korea, and 35.1 in Singapore, compared with 44.4 in North America and 42.9 in Western Europe [2]. The age-adjusted incidence of rectal cancer as per the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute database from 1975 through 2005 was 16.1 per 100,000 in the United States. Data from the United States suggests that approximately 11% of colon cancer and 18% of rectal cancer occur in individuals younger than age 50 [3]. Interestingly, a rapid increase in colorectal cancer incidence rate in economically transitioning countries

has been recently reported in the literature [4] and has been attributed to a change in the dietary habits and physical activity patterns superimposed on genetic predisposition.

The incidence of early-onset colorectal cancer is approximately 7% of the total colorectal cancer population in the West [5], however, the problem has been reported to be of a much greater magnitude in several Asian and African countries [6–7]. Similarly, half of the incident cases of colorectal cancer in the Pakistani population as reported by Bhurgri et.al have been estimated to be in young patients [8]. From this, coupled with the fact that greater than 80% of the Pakistani population is younger than 40 years [9], it can be estimated that the “at-risk" population for early-onset colorectal cancer in countries like Pakistan is much higher than the rest of the world.

These colorectal cancers are more likely to be poorly differentiated, have mucinous and signet ring features, and present at advanced stages. Familial syndromes account for approximately 20% of these cases. The majority of detailed analyses are based in North America and Europe. The results of these meta-analyses and several other studies indicate that sporadic early-onset colorectal cancer is rare in the developed countries. On the other hand, early-onset colorectal cancer is far more common in third-world countries [10]. A study conducted at the Aga Khan University Hospital by Zahir et.al revealed a 32% prevalence of sporadic early-onset colorectal cancer, of which 21% was signet ring cell carcinoma (SRCC), which is much higher than that suggested by the western data [11–12]

Primary signet-ring cell carcinoma (SRCC) is a rare variant of colorectal cancer, reportedly comprising 0.1%-2.6% of all colorectal cancers [13]. Clinical symptoms tend to occur late in the course of signet ring cell carcinoma. The disease is usually detected at an advanced stage [14], and the overall survival rate is reported to be poorer than that of colorectal adenocarcinoma [15–16]. These cancers tend to display more aggressive behavior and have a poor prognosis. This warrants early screening, diagnosis, and prompt treatment [17].

In the Southeast Asian region, it is observed that younger patients presenting with colorectal cancer show a greater tendency of having the signet cell variant. This study aims to determine the overall proportion of signet ring cell carcinoma and to report the histopathological characteristics of colorectal cancer in the Pakistani population. A further step will be to plan a multicenter prospective evaluation of genetic and epigenetic factors that play a role in the early onset of colorectal cancer and the development of the signet cell variant.

# 1. Methodology

The study was conducted at the Aga Khan University Hospital (AKUH) in Karachi, Pakistan. Exemption from the Ethics Review Committee of AKUH was obtained before the commencement of the study. The histopathology reports of the colon and/or rectum specimens diagnosed as primary colorectal carcinoma were identified through Index and Coding by the department of Hospital Information Management System (HIMS) Integrated Laboratory Management System (ILMS) and reviewed. These included all the surgical specimens submitted to AKUH from January 2002 to December 2018. Biopsies and

histopathological specimens with fragmented bowel, lack of orientation of tissue, and post chemotherapeutic complete resolution of the tumor were excluded.

Demographic and histopathological data were recorded from patient charts. These included age at diagnosis, gender, previous history of chemotherapy, and tumor characteristics namely the histopathological type, location, TNM stage, grade, lymphovascular and perineural invasion, margin, and lymph node involvement. The circumferential margin was considered involved if tumor cells were found on or < 1mm away from the margin. The tumors were divided into four different groups based on histology: classic adenocarcinoma (CA), mucinous adenocarcinoma (MAC), and signet ring cell cancers. The fourth category of rare tumors included the infrequent subtypes, squamous cell, adenosquamous, neuroendocrine, and clear cell carcinoma. Tumors that contained only a component of signet ring cells were excluded from the signet ring cell cancer group.

