

Assessing Molecular Biomarkers and Subtypes of Colorectal Cancer in the Asir Region, Saudi Arabia: A Clinical Exploration

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ABSTRACT

Background: CRC is recognized as one of the leading cancers worldwide., with its incidence influenced by genetic, molecular, and environmental factors. Understanding the distribution of molecular subtypes and biomarkers can aid in the development of targeted treatment and screening programs. This study focuses on the CRC landscape in the Asir region, a specific population in Saudi Arabia, where region-specific data on molecular subtypes remain limited. **Aim & Objectives:** The present study is conducted to analyze the prevalence of specific molecular subtypes and associated biomarkers in colorectal cancer patients from Asir region of Saudi Arabia. It also seeks to identify the most common molecular subtype and assess its association with demographic and clinical factors such as gender, age, tumor size, pathological diagnosis, and tumor grading. **Methodology:** A retrospective, observational, and analytical investigation was performed at Asir Central Hospital, Abha, Saudi Arabia, spanning from January 2021 to December 2024. The study involved 187 Saudi colorectal cancer patients who received treatment at the hospital during this period. Clinical and demographic data such as gender, age, tumor characteristics, and molecular subtype classification, were extracted and analyzed to identify potential associations. **Results:** The results displayed a statistically significant association between gender and incidence of malignant tumors ($P=0.028$), with a greater prevalence observed in males than in females. However, there was no significant link between gender and the occurrence of polyps ($P = 0.276$). The data also indicated that 44.92% of CRC cases occurred in patients aged over 50 years, highlighting an increased risk for this age group. **Conclusion:** This study concludes that CRC is more prevalent in men, particularly in those aged over 50 years. The insights into the relationship between molecular subtypes and demographic factors may inform screening programs and early detection strategies. These findings can improve patient care and public health initiatives in the Asir region.

KEYWORDS

Colorectal Cancer; Molecular Subtypes; Biomarkers; Demographic Factors; Asir Region

INTRODUCTION

CRC represents a substantial comprehensive health burden, positioned as the third most common malignancy and the second leading cause of cancer

mortality globally (1,2). According to WHO and GLOBOCAN 2020 reports (3,4), nearly 1.9 million new cases were diagnosed, comprising approximately 10% of all cancers, while about

935,000 deaths were caused to CRC, accounting for 9.4% of cancer-related mortality (5-7). Colorectal cancer shows substantial regional differences in incidence and mortality. High-HDI regions such as Northern and Southern Europe, Australia, and New Zealand exhibit the greatest burden, whereas low-HDI areas, including South-Central Asia and Western Africa, show comparatively lower rates (8,9).

Saudi Arabia reflects the global upward trend in CRC incidence, where the disease has become a significant public health issue (10). Over the past two decades, the country has seen a steady increase in cancer burden (11,12). CRC is the leading cancer in male (15.3%) and the third most common in female (9.8%). The 2018 Saudi Cancer Incidence Report documented 4,007 new CRC cases, accounting for 14.4% of all diagnosed cancers (13,14). The Saudi cancer registry shows a steady increase in CRC ASR from 2006 to 2018 for both males and females (15,16). Rates rose from 9.9 to 14.2 per 100,000 in men and from 8.8 to 11.5 per 100,000 in women. These findings signal an urgent need for deeper investigation into possible genetic, environmental, and lifestyle-related risk factors (17–19). Significant regional variation in CRC incidence is evident in Saudi Arabia, with Riyadh showing the highest rates at 21.8 per 100,000 for males and 16.5 per 100,000 for females (20–22). Other regions like Makkah, Al-Qassim, and Al-Sharqiyah also report elevated rates (23). Conversely, regions such as Asir and Al-Jawf show much lower incidence rates, with the Asir region recording 7.9 for women and 10.7 for men (24). This geographic variability may be influenced by multiple factors, including variations in access to healthcare, early detection programs, and public awareness about CRC screening and prevention measures (25).

