RAS/RAF/MAPK Pathway Mutations as Predictive Biomarkers in Middle Eastern Colorectal Cancer: A Systematic Review

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ABSTRACT

BACKGROUND: This review article aims to investigate the prevalence and spectrum of rat sarcoma (RAS) and V-Raf Murine Sarcoma Viral Oncogene Homolog B (BRAF) mutations, and their connection with geographical location, clinicopathological features, and other relevant factors in colorectal cancer (CRC) patients in the Middle East.

METHODS: A systematic literature review, employing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework, was conducted to investigate the association between the frequency of relevant mutations and the descriptive clinicopathological characteristics of CRC patients. Multiple electronic databases, including PubMed, Science Direct, Web of Science, Scopus, and Google Scholar, were searched to analyze the relevant literature.

RESULTS: A total of 19 eligible studies comprising 2960 patients with CRC were included in this review. A comprehensive analysis of the collected literature data as well as descriptive and methodological insights is provided. Men were predominant in reviewed studies for the region, accounting for 58.6%. Overall, RAS mutation prevalence was 38.1%. Kirsten RAS Viral Oncogene Homolog (KRAS) mutations were the most common, accounting for 37.1% of cases and distributed among different exons, with the G12D mutation being the most frequent in exon 2 (23.2%) followed by G12V (13.7%), G13D (10.1%), G12C (5.1%), G12A (5.04%), and G12S (3.6%). Neuroblastoma RAS Viral Oncogene Homolog (NRAS) mutations were identified in 3.3% of tumor samples, with the most common mutation site located in exons 2, 3, and 4, and codon 61 being the most common location for the region. The total mutation frequency in the BRAF gene was 2.6%, with the V600E mutation being the most common.

CONCLUSION: The distribution patterns of RAS and BRAF mutations among CRC patients exhibit notable variations across diverse ethnic groups. Our study sheds light on this phenomenon by demonstrating a higher prevalence of KRAS mutations in CRC patients from the Middle East, as compared with those from other regions. The identification of these mutations and geographical differences is important for personalized treatment planning and could potentially aid in the development of novel targeted therapies. The distinct distribution patterns of RAS and BRAF mutations among CRC patients across different ethnic groups, as well as the regional variability in mutation prevalence, highlight the need for further research in this area.

KEYWORDS: Colorectal cancer, RAS, BRAF, mutation, Middle East

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Introduction

Colorectal cancer (CRC) is one of the most prevalent cancers, ranking as the third most commonly diagnosed cancer worldwide and the fourth leading cause of cancer-related deaths.[1] Globocan 2020 data reported 1.9 million new cases of CRC globally, resulting in 935 000 CRC-related deaths.[2] By

2040, these numbers are expected to increase significantly, with annual global CRC cases predicted to reach 3.2 million.[3] Colorectal cancer incidence rates are rising worldwide in the Middle East and other regions, affecting individuals of all ages and sexes.[4,5] It is important to note that most countries with high or very high human development index (HDI) have higher CRC incidence rates than countries with lower HDI,[6] showing the effect of lifestyle factors.

RAS genes are pivotal in CRC due to their frequent mutation in this malignancy. These genes, proto-oncogenes, encode small GTPase proteins that regulate cell division and proliferation. Mutations in RAS lead to constitutively active forms, driving unchecked cell growth. KRAS and NRAS are RAS gene variants, with KRAS located on chromosome 12 and NRAS on chromosome at position 13.1.[7] KRAS mutations are more prevalent than NRAS mutations, with approximately 40% of colorectal tumors bearing KRAS mutations.[8] The most common KRAS mutations occur at codon 12 (>90%), followed by codons 13, 61, 146, and 117. NRAS mutations, sharing similar codon mutations with KRAS, are found in 5% to 10% of CRC cases.[9] BRAF, a downstream effector of RAS located on chromosome 7 (7q34), is a serine/threonine kinase. BRAF mutations, identified in approximately 8% to 12% of CRC patients,[10] activate the Mitogen-activated protein kinase (MAPK) pathway, governing cell proliferation and differentiation.[11] The most common BRAF mutation, observed in 90% of cases, is a T1799A transversion in exon 15, resulting in a valine amino acid substitution (V600E).[10] RAS and BRAF mutations correlate with aggressive tumor behavior and resistance to targeted therapy in CRC, contributing to a poorer prognosis. Recent studies[12,13] suggest that advanced-stage CRC and tumors on the right side of the colon are more likely to have RAS and BRAF mutations. Hence, detecting these mutations is crucial for assessing treatment response and tailoring treatment strategies for CRC patients.

Colorectal cancer is a highly heterogeneous disease with various tumor phenotypes that are distinguished by specific molecular and morphological features. Colorectal cancer is a highly heterogeneous disease with various tumor phenotypes that are distinguished by specific molecular and morphological features. Colorectal cancer is caused by various genetic alterations that affect tumor suppressor genes, oncogenes, and genes involved in DNA repair mechanisms. Three major pathways have been identified in CRC: chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylation phenotype (CIMP). These 3 groups have involved pathological, genetic, and clinical characteristics.[14]

Chromosomal instability is the most common genetic mechanism in CRC (85% of all CRCs). Furthermore, CIN tumors have been linked to the accumulation of mutations in several oncogenes and tumor suppressor genes including *KRAS*, *BRAF*, adenomatous polyposis coli (APC), and TP53.[15] Colorectal cancer development is primarily driven by these genetic mutations and defective cell regulation.[16] The accumulation of these mutations activates multiple signaling pathways, including the *RAS-RAF-MAPK* pathway, which plays critical roles in essential cellular processes such as angiogenesis, cell proliferation, and motility. Mutations in specific genes, such as *KRAS*, *NRAS*, and *BRAF*, contribute to the dysregulation of this pathway and are frequently observed in CRC.[17-19]

Microsatellite instability is another significant pathway found in approximately 15% of all CRC cases; however, in metastatic CRC (mCRC), the prevalence of MSI decreases to approximately 4% to 5%.[20] This highlights the crucial role of BRAF mutation status and microsatellite stability (MSS) in CRC. The interaction between these 2 factors has significant implications for disease aggressiveness and clinical management. BRAF mutation is associated with MSI through its relationship with high-level CpG island methylator phenotype (CIMP) and MLH1 promoter methylation.[21] This interaction serves as a biomarker in CRC.[22] Importantly, the combined MSI/BRAF status can serve as a prognostic molecular biomarker. For instance, compared with most subtype of microsatellite stable (MSS)/BRAF-wild-type, MSS/BRAF-mutant, microsatellite instability-high (MSI-H)/BRAF-mutant, and MSI-H/BRAF-wild-type subtypes showed different CRC-specific mortality hazard ratios.[21] Furthermore, it is noteworthy that BRAF mutant MSS CRCs are particularly aggressive, and in some cases, the MSS status seems to override the BRAF status. Therefore, understanding the interaction between BRAF mutation status and MS, as well as the broader role of MSI status in CRC, can help to stratify prognostic risk, guide clinical management in CRC, and determine eligibility for certain treatments like immunotherapy.

The importance of detecting CRC early cannot be overstated. Early-stage CRC carries a good prognosis, boasting a 5-year survival rate of 91% for colon cancer and 90% for rectal cancer.[23] However, these rates drop to 13% and 18%,[23] respectively, indicating a poor prognosis, when the cancer metastasizes to distant organs such as the liver, lungs, lymph nodes, and peritoneum.[24,25] The tumor stage at diagnosis emerges as a crucial survival determinant, with rates dropping to 14% for cases with distant metastasis.[26] Despite medical advancements, the prevalence of advanced-stage CRC diagnoses underscores the urgent need for enhanced screening strategies and early detection methods.