The data was analyzed using SPSS® version 22.0 for Windows. Continuous variables were reported as mean and standard deviation and median and interquartile range. Statistical tests used include t-test, Kruskal Wallis H test, Chi-square test for independence, Fisher's exact test, and one-way analysis of variance (ANOVA) with posthoc pairwise comparison using Bonferroni correction. A *p*-value of < 0.05 was considered statistically significant.

# 2. Results

A total number of 2,662 surgical specimens of colorectal carcinoma were identified between January 2002 and December 2018, out of which 1,708 specimens met the inclusion criteria and were used in the study. The cohort consisted of 62.4% (n = 1065) males and 37.6% (n = 643) females, with an overall mean age of 50.41 years (SD = 16.98). Mean age for males was 51.02 (SD = 16.75), and that for females was 49.40 (SD = 17.32), $p = 0.057$. Among these patients, 29.5% (n = 504) were 40 years of age or younger, 19% (n = 325) were between the ages of 41 and 50, and 51.5% (n = 879) were older than 50 years.

The frequency of signet ring cell cancer was found to be 5.4% (n = 92). All of these cancers were poorly differentiated at the time of diagnosis and had the highest frequencies of lymphovascular (55.4%) and perineural involvement (52.2%). The most commonly diagnosed cancer was adenocarcinoma, which made up 74.9% (n = 1,279) of all the colorectal cancers. Mucin secreting adenocarcinoma was the second most common, comprising 18.7% (n = 319) of the tumors, whereas rare subtypes made up the remaining 1.1% (n = 18). Of these, neuroendocrine tumors were the most frequent (n = 15) while the remaining three types were seen only in one specimen each.

The most common tumor site was the colon, with 81.2% (n = 1387) of all specimens being colonic. 13.8% (n = 235) of the tumors were found in the rectum, 4.7% (n = 80) were found at the rectosigmoid junction, and 0.4% (n = 6) were bifocal tumors, found in both the colon and rectum. Table 1 shows the characteristics of the tumors.

Table 1
Histopathological characteristics of the colorectal cancers

| | |
|---|---|
| **Lymphovascular invasion, n (%)** | **452 (26.5)** |
| **1. Yes** | **1136 (66.5)** |
| **2. No** | **120 (7.0)** |
| **3. Indeterminate** | |
| Perineural invasion, n (%) | 410 (24.0) |
| 1. Yes | 1263 (73.9) |
| 2. No | 35 (2.0) |
| 3. Indeterminate | |
| Lymph nodes received, median (IQR) | 19 (15) |
| Lymph nodes involved, median (IQR) | 1 (4) |
| Circumferential margin involved, n (%) | 239 (14.0) |
| Proximal margin involved, n (%) | 9 (0.5) |
| Distal margin involved, n (%) | 28 (1.6) |
| T, n (%) | 2 (0.1) |
| 1. Tis | 13 (0.8) |
| 2. T1 | 181 (10.6) |
| 3. T2 | 1218 (71.3) |
| 4. T3 | 294 (17.2) |
| 5. T4 | |
| N, n (%) | 744 (43.6) |
| 1. N0 | 463 (27.1) |
| 2. N1 | 487 (28.5) |
| 3. N2 | 14 (0.8) |
| 4. Nx | |
| M, n (%) | 3 (0.2) |
| 1. M1 | 50 (2.9) |
| 2. M2 | 1655 (96.9) |
| 3. Mx | |

| | |
|---|---|
| **Lymphovascular invasion, n (%)** | **452 (26.5)** |
| **1. Yes** | **1136 (66.5)** |
| **2. No** | **120 (7.0)** |
| **3. Indeterminate** | |
| Grade, n (%) | 126 (7.4) |
| 1. Well-differentiated | 1145 (67.0) |
| 2. Moderately differentiated | 437 (25.6) |
| 3. Poorly and undifferentiated | |
| Neoadjuvant chemotherapy received, n (%) | 51 (3.0) |
| 1. Yes | 1657 (97.0) |
| 2. No/Don't know | |
| a: Including < 1mm; b: Excluding < 1cm; c: Excluding < 1cm | |