Colorectal cancer is influenced by a combination of lifestyle and genetic factors in Saudi Arabia. Sedentary lifestyles, widespread obesity, and high red- and processed-meat diets are major contributors. (26,27). According to the WHO, obesity affects 24.1% of Saudi men and 33.5% of women, significantly increasing CRC risk (28). Smoking, especially among men, further heightens susceptibility. Additionally, genetic factors such as KRAS mutations are more prevalent in Saudi CRC patients (42.2%) than in Western populations (30–37%), indicating an important hereditary component (29,30). The pathogenesis of CRC is strongly influenced by mutations in KRAS, NRAS, and BRAF. Among these, KRAS mutations are particularly linked to poor clinical outcomes and resistance to EGFR-targeted therapies. In Saudi Arabia, more than 50% of CRC patients harbor KRAS

mutations (31–33), which are linked to reduced response to anti-EGFR antibodies like cetuximab and panitumumab, making disease management more complex (34,35). Microsatellite instability, a consequence of mismatch repair (MMR) deficiency, is present in about 15% of CRC cases globally, with comparable trends reported in Saudi Arabia (36). MSI-high tumors are often associated with improved outcomes and have important implications for immunotherapy selection. Despite its clinical relevance, MSI remains under-studied in the Saudi CRC population, highlighting the need for further research (37,38). Recent advances in molecular subtyping of CRC have significantly improved our understanding of the disease's biological heterogeneity (39). The four CRC subtypes—CMS1, CMS2, CMS3, and CMS4—each have distinct profiles that affect patient outcomes and treatment strategies (40). In Saudi Arabia, studies focusing on CMS subtyping are limited, but the prevalence of MSI-high tumours and the KRAS mutation rates suggest that a considerable portion of CRC patients may belong to the CMS1 and CMS4 subtypes (41). CMS1 is characterized by a favourable prognosis and responsiveness to immunotherapy, whereas CMS4 is associated with poor outcomes due to aggressive tumour biology and resistance to conventional therapies. This molecular classification is particularly relevant for improving personalized treatment approaches and optimizing clinical outcomes in Saudi CRC patients (42).

Given the significant regional disparities in CRC incidence within Saudi Arabia and the growing burden of this disease, particularly among younger populations, there is an urgent need for comprehensive molecular and epidemiological studies (43). The Asir region, situated in the southwestern part of Saudi Arabia, presents a unique opportunity for investigation due to its mid-range CRC incidence and distinct socio-cultural and dietary patterns compared to other regions (44).

Aim & Objectives:

1. To define the CRC molecular subtypes in the Asir region of Saudi Arabia and assess the prevalence of key biomarkers, including KRAS mutations, MSI status, and other genetic alterations.
2. To uncover potential drivers of CRC in this specific population by correlating molecular subtype data with clinicopathological characteristics including gender, age, tumor size, and histological subtype, the study seeks.
3. To contribute to a more personalized approach to CRC treatment for patients in Saudi Arabia, helping to develop targeted

interventions based on the region's molecular cancer profile.

MATERIAL & METHODS

Study type & Study Design: The study exclusively utilized data and tissue samples obtained from the hospital's surgical pathology laboratory, focusing on CRC patients treated at the hospital. The research adopted an observational, analytical retrospective design.

Study Setting: This study was conducted at Asir Central Hospital, a major healthcare facility situated in Abha, Saudi Arabia. Asir Central Hospital functions as a referral centre for the entire Asir region, serving a largely rural population. It provides comprehensive medical and surgical services to patients from neighbouring areas such as Bisha, Rijal Alma, Sarat Abidah, Khamis Mushait, Muhayl, Ahad Ruidah, and Zahran-al-Janoob.

Study Population: Data collection was performed using the archival records of Asir Central Hospital, covering patients identified with CRC. The sample included 187 Saudi residents diagnosed with CRC. Patients were identified through the hospital's tumour registry, which adheres to the standards of the American College of Surgeons (ACOS). Comprehensive electronic medical records (EMR) were used to gather patient demographics and clinical details, including diagnostic age, nationality, marital status, gender, tumour size, histological subtype, tumour grade, treatment modalities (surgery, chemotherapy, and/or radiotherapy), and disease extent.