In mCRC with an unmutated RAS gene, anti-epidermal growth factor receptor (EGFR) antibodies such as cetuximab and panitumumab are commonly employed. These antibodies prolong progression-free survival (PFS) and overall survival (OS) while also enhancing the overall response rate (ORR) by inhibiting the EGFR pathway.[27] Encorafenib, a BRAF inhibitor, has demonstrated efficacy in treating mCRC with the BRAF V600E mutation, particularly when combined with cetuximab. This underscores the significance of assessing the RAS/BRAF status in mCRC patients undergoing EGFR inhibition.[28] Despite the promising outcomes associated with these treatments, it is essential to consider potential side effects or limitations.

Ethnic disparities in cancer biology, including CRC, are a significant area of research. These disparities, observed among different population groups globally, are influenced by various factors such as socioeconomic status, culture, diet, stress, environment, and biology.[29] For instance, Black/African American individuals often face higher death rates for many cancer types, including CRC, despite similar rates of breast cancer.[30] Focusing on the Middle Eastern and North African context, unique genetic profiles and environmental exposures also contribute to differential patterns of CRC incidence and treatment responses, with distinct susceptibilities to CRC influenced by genetic predispositions, lifestyle factors, and socio-cultural determinants.[31] These disparities highlight the need for health care policies and practices that ensure equitable access to CRC prevention, detection, and treatment services across different ethnic groups. Therefore, this study builds on a prior review conducted by Jafari et al[32] in 2022 based on CRC in North Africa to expand the scope of the examination, by investigating the Middle East region. By incorporating this additional geographical area, our objective is to comprehensively understand the prevalence and patterns of RAS and BRAF mutations in the Middle East. This extension contributes to advancing knowledge in the field and facilitates the development of targeted strategies for CRC prevention and management across neighborhood regions. The aim of this study is to systematically review the available literature and determine the prevalence of RAS and BRAF mutations among CRC patients in the Middle East, while also examining their clinicopathological characteristics through descriptive outputs of the studies. The organization of the study is as follows. The next section provides the applied method in this study whereas the "Review Results" section provides a comprehensive analysis of the collected literature data and provides descriptive and methodological insights. "Discussion" section discusses the outputs more in-depth whereas the last section shows a fundamental gain of this study.

Methods

In this systematic review, we conducted a comprehensive examination of the literature to assess the prevalence of RAS mutations and their correlation with geographical location, clinicopathological features, and other relevant factors in CRC patients in the Middle East. To achieve this goal, we employed a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) mechanism relying on a rigorous search strategy that encompassed multiple databases, including PubMed, Science Direct, Web of Science, Scopus, and Google Scholar. Only case-control studies published between 2002 and 2022 are considered in this review study. Figure 1 summarizes the flowchart of PRISMA process. The search terms used in this study were carefully selected to capture a wide range of relevant keywords related to CRC and the Middle East region.

Our search terms specifically included variations of "colorectal cancer" or "CRC," combined with terms related to RAS mutations such as "RAS mutation," "KRAS mutation," "NRAS mutation," "BRAF mutation," "Chromosomal Instability" (or CIN), and "Microsatellite Instability" (or MSI)." In addition, we included terms specifying the Middle East region such as "Middle East," "Middle Eastern," and specific country names within the area. This comprehensive approach ensured that we captured relevant studies exploring the prevalence and characteristics of RAS mutations, BRAF mutations, and the status of CRC patients across the Middle Eastern region.

To ensure the quality and relevance of the studies included in this review, we established specific inclusion criteria. Specifically, studies must have focused on the role of the RAS gene and/or BRAF gene in CRC, analyzed also mutations in exons 2, 3, and 4 of the RAS gene, as well as exon 15 of the BRAF gene, provided sufficient information on the clinicopathological characteristics of included CRC patients, and included at least 100 CRC patients analyzed for RAS mutations. Studies that reported on MSI status were also included, even although they were limited.

After conducting an initial literature search in multiple databases, a total of 80 publications were identified. Following the removal of unrelated and duplicated records, 51 records remained, which were then screened using the title and abstract. Of these, 25 records did not meet the inclusion criteria and were subsequently excluded. The full text of the remaining 26 records was thoroughly reviewed, and 7 records were excluded due to the study status (such as unpublished study or report) provided in Figure 1. Ultimately, 19 studies met the desired criteria and were included in the review analysis. The studies were all case-control studies published between 2002 and 2022. Of the 19 included studies, 12 focused on KRAS mutations,[33-44] 3 on KRAS and NRAS mutations,[45-47] 1 on KRAS and BRAF mutations,[48] and 3 on KRAS, NRAS, and BRAF mutations.[49-51] Notably, 3 of these studies provided insight into MSI status, contributing to a more comprehensive understanding of the genetic landscape of CRC.[33,37,49] The original articles included in the present review were identified from various Middle Eastern countries, including Bahrain,[49] Iran,[33-38,45,48] Iraq,[39] Israel,[40] Jordan,[41,46] Lebanon,[50] and Saudi Arabia.[42-44,47,51] After reviewing the relevant literature, we present the descriptive patterns between RAS mutation status and the descriptive clinicopathological characteristics of CRC patients in the collected studies which are explained below.

Review Results

This section presents a comprehensive examination of the collected literature data and provides descriptive and methodological insights into the findings of the studies.

Description of sample sizes and included regions

The characteristics of *RAS* and *BRAF* mutation studies have been summarized in Tables 1 and 2, respectively. The sample