The mean age of patients with SRCC at the time of surgery was 11 years (95% CI = -15.35 to -6.67) less than that of patients with adenocarcinoma, $p < 0.001$, and 7.11 years (95% CI = -11.87 to -2.36) less than those with mucinous adenocarcinoma, $p = 0.002$. Additionally, patients with mucinous adenocarcinoma were on average 3.89 years (95% CI = -6.41 to -1.38) younger at the time of surgery than patients with adenocarcinoma, $p = 0.001$. Table 2 shows the mean age at diagnosis for the various tumor types.

Table 2
Mean age at the time of diagnosis

| Tumor histology | Mean age in years (std. deviation) |
|---|---|
| Adenocarcinoma | 51.67 (16.43) |
| Mucinous adenocarcinoma | 47.74 (17.54) |
| Signet ring cell | 40.66 (18.54) |
| Rare tumors | 57.00 (15.53) |

The histopathological characteristics associated with worse prognosis were significantly associated with the type of tumor. Age categories had a significant association with different histological types of cancer ($p < 0.001$) with the prevalence of SRCC being 9.7% in those aged ≤ 40 years with a male predominance (64.1% vs. 35.9%, p = 0.012). Lymphovascular and perineural invasion, stage, and grade were all significantly higher in SRCC than the other types. The number of lymph nodes involved in SRCC was significantly higher than in adenocarcinoma (9 vs. 0, $p < 0.001$), and mucinous adenocarcinoma (9 vs. 2, $p < 0.001$). All the cases of SRCC were poorly differentiated whereas other histological subtypes were also well differentiated or moderately differentiated ($p < 0.001$). The difference between CA and MAC was also

significant, $p < 0.001$. A comparison of other relevant tumor characteristics between the different histological types of cancer is shown in Table 3.

Table 3
Comparison of characteristics between the different histological types of cancer

| | Adenocarcinoma, n (%) | Mucinous adenocarcinoma, n (%) | Signet ring cell, n (%) | Rare tumors, n (%) | *p* value (excluding rare tumors) |
|---|---|---|---|---|---|
| **Age categories** | 337 (26.3) | 114 (35.7) | 49 (53.3) | 4 (22.2) | < 0.001 |
| 1. ≤ 40 | 245 (19.2) | 65 (20.4) | 15 (16.3) | 0 (0.0) | |
| 2. 41–50 | 697 (54.5) | 140 (43.9) | 28 (30.4) | 14 (77.8) | |
| 3. > 50 | | | | | |
| **Gender** | 776 (60.7) | 222 (69.6) | 59 (64.1) | 8 (44.4) | 0.012 |
| Male | 503 (39.3) | 97 (30.4) | 33 (35.9) | 10 (55.6) | |
| Female | | | | | |
| **Tumor location** | 1031 (80.6) | 265 (83.1) | 73 (79.3) | 18 (100.0) | 0.83 |
| 1. Colon | 178 (13.9) | 41 (12.9) | 16 (17.4) | 0 (0.0) | |
| 2. Rectum | 65 (5.1) | 12 (3.8) | 3 (3.3) | 0 (0.0) | |
| 3. Rectosigmoid | 5 (0.4) | 1 (0.3) | 0 (0.0) | 0 (0.0) | |
| 4. Bifocal | | | | | |
| **Lymphovascular invasion** | 301 (25.2) | 92 (31.3) | 51 (62.2) | 8 (47.1) | < 0.001 |
| 1. Yes | 894 (74.8) | 202 (68.7) | 31 (37.8) | 9 (52.9) | |
| 2. No | | | | | |
| **Perineural invasion** | 293 (23.3) | 63 (20.3) | 48 (53.3) | 6 (35.3) | < 0.001 |
| 1. Yes | 962 (76.7) | 248 (79.7) | 42 (46.7) | 11 (64.7) | |
| 2. No | | | | | |
| **Lymph nodes received**, median (IQR) | 19 (14) | 20 (14) | 21 (22) | 18 (12) | 0.12 |
| **Lymph nodes involved**, median (IQR) | 0 (3) | 2 (7) | 9 (12) | 2 (7) | < 0.001 |
| **Circumferential margin** | 143 (11.2) | 56 (17.6) | 36 (39.1) | 4 (22.2) | < 0.001 |
| 1. Involved | 1136 (88.8) | 263 (82.4) | 56 (60.9) | 14 (77.8) | |
| 2. Uninvolved | | | | | |