Study Duration: From January 2021 to December 2024.

Strategic for Data Collection: The molecular data, including key biomarkers such as KRAS mutations and MSI, were retrieved from pathology reports and classified using International Classification of Diseases for Oncology, Tenth Revision (ICD-10 C18–C20) guidelines. Molecular analyses were

conducted using immunohistochemistry (IHC) and polymerase chain reaction (PCR) techniques, with molecular testing conducted at King Faisal Specialist Hospital & Research Center, Riyadh.

Ethical Issues & Informed Consent: The study complied with established ethical guidelines to safeguard participant confidentiality and anonymity. The study received ethical clearance from the Ministry of Health, Directorate of Health Affairs in Asir Region, and the study was registered under IRP Log No: 11-4-2024 following review by the institutional ethics committee.

Data Analysis: Data analysis was carried out with SPSS software (version 22). The prevalence of molecular subtypes and related biomarkers was evaluated using descriptive statistics. Associations between molecular subtypes and clinical or demographic variables were analyzed using logistic regression and chi-square tests. Independent and paired t-tests were used for group comparisons, and data are reported as mean \pm SE. Statistical significance was defined as $P < 0.05$.

RESULTS

Demographics and Patient Characteristics: This study involved 187 CRC patients who presented to Asir Central Hospital between January 2021 and December 2024. Saudis comprised 95% of the cohort, while 5% were non-Saudi. There was a higher proportion of males ($n = 113$, 60%) compared to females ($n = 74$, 40%), yielding a male-to-female ratio of 1.52:1. This significant male predominance in CRC cases ($P = 0.028$ for malignant tumors) suggests that males are more frequently diagnosed with CRC, which associates with global data showing a greater incidence of CRC in men. However, the association between gender and benign tumors was not significant ($P = 0.276$), indicating similar rates of benign tumors in both sexes (Table 1).

Table 1: Age Group and Gender Distribution of Benign and Malignant Colorectal Cancer Cases (Total Cases = 187)

Age Group	Gender	Benign(%)	Malignant(%)	Total Cases(%)	P Value (Benign)	P Value (Malignant)
≥ 20	Male	2 (1.07)	0 (0.00)	2 (1.07)	0.276	0.042
	Female	0 (0.00)	0 (0.00)	0 (0.00)		
21–35	Male	10 (5.35)	8 (4.28)	18 (9.63)		
	Female	5 (2.67)	2 (1.07)	7 (3.74)		
36–50	Male	12 (6.42)	18 (9.63)	30 (16.04)		
	Female	8 (4.28)	10 (5.35)	18 (9.63)		
≥ 50	Male	20 (10.70)	54 (28.88)	74 (39.57)		
	Female	8 (4.28)	30 (16.04)	38 (20.32)		
Total	-	65 (34.76)	122 (65.24)	187 (100)	0.276	0.042

The male predominance in CRC cases observed in this study is reliable with findings from numerous epidemiological studies. Higher CRC risk in men is influenced by lifestyle factors such as greater intake of red and processed meats, smoking, and alcohol use. Delayed medical consultation further contributes to later-stage diagnoses and adverse outcomes in male patients.

Age Distribution: The study cohort ranged from 20 to 84 years in age, with a median of 58 years. Most patients (59.9%) were aged ≥50 years, consistent with worldwide CRC patterns where incidence rises sharply after 50 (45).

The age groups were shown in table 2.

Table: 2 Distribution of Individuals by Age Group

Age Group	Number of Individuals=n	Percentage (%)
≥ 20 years old	2	1.07
21–35 years old	25	13.37
36–50 years old	48	25.67
≥ 50 years old	112	59.89

A substantial correlation was found between patient age and the occurrence of malignant tumors (P= 0.042). As expected, malignant cases were more common in older individuals, especially those aged ≥ 50 years. This pattern reflects the global trend of increasing cancer risk with age, which is attributed to accumulated genetic mutations and longer exposure to carcinogenic factors.