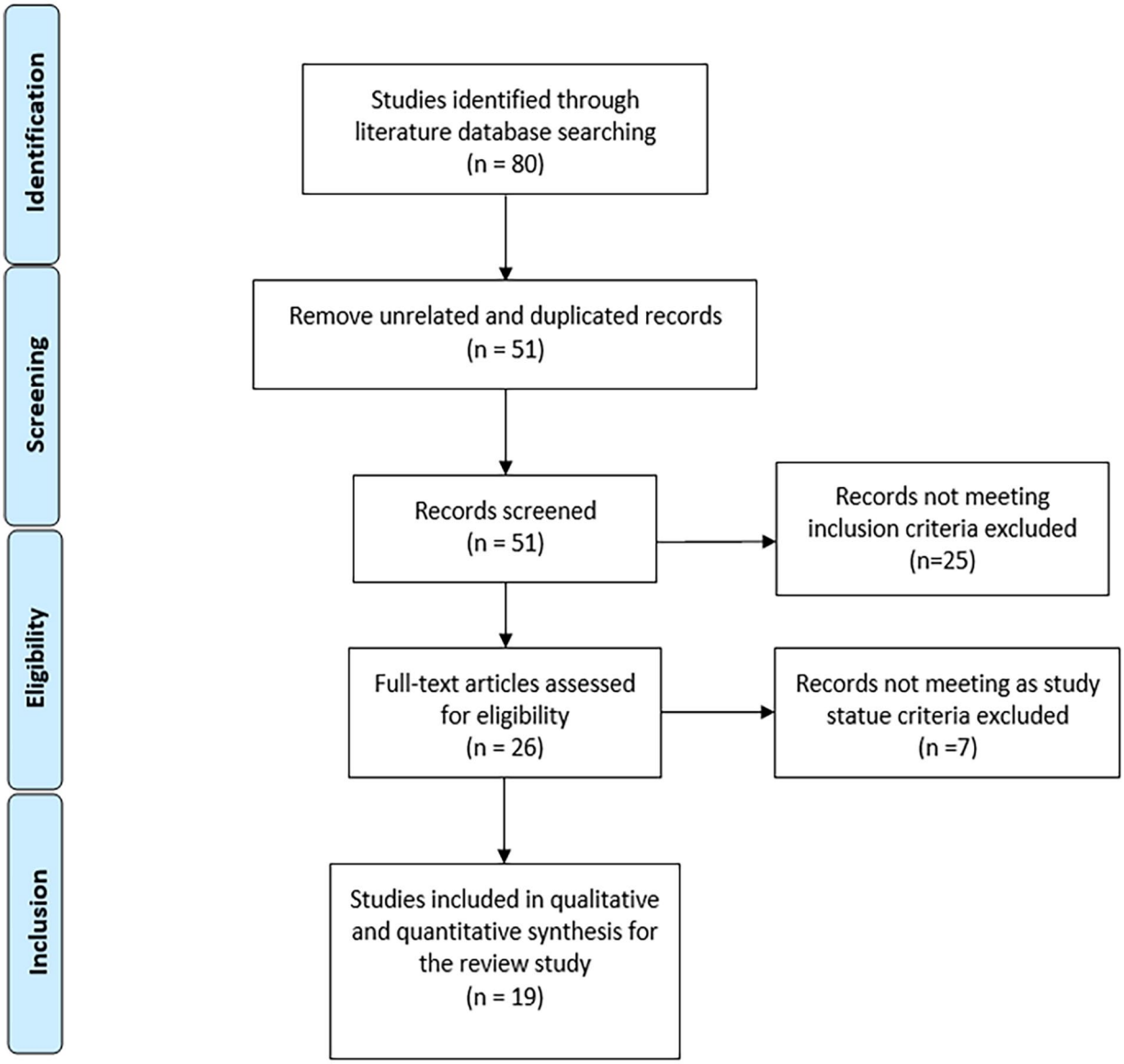

Figure 1. Flowchart of PRISMA process.

sizes of the studies analyzing *RAS* and *BRAF* mutations ranged from 33 to 1000 patients. Most analyzed patients, 92.6% (2742 of 2960), were derived from studies conducted in the Middle Eastern region, including Iran (8 studies, 1647 patients),[33-38,45,48] Iraq (1 study, 50 patients),[39] Israel (1 study, 105 patients),[40] Jordan (2 studies, 290 patients),[41,46] Lebanon (1 study, 273 patients),[50] and Saudi Arabia (5 studies, 423 patients).[42-44,47,51] Especially, 2 studies, 1 from Bahrain (172 patients)[49] and 1 from Saudi Arabia (46 patients),[43] did not provide information on the distribution of *RAS* mutations.

Specimens and methods used in the RAS and BRAF mutation identification

In most studies investigating mutations in *KRAS*, *NRAS*, and *BRAF* genes within Middle Eastern populations, formalin-fixed paraffin-embedded (FFPE) tissues were used as specimens. These specimens included both biopsies and resection materials. DNA extraction was performed on tissue samples utilizing paraffin block DNA extraction kits. Among Middle Eastern series, exon 2, 3, and 4 mutations of *KRAS* and *NRAS* genes were analyzed in 15.7% (3 of 19).[45-47] In 12 studies (15.7%, 3 of 19),[33-44] exon 2, 3, and 4 mutations of the *KRAS* gene were evaluated and whereas *NRAS* exons 2 and/or 3 were evaluated in 26.3% of studies.[45-47,50,51] Most studies (94.7%, 18 of 19)[33-48,50,51] assessed *KRAS* mutations in exon 2 codons 12 and 13. *BRAF* gene mutations were analyzed in 21.1% (4 of 19) studies.[48-51] Microsatellite instability was examined in a subset of these studies (15.7%, 3 of 19), whereas the remaining studies did not report on MSI.[33,37,49] One study from Bahrain (172 patients) did not mention specific exons genotyped.[49] Various molecular methods were employed for mutation screening, with sequencing assays being the most widely used method (21.1% of studies).[33,37,40,48] Other methodologies described in the considered studies included Pyrosequencing,[35,36,45,49] Sanger sequencing,[34,38,41] array-based techniques such as ARRAY[43]

Table 1. Details of studies investigating *KRAS*, *NRAS*, and *BRAF* genes in the Middle East (+, including genetic analysis;–, not including genetic analysis).

COUNTRY / AUTHOR (REFERENCE)	MATERIALS	KRAS			*NRAS*			*BRAF*	DETECTION METHOD
		EXON 2	EXON 3	EXON 4	EXON 2	EXON 3	EXON 4	EXON 15	
Bahrain									
Al Shaikh and Shubbar[49]	FFPE	–	–	–	–	–	–	+	PCR/ Pyrosequencing
Iran									
Shemirani et al[33]	Fresh tissue	+	–	–	–	–	–	–	PCR/Sequencing
Omidifar et al[34]	FFPE	+	–	–	–	–	–	–	PCR/Sanger sequencing
Yari et al[48]	FFPE	+	+	–	–	–	–	+	PCR/Sequencing
Amirifard et al[35]	FFPE	+	–	–	–	–	–	–	PCR/ Pyrosequencing
Naseri et al[45]	FFPE	+	–	–	–	–	+	–	PCR/ Pyrosequencing
Niya et al[36]	FFPE	+	–	–	–	–	–	–	HRM/ Pyrosequencing
Bishehsari et al[37]	FFPE	+	+	–	–	–	–	–	PCR/Sequencing
Hamzehzadeh et al[38]	Fresh tissue	+	–	–	–	–	–	–	HRM/Sanger sequencing
Iraq									
Al-Allawi et al[39]	FFPE	+	–	–	–	–	–	–	PCR/Hybridization StripAssay
Israel									
Kislitsin et al[40]	Frozen tissue	+	–	–	–	–	–	–	PCR/Sequencing
Jordan									
Elbjeirami et al[41]	FFPE	+	–	–	–	–	–	–	PCR/Sanger sequencing
Awidi et al[46]	FFPE	+	+	+	+	+	–	–	PCR/Hybridization StripAssay
Lebanon									
Baba et al[50]	FFPE	+	+	+	+	+	–	+	PCR/Hybridization StripAssay
Saudi Arabia									
Bader et al[42]	FFPE	+	–	–	–	–	–	–	PCR/LCD Array
Zekri et al[43]	FFPE	+	–	–	–	–	–	–	PCR/Array
Zahrani et al[44]	FFPE	+	–	–	–	–	–	–	PCR/LCD Array
Mulla et al[47]	FFPE	+	–	–	+	+	–	–	PCR/Next-generation sequencing
Saharti[51]	FFPE	+	+	+	–	+	–	+	PCR/Next-generation sequencing

Abbreviation: HRM, high-resolution melting.

Table 2. Characteristics and clinicopathologic features of studies included in this review.