| | Adenocarcinoma, n (%) | Mucinous adenocarcinoma, n (%) | Signet ring cell, n (%) | Rare tumors, n (%) | *p* value (excluding rare tumors) |
|---|---|---|---|---|---|
| **T** | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | < 0.001 |
| 1. Tis | 12 (0.9) | 1 (0.3) | 0 (0.0) | 0 (0.0) | |
| 2. T1 | 163 (12.7) | 14 (4.4) | 3 (3.3) | 1 (5.6) | |
| 3. T2 | 931 (72.8) | 222 (69.6) | 50 (54.3) | 15 (83.3) | |
| 4. T3 | 171 (13.4) | 82 (25.7) | | | |
| 5. T4 | | | 39 (42.4) | 2 (11.1) | |
| **N** | 631 (49.3) | 102 (32.0) | 4 (4.3) | 7 (38.9) | < 0.001 |
| 1. N0 | 353 (27.6) | 94 (29.5) | 15 (16.3) | 1 (5.6) | |
| 2. N1 | 284 (22.2) | 120 (37.6) | | | |
| 3. N2 | 11 (0.9) | 3 (0.9) | 73 (79.3) | 10 (55.6) | |
| 4. Nx | | | 0 (0.0) | 0 (0.0) | |
| **Grade** | 114 (8.9) | 10 (3.1) | 0 (0.0) | 2 (11.1) | < 0.001 |
| 1. Well-differentiated | 960 (75.1) | 180 (56.4) | 0 (0.0) | | |
| 2. Moderately differentiated | 204 (16.0) | 129 (40.4) | 92 (100.0) | 5 (27.8) | |
| 3. Poorly differentiated | | | | 11 (61.1) | |

a: Tumors present in both colon and rectum; b: Including < 1mm;

# 3. Discussion

Based on the trend observed in our institution, it was noted that colorectal carcinoma was more frequently diagnosed in males than in females. These trends are in concordance with previous studies carried out worldwide that compare the incidence of colorectal carcinomas in both sexes. In a study conducted by Murphy et al, it was revealed that rates of CRC in males were higher than females at all subsites for all racial/ethnic groups, with the single exception of proximal CRC sites for American Indians/Alaskan Natives, where female rates were slightly higher than male [19]. Data from the UK reflect previous studies [20, 21] in showing that the overall incidence of bowel cancer is higher in males than in females [22]. It has been hypothesized that the increased vulnerability in men could be due to multiple behavioral and genetic factors, such as increased intake of red meat, alcohol, and tobacco smoking. [23, 24, 25]. Furthermore, the obesity-related metabolic pathways that are implicated in colorectal cancer are

thought to be more heavily influenced by visceral abdominal fat that men tend to accumulate more of compared with women, in whom subcutaneous fat is more common [26].