Table 2: Age Group-Wise Distribution of Benign and Malignant Cases Across Diagnoses and Tumor Grades (Total Cases = 187)

Age Group	Diagnosis (Benign)	Total Benign (%)	Grading (Malignant)	Total Malignant (%)	P Value (Benign)	P Value (Malignant)
≥ 20	Inflammation: 2 (3.08) Adenoma: 0 (0.00) Other: 0 (0.00)	2 (1.07)	Grade 1: 0 (0.00) Grade 2 & 3: 0 (0.00) Grade 4: 0 (0.00)	0 (0.00)	0.578	0.821
21–35	Inflammation: 10 (15.38) Adenoma: 2 (3.08) Other: 3 (4.62)	15 (8.02)	Grade 1: 1 (0.82) Grade 2 & 3: 7 (5.74) Grade 4: 2 (1.64)	10 (5.35)		
36–50	Inflammation: 11 (16.92) Adenoma: 4 (6.15) Other: 5 (7.70)	20 (10.70)	Grade 1: 0 (0.00) Grade 2 & 3: 24 (19.67) Grade 4: 4 (3.28)	28 (14.97)		
≥ 50	Inflammation: 11 (16.92) Adenoma: 14 (21.54) Other: 3 (4.62)	28 (14.97)	Grade 1: 0 (0.00) Grade 2 & 3: 80 (65.57) Grade 4: 4 (3.28)	84 (44.92)		
Total	Inflammation: 34 (52.31) Adenoma: 20 (30.77) Other: 11 (16.92)	65 (34.76)	Grade 1: 1 (0.82) Grade 2 & 3: 111 (90.98) Grade 4: 10	122 (65.24)	0.578 0.005 0.741	0.018 0.648

(8.20)

Older adults (≥ 50 years) were more prone to malignant CRC, aligning with worldwide data that recognize age as a key risk factor (Table 3). Age was significantly correlated with malignancy severity, with most patients exhibiting grade 2 or 3 adenocarcinoma. These results emphasize the need for age-focused screening, given the substantially better outcomes associated with early-stage CRC detection.

Histopathological Diagnosis: Among the 187 patients, 65 (34.76%) were diagnosed with benign colorectal lesions. Inflammatory mucosa was the most common benign diagnosis (52.31%), followed by adenoma (30.77%) and other diagnoses (16.92%). A considerable correlation was found between age and adenoma cases ($P = 0.005$), with adenoma being more prevalent in patients aged over 50 years. No substantial association was observed between age and inflammation ($P = 0.578$). Among the 122 malignant cases, the majority were diagnosed with moderately differentiated adenocarcinoma (grades 2 and 3), accounting for 90.98% of the cases. There was a substantial correlation between age and the occurrence of grades 2 and 3 malignancies ($P = 0.018$), with older patients more likely to present with these grades. High-grade malignancies (grade 4) were relatively rare, occurring in only 8.2% of the cases.

Molecular and Immunohistochemical Biomarkers: Molecular analysis of biomarkers revealed a varied prevalence, with HER2 being the most frequently tested biomarker (22.46%), followed by KRAS (19.79%) and MSI (16.58%). KRAS mutations were more commonly detected, with 23 positive results out of 37 tests, highlighting the importance of this biomarker in the CRC molecular landscape.

KRAS mutations have been widely reported as a key driver of CRC, particularly in cases resistant to EGFR inhibitors such as panitumumab and cetuximab. The high prevalence of KRAS mutations in the Asir region supports the growing need for personalized treatment strategies that consider genetic variations (table 4).