COUNTRY AUTHOR (REFERENCE)	SAMPLE SIZE	MEAN YEARS (±SD)	WOMEN/ MEN, NO (%)	TUMOR SITE, NO (%)			STAGES, NO (%)	TUMOR GRADE
				COLON		RECTUM		
				RIGHT	LEFT			
Bahrain								
Al Shaikh and Shubbar[49]	172	60	79 (46%)/93 (54%)	NA	NA	38 (22%)	I: 6 (4%) II: 17 (10%) III: 47 (27%) IV: 21 (12%)	Well: 5 (3%) Moderate: 145 (83%) Poor: 10 (6%)
Iran								
Shemirani et al[33]	95	49	22 (23%)/73 (76%)	NA	NA	NA	NA	NA
Omidifar et al[34]	100	59.08 (±15.55)	45 (45%)/55 (55%)	NA	NA	NA	NA	NA
Yari et al[48]	100	59.60 (±15.24)	36 (36%)/64 (64%)	29 (29%)	30 (30%)	41 (41%)	I: 11 (11%) II: 17 (17%) III: 59 (59%) IV: 13 (13%)	W: 8 (8%) M: 78 (78%) P: 14 (14%)
Amirifard et al[35]	33	51.48 (±12.6)	7 (21%)/26 (79%)	NA	NA	15 (45%)	NA	W: 22 (66.7%) M: 7 (21.2%) P: 3 (9.1%)
Naseri et al[45]	50	61.3 (±13)	15 (30%)/35 (70%)	26 (52%)	NA	13 (26%)	II: 2 (4%) III: 11 (22%)	W: 15 (30%) M: 18 (36%)
Niya et al[36]	1000	NA	427 (42.7%)/573 (57.3%)	NA	NA	NA	NA	W: 439 (43.9%) M: 384 (38.4%) P: 164 (16.4%)
Bishehsari et al[37]	182	NA	79 (43.3%)/103 (56.6%)	58 (32%)	65 (35.7%)	53 (29%)	NA	NA
Hamzehzadeh et al[38]	87	NA	36 (41.3%)/51 (58.6)	76 (87.3%)	NA	11 (12.6%)	NA	W: 16 (18.3%) M: 67 (77%) P: 4 (4.6%)
Iraq								
Al-Allawi et al[39]	50	59 ± 15.25	23 (46%)/27 (54%)	10 (20%)	12 (24%)	28 (56%)	I: 12 (24%) II: 13 (26%) III: 23 (46%) IV: 2 (4%)	W: 10 (20%) M: 31 (62%) P: 9 (18%)

(Continued)

Table 2. (Continued)

COUNTRY AUTHOR (REFERENCE)	SAMPLE SIZE	MEAN YEARS (±SD)	WOMEN/ MEN, NO (%)	TUMOR SITE, NO (%)			STAGES, NO (%)	TUMOR GRADE
				COLON		RECTUM		
				RIGHT	LEFT			
Israel								
Kislitsin et al[40]	105	NA	NA	NA	NA	33 (31%)	NA	W: 7 (7%) M: 37 (35%) P: 2 (2%)
Jordan								
Elbjeirami et al[41]	100	55	45 (45%)/55 (55%)	58 (58%)	NA	22 (22%)	I: 0 (0%) II: 5 (5%) III: 8 (8%) IV: 87 (87%)	NA
Awidi et al[46]	190	58	76 (40%)/114 (60%)	62 (32.63%)	107 (56.32%)	5 (2.63%)	NA	NA
Lebanon								
Baba et al[50]	273	58	112 (41%)/160 (59%)	41 (15%)	163 (60%)	NA	NA	NA
S. Arabia								
Bader et al[42]	83	55	35 (42.2%)/48 (57.8%)	63 (76%)	NA	20 (24%)	I: 3 (3.6%) II: 8 (9.63%) III: 15 (18.07%) IV: 57 (68.67%)	W: 7 (8.43%) M: 68 (81.92%) P: 8 (9.63%)
Zekri et al[43]	46	61	16 (34%)/30 (65%)	17 (37%)	4 (9%)	8 (17%)	II: 14 (30%) III: 15 (33%) IV: 17 (37%)	W: 1 (2%) M: 38 (83%) P: 7 (15%)
Zahrani et al[44]	150	56.7	NA	21 (18%)	123 (82%)	32 (21.3%)	I: 2 (1%) II: 22 (14.6%) III: 26 (17.3%) IV: 100 (66.6)	NA
Mulla et al[47]	51	60.2	25 (49%)/26 (51%)	14 (27.5%)	37 (72.5%)	NA	I: 5 (9.8%) II: 13 (25.5%) III: 16 (31.4%) IV: 17 (33.33%)	W: 6 (11.8%) M: 43 (84.3%) P: 2 (3.9%)
Saharti[51]	93	57.3	NA	NA	NA	NA	NA	NA

Abbreviations: M, moderately differentiated; No (%), percentage of number of individuals (women/men); NA, not available; P, poorly differentiated; SD, standard deviation; W, well differentiated.

and LCD Array,[42,44] next-generation sequencing,[47,51] and hybridization StripAssay.[39,46,50] A summary of the details of these studies is presented in Table 1.

Statistical analysis in most studies performed using the chi-squared test and SPSS software, and a *P* value less than .05 was considered to indicate statistical significance. The chi-squared

test is a widely employed statistical analysis in research that aims to evaluate the independence or association between categorical variables. It proves especially valuable when dealing with data that involves frequencies or counts distributed across distinct categories. Through a comparison of observed and expected frequencies, the chi-square test calculates a test statistic that adheres to the chi-square distribution. This test statistic quantifies the degree of deviation between the observed and expected frequencies, providing insights into whether a significant association exists between the variables being examined.

Patients' clinicopathological characteristics

A total of 2960 patients diagnosed with CRC were included in this analysis. The median age of patients was 57 years with a range of 49 to 74 years. Among the studies considered, men constituted the predominant proportion, accounting for 1533 (58.6%) of 2612 patients. However, the men-to-women ratio was not available in 3 studies, 1 from Israel[40] and 2 from Saudi Arabia.[44,51]

Tumor site information was available for a subset of the specimens. It was found that 23.6% (319 of 1348) of the tumors were located in the rectum,[35,37-46,48,49] 34.8% (475 of 1362) were located in the right colon,[37-39,41-48,50] and 51.9% (541 of 1042) were located in the left colon.[37,39,43,44,46-48,50] Furthermore, the percentages of patients with well-differentiated, moderately differentiated, and poorly differentiated histology were 30.1%,[35,36,38-40,42,43,45,47-49] 51.5%,[35,36,38-40,42,43,45,47-49] and 12.5%,[35,36,38-40,42,43,47-49] respectively. Of the tumors, 41.7% (314 of 752) were reported to be in stage IV.[39,41-44,47-49] Formalin-fixed paraffin-embedded blocks were the primary source of specimens in 16 studies,[34-37,39,41-51] whereas fresh tissue was used in 2 studies[33,38] and frozen tissue in 1 study.[40] Further details regarding the baseline characteristics and clinicopathologic features of the enrolled studies can be found in Table 2.

RAS and BRAF mutation prevalence

The prevalence of *RAS* mutations among CRC patients in the Middle East region was found to be 1128 (38.1%) of 2960 based on analysis of available studies. Iran had the highest *RAS* mutation prevalence at 33.6% (336 of 1000),[36] whereas the lowest prevalence also was observed in another study from Iran at 6.3% (6 of 95).[33] The prevalence of *BRAF* mutations in the region was 2.6% (17 of 638),[48-51] with the highest prevalence observed in Iran at 7%[48] and the lowest in Saudi Arabia at 2.2%.[51] A summary of *RAS* and *BRAF* mutation prevalence in the Middle East is presented in Table 3.