We also discovered that only about half of the study population was comprised of patients older than 50 years. This was like the study conducted in the USA using the SEER data that showed that the number of cases of colon and rectal cancers for individuals aged 50 and older (72.4% colon cancers, 27.6% rectal cancers) greatly outweighed those diagnosed in individuals aged 20–49 (60.4% colon cancers,39.6% rectal cancers) [27]. Although the incidence of CRC is greater in a population aged more than 50, there has been a recent trend of increasing rates of CRC in the younger population in America, Canada, and Australia [28, 29, 30]. These alarming shifts have brought about an update in the guidelines recommended by the American Cancer Society, lowering the recommended age for screening to 45 years [31].

Our study further revealed that the most common colorectal cancer histology was adenocarcinoma. According to the WHO classification of tumors of the digestive system, more than 90% of colorectal carcinomas originate from the epithelial cells of the mucosa lining the gastrointestinal system and are thus adenocarcinomas [32]. We report a higher percentage of the well-differentiated tumor on grading (7.4%) as compared to a study conducted in a tertiary care hospital by Patil et al that reports it to be 2.6% [33]. According to a meta-analysis to assess the prevalence of cancer in Pakistan, the prevalence of colorectal cancer is around 5% [34]. Interestingly it was also noted that the incidence rates of colorectal cancer are lower in Karachi as compared to the rates in Northern and Southwestern Pakistan, which was attributed to the high consumption of smoked meat by Pathans and Balochis, the major ethnic groups living in those areas respectively [34].

Five percent of our population had signet ring cell morphology which is historically associated with poorer prognostic factors. This was also indicated in the present study by a higher proportion of lymphovascular invasion (55.4%), perineural invasion (55.2%), and stage at presentation in the signet ring cell cancers when compared to the other histologic subtypes.

Another striking feature of signet ring cell carcinoma in our study was that 100% of the tumors were poorly differentiated, further adding to the poor prognostic factors. These results are similar to a Korean study that revealed that signet-ring cell cancers presented at higher stage (III/IV, 80.9 percent) more often than mucinous (52.8 percent) and adenocarcinoma (49.5 percent), and also had worse tumor grade (high grade: signet-ring cell, 73.5 percent; mucinous, 20.9 percent; adenocarcinoma, 17.5 percent) [35]. While they found the frequency of signet ring cell carcinoma to be higher than that in the western population (1–2%) [36], literature from India reports a considerably greater prevalence of signet ring cell carcinoma, ranging from 11.4 to 13.5 percent [37]. Our burden of SRCC among patients aged ≤ 40 years is much higher than the 0.9% prevalence reported by Nitsche et al. in a longitudinal cohort of 3,479 patients from Germany [38]. Another study conducted in Pakistan revealed a very high frequency (21.3%) of SRCC in patients aged 45 years or below as compared to 9.7% in the less than or equal to 40 years' age group in our study [11]. However, the overall prevalence of SRCC from the handful of previous small sample

studies available from Karachi has reported a frequency of 3–5% [39, 40], while those from Lahore, another large metropolitan city in a different part of the country, have reported rates as high as 11% [41].

Our audit is the largest single-center audit of 1,708 specimens with colorectal cancer from all over Pakistan. There is a possibility of referral bias which would be a limitation of the study. Because our data were collected from histopathological reports of tumor specimens, the majority of which were operated outside of the hospital, we could not differentiate between hereditary and sporadic cases of colorectal cancer, and we were unable to capture data related to dietary and other risk factors (obesity, smoking status, and ethnicity) and 10 years' survival rate.

This audit can help us to get an idea about the demographics of colorectal cancer patients and the number of patients who are likely to benefit from biological and recent immunological therapy targeting the molecular level of colorectal cancer and the various oncogenes and protooncogenes associated with colorectal cancer. This can be further used for strategic planning for development and financial allocation to tertiary care hospitals and research centers. We also suggest strict screening protocols to be followed as suggested by the guidelines since the majority of our population presents with end-stage disease. Approximately one-third of the specimens received at our center belonged to patients who were younger than 40 years of age. In this population, single flexible sigmoidoscopy for screening appears to be an attractive option and can be evaluated for cost–benefit analysis. However, keeping in mind the financial costs and an out-of-pocket health care system in Pakistan, strengthening symptom-based algorithms for the diagnosis of CRC should be actively worked upon.