Table 4: Analysis of Biomarker Prevalence and Detection Methods in the Asir Region

Biomarker	Total Cases	Test Conducted	Positive Results	Prevalence (%)	Detection Method
HER2	187	42	3	22.46	Molecular
KRAS	187	37	23	19.79	Molecular

MSI	187	31	4	16.58	Molecular
BRAF	187	15	2	8.02	Molecular
CK7	187	14	5	7.49	IHC
NRAS	187	14	1	7.49	Molecular

DISCUSSION

A thorough evaluation of CRC in Asir region of Saudi Arabia is presented, covering patient demographics, tumor histopathology, and molecular markers (46,47). The results offer important insights into the epidemiology and biology of CRC in this region and highlight key trends that align with global patterns while also identifying region-specific findings. These insights have significant implications for developing targeted prevention, screening, and treatment strategies tailored to the local population (48).

The study revealed a male predominance in CRC cases, with men accounting for 60% of the total cases. This aligns with global data indicating that men are at a extreme threat of increasing CRC compared to women (49). Higher CRC rates in men are linked to lifestyle factors such as increased red meat intake, smoking, alcohol consumption, and reduced engagement in preventive health practices. Additionally, men are often more likely to be diagnosed at later stages of the disease, contributing to poorer outcomes. In Saudi Arabia, the lifestyle changes that have accompanied rapid urbanization and economic growth, particularly among men, may also provide to the increasing incidence of CRC (50). Consumption of red and processed meats along with a sedentary lifestyle elevates CRC risk. Encouraging healthier behaviors through targeted public health campaigns, especially for men, could reduce disease incidence. The risk of CRC increases substantially with age, particularly beyond 50 years, making age the most prominent risk factor. In this study, the majority of CRC cases (59.89%) were observed in patients aged 50 and above. This finding is consistent with global epidemiological data, where CRC incidence sharply rises in older age groups. The accumulation of genetic mutations over time and prolonged exposure to environmental carcinogens contribute to the heightened risk in older adults. However, it is noteworthy that 40.11% of the cases in this study were diagnosed in individuals younger than 50, indicating a significant proportion of early-onset CRC. This trend has been observed globally, with

increasing reports of CRC in younger populations. CRC diagnosed at a younger age tends to be more aggressive, and younger individuals often exhibit advanced disease at presentation. The reasons for this trend are not fully understood but may include genetic predispositions, lifestyle factors, and changes in gut microbiota. Given the relatively high proportion of initial-onset CRC cases in Asir region, targeted screening programs for younger populations may be warranted.

The study's histopathological analysis revealed that 65.24% of the cases were malignant, with moderately differentiated adenocarcinoma (grades 2 and 3) being the utmost common. According to this finding with global data, where adenocarcinoma is the predominant histological subtype of CRC. The significant association between age and tumor grade, with older patients more likely to present with moderately differentiated tumors, highlights the significance of early finding and intervention. Benign lesions, such as inflammatory mucosa and adenomas, were also common, accounting for 34.76% of cases. Adenomas are recognized as precursors to CRC, and their detection provides an opportunity for preventive measures through polypectomy and surveillance. The significant association between age and adenoma cases in this study ($P = 0.005$) underscores the need for regular screening, especially in older populations, to identify and remove precancerous lesions before they progress to malignancy.

The molecular analysis of biomarkers in the current study revealed a high prevalence of KRAS mutations (19.79%) and MSI (16.58%). The presence of KRAS mutations impacts treatment decisions, as they confer resistance to EGFR-targeted therapies like panitumumab and cetuximab, necessitating the use of non-EGFR-based chemotherapy strategies. The relatively high prevalence of KRAS mutations in the Asir region is consistent with other studies conducted in Middle Eastern populations, which have reported similarly high mutation rates compared to Western populations. The prevalence of MSI in this study (16.58%) is also significant, as MSI is a key marker for recognizing patients who might benefit from immunotherapy. MSI-high CRCs are often more responsive to immunotherapy agents such as pembrolizumab (51). The detection of MSI in a substantial proportion of CRC patients in the Asir region highlights the potential for expanding the use of immunotherapy in this population. MSI testing should be considered as part of routine diagnostic workups for CRC to detect patients who are utmost likely to advantage from immunotherapeutic approaches.