RAS and BRAF mutation spectrum

The prevalence of *KRAS*, *NRAS*, and *BRAF* mutations has been reported in 19,[33-51] 6,[45-47,49-51] and 4[48-51] of the 19 included studies, respectively. In total, *KRAS* mutations were most frequently detected among Middle East patients with CRC, accounting for 37.1% (1098 of 2960).[33-51] Iran highlights a wide range of *KRAS* mutation rates, ranging from 6.3% (6 of 95)[33] to 33.6% (336 of 1000),[36] as compared with other countries from the region. Overall, *KRAS* mutations were distributed among the different exons as follows: 97.9% (1030 of 1052) exon 2,[33-51] 1.9% (7 of 361) exon 3,[37,46,48,50,51] and 5.6% (15 of 264) exon 4[46,50,51] (Table 3). As seen in Table 4 (see Appendix), the G12D was the most frequently identified exon 2 mutation (23.2%, 239 of 1030),[33-42,44-48,50,51] followed by G12V (13.7%, 142 of 1030),[35-42,44-48,50,51] G13D (10.1%, 105 of 1030),[34-42,44-46,48,50,51] G12C (5.1%, 53 of 1030),[34-42,44,46-48,50,51] G12A (5.0%, 52 of 1030),[34,36,38,39,41,44,46-48,50,51] G12S (3.6%, 38 of 1030).[34-36,38-42,44,46,47,50,51] G12R, G13C, and G13R are less than 5%.[33,34,36,41,44,50,51] However, there are important differences among Middle East countries. In Lebanon, there is a higher prevalence of G12D mutation 49.[50] The most frequent mutation type in exon 3 was Q61H (85%, 6 of 7).[46,48,50,51] In exon 4, the most common mutation was K117N (33.3%, 9 of 15),[46,48,50,51] followed by A146T (33%, 5 of 15)[46,50,51] and A146V (6.6%, 1 of 15).[50] One study from Saudi Arabia found a G138E mutation.[51]

NRAS total mutations were identified in 30 (3.3%) of 892[45-47,49-51] tumor samples. A higher prevalence of *NRAS* mutations has been reported in Lebanon (5.8%, 16 of 273).[50] Overall, the common mutation site of the *NRAS* gene was located in exons 2, 3, and 4 with 40% (12 of 30),[46,47,50] 40% (12 of 30),[46,47,50,51] and 3% (1 of 30)[45] of CRC patient (Table 3). *NRAS* mutations were more common in codon 61, accounting for 40% (12 of 30)[46,47,50,51] (Table 3). The most common mutations were G12D in exon 2 and Q61L in exon 3 and accounted for 58% (7 of 12)[47,50] and 41% (5 of 12)[47,50,51] of patients with CRC, respectively (Table 4). The total mutation frequency in the *BRAF* gene was 2.6% (17 of 638) as reported in the literature.[48-51] The highest frequency of *BRAF* mutations was found in Iran, where it was reported in 7% (7 of 100) of patients with CRC.[48] Overall, the *BRAF* V600E mutation frequency was 2.6% (17 of 638),[48-51] as shown in Tables 3 and 4.

In addition to the mutation analysis, some studies also investigated MSI and microsatellite stability (MSS). In Bahrain, MSI was observed in 11% (19 of 172) of the cases, whereas 58% (100 of 172) were found to be MSS.[49] In Iran, 2 studies reported on MSI and MSS. One study reported MSI in 17% of the cases, with the remaining 83% being MSS.[33] The other study found a slightly higher rate of MSI at 24.5%, with MSS accounting for 80.6% of the cases.[37] These findings on MSI and MSS add another layer of complexity to the genetic landscape of CRC in the Middle East, complementing the mutation data on KRAS, NRAS, and BRAF genes.

Discussion

This systematic review conducted on the prevalence of RAS and BRAF mutations in CRC patients in the Middle East

Table 3. KRAS, NRAS, and BRAF mutation rates in Middle East populations in this review.

COUNTRY AUTHOR	GENE FREQUENCY, NO (%)		*KRAS* EXON 2		*KRAS* EXON 3		*KRAS* EXON 4		*NRAS* EXON 2		*NRAS* EXON 3		*NRAS* EXON 4		*BRAF* EXON 15
	KRAS	*NRAS*	C12	C13	C59	C61	C117	C146	C12	C13	C59	C61	C117	146	V600E
Bahrain															
Al Shaikh and Shubbar[49]	46 (27%)	3 (2%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	6 (3.5%)
Iran															
Shemirani et al[33]	6 (12.5%)	NA	5 (83%)	1 (17%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Omidifar et al[34a]	32 (32%)	NA	23 (71.8%)	8 (25%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Yari et al[48]	29 (29%)	NA	21 (77.8%)	6 (22.2%)	NA	2 (2%)	NA	NA	NA	NA	NA	NA	NA	NA	7 (7%)
Amirifard et al[35]	12 (36.3%)	NA	11 (91.7%)	1 (8.3%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Naseri et al[45]	14 (28%)	1 (2%)	10 (71.4%)	4 (28.5%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (100%)	NA
Niya et al[36]	336 (33.6%)	NA	286 (85.1%)	50 (14.9%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Bishehsari et al[37]	68 (37.4%)	NA	45 (66%)	22 (32.5%)	NA	1 (1.5%)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hamzehzadeh et al[38]	25 (28.7%)	NA	18 (72%)	7 (28%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Iraq															
Al-Allawi et al[39b]	24 (48%)	NA	21 (89.7%)	3 (10.3%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Israel															
Kislitsin et al[40]	44 (42%)	NA	32 (73%)	12 (27%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Jordan															
Elbjeirami et al[41]	44 (44%)	NA	39 (89%)	5 (11%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Awidi et al[46]	92 (48%)	6 (6%)	75 (82%)	13 (17%)	NA	1 (1.08%)	2 (2%)	6 (6%)	1 (1.08%)	2 (2.17%)	NA	3 (3.26%)	NA	NA	NA
Lebanon															
Baba et al[50c]	130 (47.6%)	16 (7.8%)	107 (82.30%)	17 (13.07%)	NA	1 (0.8%)	1 (0.8%)	2 (1.53%)	6 (37.5%)	2 (12.5%)	NA	6 (37.5%)	NA	NA	2 (1.2%)
Saudi Arabia															
Bader et al[42]	35 (42.2%)	NA	31 (88%)	4 (11%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Zekri et al[43]	15 (32%)	NA	13 (87%)	2 (13%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Zahrani et al[44]	84 (56%)	NA	73 (48.7%)	11 (7.3%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Mulla et al[47]	20 (91%)	2 (9%)	15 (75%)	4 (20%)	NA	NA	NA	NA	1 (50%)	NA	NA	1 (50%)	NA	NA	NA
Saharti[51d]	42 (45.2%)	2 (2.2%)	32 (76.19%)	3 (7.14%)	NA	2 (4.76%)	2 (4.76%)	2 (4.76%)	NA	NA	NA	2 (2.2%)	NA	NA	2 (2.2%)

Abbreviations: C, codon (eg, C12: codon 12); NA, not available.
[a]One case (3.1% of mutant cases) had a mutation in both codons 12 and 13 of KRAS.
[b]With 24 mutations in KRAS exon 2 (3 patients had double mutations in codon 12, whereas 1 patient had triple mutations with 2 in codon 12 and 1 in codon 13).
[c]The study revealed the presence of concomitant mutations in 2 out of 130 positive CRC cases with positive KRAS mutations; notably, 2 patients also exhibited concomitant mutations in NRAS.
[d]The presence of the KRAS G138E mutation in the analyzed sample.

sheds light on significant disparities compared with other regions stated below, underscoring the complexity of genetic and environmental factors influencing RAS (KRAS and NRAS) and BRAF mutation occurrence. Understanding these differences is crucial for tailoring effective prevention and treatment strategies in the region.