# 4. Conclusion

Large scale data from Pakistan is scarce and most prevalence data comes from small single-institution studies. Significant variations exist in these studies from different parts of the country. However, they all agree on the fact that the Pakistani population tends to present with colorectal cancer at a younger age and with poorer prognostic features including higher rates of signet ring cell cancer. Low rates of screening and lack of a national data source are two of the major problems that need to be solved hastily to address the burden of the disease on the population.

# Declarations

### Ethics approval and consent to participate.

This study was reviewed by the ethical review committee of Aga Khan University Hospital and was granted exemption before any data collection began. (2022-0442-20988)

### Consent for publication

Not Applicable

### Availability of data and material

Upon request

### Competing interests

None of the authors have any conflicts of interests to disclose


### Funding

Not applicable


### Authors' contributions

NF, SS, MM, SK and KG were responsible for devising the study and overseeing the data collection and reviewing the manuscript. NF, SS, UJ, AS collected the data. NF wrote the manuscript. SV performed the statistical analysis. AS reviewed the manuscript.

All authors have read and approved the manuscript


### Acknowledgements

Not applicable


# References


1. Sung JJ, Lau JY, Goh KL, et al. Increasing incidence of colorectal cancer in Asia: implications for screening. Lancet Oncol 2005;6:871–6.
2. World Health Statistics Annual. Geneva: WHO Databank
3. Meyer JE, Narang T, Schnoll-Sussman FH, et al. Increasing incidence of rectal cancer in patients aged younger than 40 years: an analysis of the surveillance, epidemiology, and end results database. Cancer. 2010;116:4354–4359.
4. M. M. Center, A. Jemal, and E. Ward, “International trends in colorectal cancer incidence rates,” Cancer Epidemiology Biomarkers and Prevention, vol. 18, no. 6, pp. 1688–1694, 2009.
5. S. Ashenafi, “The frequency of large bowel cancer as seen in Addis Ababa University, Pathology Department,” Ethiopian Medical Journal, vol. 38, no. 4, pp. 277–282, 2000.
6. M. H. Chew, P. K. Koh, K. H. Ng, and K. W. Eu, “Improved survival in an Asian cohort of young colorectal cancer patients: an analysis of 523 patients from a single institution,” International Journal of Colorectal Disease, vol. 24, no. 9, pp. 1075–1083, 2009.
7. M. V. de Silva, M. S. Fernando, and D. Fernando, “Comparison of some clinical and histological features of colorectal carcinoma occurring in patients below and above 40 years,” The Ceylon Medical Journal, vol. 45, no. 4, pp. 166–168, 2000.