Additionally, HER2 expression was detected in 22.46% of cases. HER2 amplification, while more common in breast and gastric cancers, is observed in some CRC patients, suggesting that HER2-targeted therapies like trastuzumab may be beneficial (Sartore-Bianchi *et al.*, 2019). The use of HER2-targeted therapies in CRC is still evolving, but these findings suggest that it may be a viable option for a subset of patients in the Asir region.

The findings of this study underscore the need for improved CRC screening programs in the Asir region. Given the high proportion of CRC cases in individuals over 50 and the relatively high incidence of early-onset CRC, age-based screening should be prioritized. It is still the gold standard of screening for colorectal cancer to perform a colonoscopy, as it acknowledges for the detection and exclusion of precancerous polyps. However, the development of non-invasive screening methods, such as stool-based tests for molecular markers (e.g., FIT-DNA tests), may increase participation rates and facilitate earlier detection, particularly in younger populations.

The elevated prevalence of KRAS mutations and MSI in the Asir population highlights the importance of individualized treatment approaches. Molecular profiling should be routinely performed to guide treatment decisions, particularly in metastatic CRC cases where targeted therapies and immunotherapy may offer substantial benefits.

This study specifies effective discernments into the epidemiology and molecular landscape of CRC in the Asir region, but there are several limitations that must be focused in the future research. Being a single-center, retrospective study, the findings cannot establish causality and may not be entirely generalizable to the wider Saudi population. A multicenter, prospective study would provide a more comprehensive understanding of CRC incidence, risk factors, and molecular characteristics across different regions of the country. Additionally, further research into the genetic and environmental factors contributing to CRC in the Asir region is warranted. While physical inactivity and diet are recognized CRC risk factors, recent studies suggest that genetics and gut microbiota changes may contribute importantly to early-onset CRC. Investigating these factors in the local population could assist in identification of high-risk groups as well as update targeted restraint approaches.

The overall study highlights the considerable impact of colorectal cancer in the Asir region, with marked disparities by age and gender. The common presence of KRAS mutations and MSI highlights the role of molecular profiling in treatment planning.

Expansion of screening programs and personalized therapies is recommended, alongside further research into genetic, environmental, and long-term treatment outcomes in Saudi CRC patients.

CONCLUSION

The findings underscore colorectal cancer as a major health concern in the Asir region, with significant age- and gender-related differences. The excessive prevalence of KRAS mutations and MSI highlights the consequence of molecular profiling in guiding treatment decisions and developing patient outcomes. These findings call for the expansion of CRC screening programs and the adoption of personalized treatment approaches to address the unique needs of the local population. Further research is needed to explore the environmental and genetic factors influencing CRC in this region, as well as to evaluate the long-term outcomes of targeted therapies in Saudi CRC patients.

RECOMMENDATION

Due to the high prevalence of KRAS mutations and MSI in the Asir region, we recommend expanding age- and gender-specific CRC screening and implementing routine molecular profiling to guide personalized treatment. Further research is needed to investigate local genetic and environmental risk factors and evaluate the long-term effectiveness of targeted therapies in Saudi patients.

LIMITATION OF THE STUDY

The potential limitations of the study are the lack of investigation into specific causal environmental and genetic factors, and the absence of long-term outcome data regarding targeted therapies.

RELEVANCE OF THE STUDY

This study is highly relevant as it provides critical data on local molecular profiles, necessitating the implementation of region-specific screening and personalized treatment strategies to improve colorectal cancer outcomes in Asir.

AUTHORS CONTRIBUTION

All authors have contributed equally.

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Nil

CONFLICT OF INTEREST

There is no conflict of interest.

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DECLARATION OF GENERATIVE AI AND AI ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

The authors haven't used any generative AI/AI assisted technologies in the writing process.

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