The prevalence of KRAS gene mutation in CRC patients varies globally, ranging from 11% to 66.1% (mostly 30%-45%).[52] This diversity in findings may be attributed to factors such as ethnicity, geographical area, environmental differences, and lifestyle.[53-56] KRAS mutation correlates with various clinical and clinicopathological features in CRC populations, including sex,[57-61] age at diagnosis (>50 years),[58] tumor location,[56,57,61] tumor differentiation,[56,61-63] and Tumor, Lymph-node, Metastasis (TNM) stage.[60] However, some studies did not find significant associations[64,65] in this context. In our study, men constituted most (58.6%) of the cohort, with tumor sites predominantly in the left colon (51.9%). Tumor differentiation varied, with 30.1%, 51.5%, and 12.5% classified as well-differentiated, moderately differentiated, and poorly differentiated, respectively. Stage IV was reported for 41.7% of tumors. Although some studies suggest a higher likelihood of mutant KRAS in women,[66,67] others indicate the opposite trend.[43,68]

This review shows a higher prevalence of KRAS mutations among Middle Eastern CRC patients compared with some other regions, suggesting unique genetic profiles within the region. The results showed that the frequency of KRAS mutations in the Middle Eastern population was 37.1%, which is consistent with reported data from other Asian countries such as China (32%),[69] Japan (33.5%),[70] and Taiwan (33.5%),[71] as well as from Western countries including the United States (35.7%, 35%, and 31%),[72-74] France (33.8%),[75] and the United Kingdom (36.9%).[76] However, there were variations when compared to some other regions such as Germany (41%),[77] Italy (62.2%, 43%, 43%, and 52.2%),[78-81] Turkey (44%),[82] India (20.5% and 23%),[52,83] Pakistan (13%),[84] Morocco (24%),[85] Egypt (11% and 18.4%),[86,87] Thailand (23%),[88] and Korea (20.7%).[89] Our study findings also align with prior research, indicating that most KRAS mutations in CRC patients occur in codons 12 and 13.[90,91] For instance, Dobre et al[92] found that 79.3% of KRAS mutations were in codon 12 and 19.7% in codon 13. Similarly, in India, KRAS mutations were detected in 87% and 13% of cases in codons 12 and 13, respectively.[93] Consistent results were reported in a large-scale study in Brazil, with KRAS mutations in codons 12 and 13 found in 87% and 13% of patients, respectively.[68] However, a study on the Greek population reported a lower frequency of KRAS mutations in codon 12, at 29.3%.[94] Various genetic and environmental factors contribute to the frequency and distribution of KRAS mutations, leading to variations across different ethnic populations. Notably, KRAS G12D and G12V mutations were the most common, followed by G12S, G12A, and G12C. In our study, the most prevalent KRAS mutations observed in CRC patients were G12D (23.2%) and G12V (13.8%), followed by G12C (5.2%), G12A (5.0%), and G12S (3.6%). In addition, we identified a p.G13D mutation in 10.1% of cases. Comparing our findings to North African populations, previous studies[85,95-109] reported variations in the frequency and distribution of KRAS mutations in CRC patients from this region. For example, in Morocco, the frequency ranged from 23.9% to 51%,[85,95-99] while in Tunisia, it ranged from 23.1% to 68.2%.[100-106] Algerian studies reported a KRAS mutation frequency of 31.4% to 50%,[107,108] whereas in Libya, it was 38.2%.[109]

Colorectal cancer in Arab patients also exhibits a distinct histological pattern, with a higher incidence of mucinous adenocarcinoma (10.1%) compared with Western populations (6.0%).[110] This suggests potential differences in tumor biology or genetic factors specific to the Middle East. However, comprehensive data on rarer subtypes such as signet ring cell carcinoma or medullary carcinoma are limited in the Middle East, making direct comparisons challenging. The geographical variations in CRC subtype distribution could be attributed to factors such as genetic diversity, lifestyle habits, and health care accessibility. These findings highlight the importance of region-specific epidemiological studies for developing tailored prevention and management strategies.

In the context of the NRAS gene, mutations in NRAS codons 12, 13, 61, and 146 exhibit similar effects to KRAS activation. In our review, NRAS mutations were observed in 3.3% of CRC tumor samples, predominantly in exons 2, 3, and 4, representing 4%, 40%, and 3% of cases, respectively. Particularly, codon 61 was the most frequently mutated site, accounting for 40% of cases. The most prevalent mutations were G12D in exon 2 and Q61L in exon 3, found in 40% and 41% of CRC patients, respectively. Other studies have also reported NRAS mutations in CRC patients, with mutation rates varying across different populations. For instance, Irahara et al[111] reported NRAS mutations in 2.2% of their patients, consistent with our findings. Similarly, Chinese and Greek/Romanian patients had mutation rates of 4.2% and 9.6%, respectively.[62,112] In Moroccan studies, Q61K and Q61R were the most common NRAS mutations, accounting for 2.6% and 1.8% of cases, respectively.[97] Focusing on BRAF gene, the most common mutation, V600E, results from a substitution at c.1799T > A. Our review identified a prevalence of 2.6% for BRAF V600E, which is lower than the reported global rates of 5% to 15%.[113-117] The incidence of BRAF mutations varies significantly across populations, with Taiwan recording the lowest at 1% and the Netherlands and the United States reporting the highest at 19.8% and 21.8%, respectively.[52-56,62,68,71-109,111-116] Interestingly, Asian populations generally exhibit lower incidences, with rates ranging from 3.8% to 7% in China and 4.7% to 6.7% in Japan.[118]

Microsatellite instability is a crucial factor in CRC, impacting prognosis, treatment response, and disease management.[119]

Our systematic review assessed MSI status in a limited subset of studies, underlining its clinical significance. Microsatellite instability-high tumors, often linked with BRAF mutations, display different outcomes compared with microsatellite stable (MSS) tumors. The combined MSI/BRAF status serves as a valuable prognostic and predictive marker in CRC.[21] One recent study[120] indicates that both mismatch repair (MMR)-deficient and MMR-proficient tumors, subsets of MSI-H and MSS tumors, can respond to neoadjuvant immunotherapy with ipilimumab, nivolumab, and celecoxib for mismatch repair proficient (pMMR). This treatment, which was well-tolerated by patients, resulted in pathological responses in all mismatch repair deficiency (dMMR) tumors and in 27% of pMMR tumors. These findings suggest the potential for this approach to become a standard of care for specific colon cancer patients. However, the presence of inconsistencies in MSI reporting underscores the need for standardized methodologies. Our findings enhance our understanding of CRC's molecular landscape, promoting personalized treatment approaches.

These findings underscore the heterogeneity of CRC biology and the importance of comprehensive molecular profiling for guiding treatment decisions. Such insights emphasize the significance of regional variations in understanding CRC pathogenesis and tailoring personalized treatment approaches that are touched on below.

Cancer development, including CRC, is influenced by a myriad of factors, ranging from genetic predisposition to environmental exposures whereas multi-gene mutation signatures are used for providing diagnosis, pathological classification, staging, and prognosis.[121] Environmental factors (eg, lifestyle related factors such as improper diets and alcohol consumption, and exposure to pathogenic bacteria) are recognized as contributors to CRC development.[122] Although environmental factors generally play a predominant role in most common cancers, it is important to note that a significant proportion of cancer-related mutations stem from random DNA replication errors, underscoring the combined influence of inherited and environmental factors.[123] Some studies indicate that both genetic and environmental factors contribute to approximately 92% of cancer risk variation across various tissues.[124] Encouraging a high-fiber diet, weight management, smoking cessation, and physical activity are lifestyle interventions aimed at addressing modifiable risk factors linked to CRC. Screening methods, such as colonoscopy and stool-based tests like fecal immunochemical tests (FITs), are pivotal for early detection, particularly in resource-limited settings where FIT is more preferred. National screening initiatives, like organized FIT programs in countries such as Israel and Qatar, target specific age groups.[125] In addition, endoscopic procedures offer a direct visualization of the colon and rectum, enabling the detection and removal of precancerous lesions and early stage tumors before they progress. It is noteworthy that the incidence rates of CRC have seen a reduction of up to 50% in older age groups in the United States, coinciding with the widespread adoption of screening colonoscopy.[126] This is despite the presence of adverse CRC risk factors and a rise in CRC incidence in younger age groups. Integrating both stool-based tests and endoscopic procedures offers a comprehensive approach to CRC management, enhancing the ability to identify high-risk individuals and facilitating personalized treatment strategies. Although lifestyle interventions and screening programs are crucial for CRC prevention, their effectiveness may vary across different cultural and resource contexts in the Middle East; therefore, tailored region-specific guidelines are essential to optimize participation and efficacy in prevention efforts.[125]