8. Y. Bhurgri, T. Khan, N. Kayani et al., “Incidence and current trends of colorectal malignancies in an unscreened, low risk population,” Asian Pacific Journal of Cancer Prevention, vol. 12, no. 3, pp. 703–708, 2011.
9. P. Demographic, Health Survey 2006–2007 [Preliminary Report], National Institute of Population Studies, Islamabad, Pakistan; IRD/Macro International, Columbia, Mass, USA, 2007.
10. S. Gupta, D. Bhattacharya, A. N. Acharya, S. Majumdar, P. Ranjan, and S. Das, “Colorectal carcinoma in young adults: a retrospective study on Indian patients: 2000–2008,” Colorectal Disease, vol. 12, no. 10, pp. e182–e189, 2010.
11. Muhammad Nauman Zahir, Eisha Mahpara Azhar,Sobia Rafiq, Kulsoom Ghias, and Munira Shabbir-Moosajee,“Clinical Features and Outcome of Sporadic Colorectal Carcinoma in Young Patients: A Cross-Sectional Analysis from a Developing Country” ISRN Oncology,Volume 2014 (2014), Article ID 461570.
12. J. B. O'Connell, M. A. Maggard, E. H. Livingston, and C. K. Yo, “Colorectal cancer in the young,” American Journal of Surgery, vol. 187, no. 3, pp. 343–348, 2004.
13. Anthony T, George R, Rodriguez-Bigas M, Petrelli NJ. Primary signet-ring cell carcinoma of the colon and rectum. Ann Surg Oncol. 1996;3:344–348.
14. Psathakis D, Schiedeck TH, Krug F, Oevermann E, Kujath P, Bruch HP. Ordinary colorectal adenocarcinoma vs. primary colorectal signet-ring cell carcinoma: study matched for age, gender, grade, and stage. Dis Colon Rectum. 1999;42:1618–1625.
15. Chen JS, Hsieh PS, Chiang JM, Yeh CY, Tsai WS, Tang R, Changchien CR, Wu RC. Clinical outcome of signet ring cell carcinoma and mucinous adenocarcinoma of the colon. Chang Gung Med J. 2010;33:51–57.
16. Tung SY, Wu CS, Chen PC. Primary signet ring cell carcinoma of colorectum: an age- and sex-matched controlled study. Am J Gastroenterol. 1996;91:2195–2199.
17. Makino T1, Tsujinaka T, Mishima H, Ikenaga M, Sawamura T, Nakamori S, Fujitani K, Hirao M, Kashiwazaki M, Masuda N, Takeda M, Mano M. Primary signet-ring cell carcinoma of the colon and rectum: report of eight cases and review of 154 Japanese cases.
18. Tamhankar AS, Ingle P, Engineer R, Bal M, Ostwal V, Saklani A. Signet ring colorectal carcinoma: Do we need to improve the treatment algorithm?. World J Gastrointest Oncol. 2016;8(12):819–825. doi:10.4251/wjgo.v8.i12.819
19. Murphy G, Devesa SS, Cross AJ, Inskip PD, McGlynn KA, Cook MB. Sex disparities in colorectal cancer incidence by anatomic subsite, race and age. Int J Cancer. 2011;128(7):1668–1675. doi:10.1002/ijc.25481
20. Cook MB, Dawsey SM, Freedman ND, Inskip PD, Wichner SM, Quraishi SM, et al. Sex disparities in cancer incidence by period and age. Cancer Epidemiol Biomark Prev. 2009;18:1174–1182. doi: 10.1158/1055-9965.EPI-08-1118.
21. European Commission. The State of Men’s Health in Europe Report (Extended report) Luxembourg: European Commission; 2011.