The current standard of treatment for CRC in Middle Eastern countries generally follows international guidelines and recommendations. Treatment approaches for CRC typically involve a multidisciplinary team of health care professionals and may include a combination of surgery, chemotherapy, radiation therapy, targeted therapy, and immunotherapy, depending on the stage and characteristics of the cancer. Surgical resection of the tumor is often the primary treatment for localized disease, whereas adjuvant chemotherapy may be recommended for certain stages. For advanced or mCRC, systemic therapies such as chemotherapy, targeted therapy (eg, anti-EGFR or anti-Vascular Endothelial Growth Factor (anti-VEGF) agents), and immunotherapy (eg, checkpoint inhibitors) are commonly used methods.[127]

Personalized medicine is transforming CRC treatment by tailoring strategies to each patient's genetic profile, potentially enhancing therapy effectiveness and reducing side effects. This includes targeted therapies that precisely attack cancer cells with specific mutations. Studying ethnic differences in CRC tumor biology is crucial, as it can reveal significant variations in disease progression and response to treatment. For instance, research has shown that Black, White, and Asian/Pacific Islander patients with early onset CRC have different patterns of non-silent mutations.[128] However, most large phase 2 to 3 clinical trials predominantly recruit participants from Western countries, potentially leading to a lack of representation of Middle Eastern populations. This is a significant issue because drugs are approved based on the results of these trials, which may not fully account for the unique genetic and environmental factors influencing CRC tumor biology in the Middle East.[129] Therefore, it is important to suggest for more inclusive clinical trials that adequately represent diverse populations, including those in the Middle East. This could lead to a better understanding of ethnic differences in CRC tumor biology and more effective, personalized treatment strategies. In the context of these personalized strategies, immunotherapy, which uses the body's immune system to combat cancer, has shown promise, especially for CRC types with high microsatellite instability (MSI-H) or dMMR.[130] Liquid biopsy techniques further advance personalized medicine by enabling non-invasive monitoring of disease progression and treatment response.[131] In addition, the integration of artificial intelligence and machine learning in oncology can help predict outcomes, guide

treatment decisions, and identify new therapeutic targets. However, these approaches are still under investigation, and their clinical implementation requires further validation. The availability and accessibility of these treatments may also vary across regions due to health care resource disparities.[132]

The clinical implications of RAS and BRAF mutations in CRC patients in the Middle East are significant. These mutations, including KRAS, NRAS, and BRAF, can influence disease progression and treatment effectiveness. Patients with these mutations face challenges in treatment selection due to their resistance to anti-EGFR therapies such as cetuximab and panitumumab. For instance, KRAS and NRAS mutations necessitate a focus on chemotherapy-based treatments like FOLFOX or FOLFIRI. BRAF V600E mutations, linked to poor prognosis and anti-EGFR resistance, may benefit from combination therapies such as FOLFOXIRI or targeted therapies such as BRAF and mitogene-activated protein kinase kinase (MEK) inhibitors.[133] Knowledge of a patient's mutation status can guide personalized treatment plans, combining chemotherapy and targeted therapies to enhance treatment efficacy. Moreover, understanding the genetic landscape of CRC can inform targeted screening strategies for earlier detection and guide research efforts toward studying prevalent mutations. Participation in clinical trials exploring novel therapies is also crucial for advancing treatment options for these patients. Although genetic testing is crucial for individual patients, understanding the broader genetic landscape of CRC in different populations can inform treatment, screening, and research strategies, ultimately contributing to improved patient outcomes.[134]

In the rapidly evolving field of cancer genomics, it is crucial to consider the potential impact of a broader spectrum of genetic alterations in CRC. For instance, mutations in homologous recombination repair (HRR) genes such as breast cancer gene (BRCA) and ataxia-telangiectasia mutated (ATM) are gaining attention in the oncology community. These genes play a critical role in DNA repair, and their mutations can lead to genomic instability, a hallmark of cancer.[135] Moreover, the prevalence of HRR mutations can vary across different geographical regions as stated along with the review. This geographical variation could be due to differences in genetic backgrounds, environmental factors, or a combination of both. Understanding these geographical differences in mutation prevalence could provide valuable insights into the regional variations in CRC pathogenesis and response to treatment. Importantly, these mutations can confer sensitivity to poly (adenosine diphosphate (ADP)-ribose) polymerase (PARP) inhibitors, a class of targeted cancer drugs. Poly (ADP-ribose) polymerase inhibitors work by trapping PARP proteins on damaged DNA, which leads to the formation of cytotoxic DNA lesions and ultimately results in cell death.[136] Although PARP inhibitors have shown efficacy in treating cancers with BRCA1/2 mutations, they are also being investigated for other types of cancers with HRR gene mutations or deficiencies, as well as in tumors with high levels of replicative stress. It is important to note that PARP inhibitors are not effective in all patients with HRR gene mutations, and further research is needed to identify predictive biomarkers of response. Nonetheless, PARP inhibitors represent a promising avenue for targeted cancer therapy and have the potential to improve outcomes for patients with HRR-deficient tumors.[136]

Genetic testing plays a pivotal role in the early detection and intervention of diseases, particularly in the field of cancer disease. One of the key advantages of genetic testing in the context of CRC is its potential for early identification. Certain genetic mutations are known to significantly increase the risk of CRC. By identifying these mutations in individuals, we can classify them as high risk. Then, individuals can be monitored more closely for the early signs of CRC, allowing for earlier intervention and potentially better outcomes.[137] The detection of mutations such as RAS and BRAF genes can significantly contribute to the early detection and management of CRC, demonstrating the transformative potential of the advanced diagnostic tools. This proactive approach to early identification is essential as it enables the implementation of preventive measures and early treatments, potentially altering the disease's course.[137]

One recent study[138] has shed light on a significant disruption in DNA repair processes in digestive system cancers, marked by the simultaneous loss of MLH1, PMS2, and MSH6 immuno-expression. This disruption could have far-reaching effects on how we understand and treat a variety of cancers, including CRC. This study found that several MMR/HRR-related genes were affected, including ATM, BARD1, BRCA1, CDK12, CHEK1, CHEK2, FANCA, MLH1, MSH6, PALB2, and TP53. These findings could have a direct impact on the efficacy of PARP inhibitors in the treatment of CRC.

This systematic review possesses a notable strength in its comprehensive examination of studies conducted across various countries in the Middle East, encompassing diverse populations. By including a substantial number of studies while upholding statistical power, a thorough comprehension of the prevalence and range of RAS and BRAF mutations within the region were achieved. However, it is essential to acknowledge the limitations of the review, including data heterogeneity due to variations in specimen types and genotyping methods, as well as potential biases arising from limited accessibility to molecular testing. For example, some studies employed sequencing to confirm mutations, whereas others did not follow this approach. Moreover, demographic diversity within the region may contribute to variability in study results, warranting cautious interpretation.

Conclusions

In essence, this systematic review provides valuable insights into the molecular landscape of CRC in the Middle East, highlighting the importance of region-specific considerations in both research and clinical practice. The distribution patterns

of RAS and BRAF mutations among CRC patients exhibit notable variations across diverse ethnic groups. Our study sheds light on this phenomenon by demonstrating a higher prevalence of KRAS mutations in CRC patients from the Middle East, as compared with those from several regions. The identification of these mutations and geographical differences is important for personalized treatment planning and could potentially aid in the development of novel targeted therapies. Further studies are needed to address the identified gaps and enhance our understanding of CRC pathogenesis and treatment outcomes in the region. Also, more studies are needed to investigate histopathology, in addition to genetic alterations, as hematoxylin and eosin (H&E) histopathology remains the cornerstone of establishing cancer diagnosis.