22. White A, Ironmonger L, Steele RJC, Ormiston-Smith N, Crawford C, Seims A. A review of sex-related differences in colorectal cancer incidence, screening uptake, routes to diagnosis, cancer stage and survival in the UK. BMC Cancer. 2018;18(1):906. Published 2018 Sep 20. doi:10.1186/s12885-018-4786-7
23. Bates B, Cox L, Nicholson S, Page P, Prentice A, Steer T, et al. National Diet and Nutrition Survey: Results from Years 5 and 6 (combined) of the Rolling Programme (2012/2013–2013/2014) London: Public Health England; 2016.
24. Schütze M, Boeing H, Pischon T, Rehm J, Kehoe T, Gmel G, et al. Alcohol attributable burden of incidence of cancer in eight European countries based on results from prospective cohort study. BMJ. 2011;342:d1584. doi: 10.1136/bmj.d1584.
25. Chang LC, Wu MS, Tu CH, Lee YC, Shun CT, Chiu HM. Metabolic syndrome and smoking may justify earlier colorectal cancer screening in men. Gastrointest Endosc. 2014;79:961–969. doi: 10.1016/j.gie.2013.11.035.
26. Frezza EE, Wachtel MS, Chiriva-Internati M. Influence of obesity on the risk of developing colon cancer. Gut 2006;55:285–91
27. https://new.hindawi.com/journals/jce/2019/9841295/
28. Siegel RL, Fedewa SA, Anderson WF, et al. Colorectal cancer incidence patterns in the United States, 1974-2013. J Natl Cancer Inst. 2017;109:djw322.
29. Brenner DR, Heer E, Sutherland RL, et al. National Trends in Colorectal Cancer Incidence Among Older and Younger Adults in Canada. JAMA Netw Open. 2019;2(7):e198090. Published 2019 Jul 3. doi:10.1001/jamanetworkopen.2019.8090
30. Moe Kyaw and Joseph JY Sung, Young-onset colorectal cancer in the Asia–Pacific region, Medical Journal of Australia, 205, 10, (450–451), (2016).
31. A. M. D. Wolf, E. T. H. Fontham, T. R. Church et al., “Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society,” CA: A Cancer Journal for Clinicians, vol. 68, no. 4, pp. 250–281, 2018.
32. Hamilton SR, Bosman FT, Boffetta P, et al. Carcinoma of the colon and rectum. In: WHO Classification of Tumours of the Digestive System. Bosman FT, Carneiro F, Hruban RH, Theise ND, eds. Lyon: IARC Press, 2010:134–46.
33. Patil PS, Saklani A, Gambhire P, et al. Colorectal Cancer in India: An Audit from a Tertiary Center in a Low Prevalence Area. Indian J Surg Oncol. 2017;8(4):484–490. doi:10.1007/s13193-017-0655-0.
34. Idrees R, Fatima S, Abdul-Ghafar J, Raheem A, Ahmad Z. Cancer prevalence in Pakistan: meta-analysis of various published studies to determine variation in cancer figures resulting from marked population heterogeneity in different parts of the country. World J Surg Oncol. 2018;16(1):129. Published 2018 Jul 5. doi:10.1186/s12957-018-1429-z
35. Kang H, O’Connell JB (2005) Maggard Ma, et al.: A 10-year outcomes evaluation of mucinous and signet-ring cell carcinoma of the colon and rectum. Dis Colon Rectum 48:1161–1168

36. Nitsche U et al (2013) Mucinous and signet-ring cell colorectal cancers differ from classical adenocarcinomas in tumor biology and prognosis. Ann Surg 258(5):775–782
37. Pokharkar AB, Bhandare M, Patil P, Mehta S, Engineer R, Saklani AP. Young Vs Old Colorectal Cancer in Indian Subcontinent: a Tertiary Care Center Experience. Indian J Surg Oncol. 2017;8(4):491–498. doi:10.1007/s13193-017-0670-1
38. Nitsche U, Zimmermann A, Späth C, Müller T, Maak M, Schuster T, Slotta-Huspenina J, Käser SA, Michalski CW, Janssen KP, Friess H. Mucinous and signet-ring cell colorectal cancers differ from classical adenocarcinomas in tumor biology and prognosis. Annals of surgery. 2013 Nov;258(5):775.
39. Shaikh AJ[1], Raza S, Shaikh AA et al. Demographics, pathologic patterns and long-term survival in operable colon cancers: local experience in Pakistan. Asian Pac J Cancer Prev. 2009 Jul-Sep;10(3):361–4
40. Hashmi AA, Hashmi SK, Ali N, et al. Clinicopathologic features of colorectal carcinoma: features predicting higher T-stage and nodal metastasis. BMC Res Notes. 2018;11(1):52. Published 2018 Jan 19. doi:10.1186/s13104-018-3183-2
41. Nabi U1, Nagi AH, Riaz S, Sami W. Morphological evaluation of colorectal carcinoma with grading staging and histological types. J Pak Med Assoc. 2010 Dec;60(12):998–1001.