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Author Contributions
SB and AL conceived the study, exploited review data, and coordinated and drafted the paper. SB, FH, TB, CH, TM, and RT participated in the study design. SB, AL, MJ, SE, and WB involved in review analyses. SB, HE, IAL, MO, MI, KE, ND, and YS reviewed the manuscript. All authors have read and agreed to the version of the manuscript.

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Appendix

Table 4. Frequency and distribution of KRAS, NRAS, and BRAF mutations.

COUNTRY AUTHOR (REFERENCE)	GENE	EXON	CODON	AMINO ACID	NUCLEOTIDE	PROTEIN	FREQUENCY, NO (%)
Bahrain							
Al Shaikh and Shubbar[49]	KRAS	NA	NA	NA	NA	NA	NA
	NRAS	NA	NA	NA	NA	NA	NA
	BRAF	15	600	V600E	1799T > A	p.Val600Glu	6 (3.5%)
Iran							
Shemirani et al.[33]	KRAS	2	12	G12D	c.35G > A	p.Gly12Asp	5 (83%)
			13	G13C	c.37G > T	p.Gly13Cys	1 (17%)
Omidifar et al.[34]	KRAS	2	12	G12A	c.35G > C	p.Gly12Ala	12 (12%)
				G12D	c.35G > A	p.Gly12Asp	9 (9%)
				G12S	c.34G > A	p.Gly12Ser	1 (1%)
				G12C	c.34G > T	p.Gly12Cys	1 (1%)
			13	G13D	c.38G > A	p.Gly13Asp	6 (6%)
				G13S	c.38G > C	p.Gly13Ser	1 (1%)
				G13R	c.37G > C	p.Gly13Arg	1 (1%)
Yari et al.[48]	KRAS	2	12	G12C	c.34G > T	p.Gly12Cys	1 (3.7%)
				G12D	c.35G > A	p.Gly12Asp	13 (48.1%)
				G12A	c.35G > C	p.Gly12Ala	1 (3.7%)
				G12V	c.35G > T	p.Gly12Val	6 (22.2%)
			13	G13D	c.38G > A	p.Gly13Asp	6 (22.2%)
		3	61	Q61H	c.183A > C	p.Gln61His	2 (100%)
	BRAF	15	600	V600E	1799T > A	p.Val600Glu	7 (7%)

(Continued)

Table 4. (Continued)

COUNTRY AUTHOR (REFERENCE)	GENE	EXON	CODON	AMINO ACID	NUCLEOTIDE	PROTEIN	FREQUENCY, NO (%)
Amirifard et al.[35]	KRAS	2	12	G12V	c.35G > T	p.Gly12Val	3 (25%)
				G12D	c.35G > A	p.Gly12Asp	5 (41%)
				G12S	c.34G > A	p.Gly12Ser	1 (8.3%)
				G12C	c.34G > T	p.Gly12Cys	1 (8.3%)
			13	G13D	c.38G > A	p.Gly13Asp	1 (8.3%)
Naseri et al.[45]	KRAS	2	12	G12D	c.35G > A	p.Gly12Asp	5 (35%)
				G12V	c.35G > T	p.Gly12Val	5 (35%)
			13	G13D	c.38G > A	p.Gly13Asp	4 (28%)
	NRAS	4	146	A146T	c.436G > A	p.A146T	1 (100%)
Niya et al.[36]	KRAS	2	12	G12A	c.35G > C	p.Gly12Ala	NA
				G12C	c.34G > T	p.Gly12Cys	NA
				G12D	c.35G > A	p.Gly12Asp	NA
				G12F	c.34_35GG > TT	p.Gly12Phe	NA
				G12R	c.34G > C	p.Gly12Arg	NA
				G12S	c.34G > A	p.Gly12Ser	NA
				G12V	c.35G > T	p.Gly12Val	NA
			13	G13D	c.38G > A	p.Gly13Asp	NA
Bishehsari et al.[37]	KRAS	2	12	G12D	c.35G > A	p.Gly12Asp	16 (8.8%)
				G12C	c.34G > T	p.Gly12Cys	9 (4.9%)
				G12V	c.35G > T	p.Gly12Val	18 (9.9%)
			13	G13D	c.38G > A	p.Gly13Asp	21 (11.5%)
Hamzehzadeh et al.[38]	KRAS	2	12	G12D	c.35G > A	p.Gly12Asp	7 (28%)
				G12V	c.35G > T	p.Gly12Val	4 (16%)
				G12A	c.35G > C	p.Gly12Ala	3 (12%)
				G12S	c.34G > A	p.Gly12Ser	3 (12%)
				G12C	c.34G > T	p.Gly12Cys	1 (4%)
			13	G13D	c.38G > A	p.Gly13Asp	7 (28%)
Iraq							
Al-Allawi et al.[39]	KRAS	2	12	G12V	c.35G > T	p.Gly12Val	9 (31%)
				G12D	c.35G > A	p.Gly12Asp	7 (24.1%)
				G12A	c.35G > C	p.Gly12Ala	5 (17.2%)
				G12C	c.34G > T	p.Gly12Cys	3 (10.3%)
				G12S	c.34G > A	p.Gly12Ser	2 (6.9%)
			13	G13D	c.38G > A	p.Gly13Asp	3 (10.3%)

(Continued)

Table 4. (Continued)

COUNTRY AUTHOR (REFERENCE)	GENE	EXON	CODON	AMINO ACID	NUCLEOTIDE	PROTEIN	FREQUENCY, NO (%)
Israel							
Kislitsin et al.[40]	KRAS	2	12	G12C	c.34G > T	p.Gly12Cys	4 (14%)
				G12S	c.34G > A	p.Gly12Ser	4 (14%)
				G12V	c.35G > T	p.Gly12Val	7 (23%)
				G12D	c.35G > A	p.Gly12Asp	14 (43%)
			13	G13D	c.38G > A	p.Gly13Asp	12 (27%)
Jordan							
Elbjeirami et al.[41]	KRAS	2	12	G12D	c.35G > A	p.Gly12Asp	24 (54.5%)
				G12V	c.35G > T	p.Gly12Val	6 (13.6%)
				G12C	c.34G > T	p.Gly12Cys	5 (11.4%)
				G12A	c.35G > C	p.Gly12Ala	2 (4.5%)
				G12R	c.34G > C	p.Gly12Arg	2 (4.5%)
				G12S	c.34G > A	p.Gly12Ser	1 (2.3%)
			13	G13D	c.38G > A	p.Gly13Asp	5 (11.4%)
Awidi et al.[46]	KRAS	2	12	G12D	c.35G > A	p.Gly12Asp	18 (19.56%)
				G12A	c.35G > C	p.Gly12Ala	16 (17.39%)
				G12T	c.(34G > A; 35G > C)	p.Gly12Thr	13 (14.13%)
				G12V	c.35G > T	p.Gly12Val	10 (10.87%)
				G12S	c.34G > A	p.Gly12Ser	3 (3.26%)
				G12C	c.34G > T	p.Gly12Cys	2 (2.17%)
			13	G13D	c.38G > A	p.Gly13Asp	7 (7.60%)
				G13A	c.38G > C	p.Gly13Ala	6 (6.52%)
		3	61	Q61H	c.183A > C	p.Gln61His	1 (1.08%)
		4	117	K117N	c.351A > C	p.Lys117Asn	6 (6.52%)
			146	A146T	c.436G > A	p.Ala146Thr	2 (2.17%)
	NRAS	2	12	G12V	c.35G > T	p.Gly12Val	1 (1.08%)
			13	G12C	c.37G > T	p.Gly13Cys	1 (1.08%)
				G13A	c.38G > C	p.Gly13Ala	1 (1.08%)
		3	61	Q61R	c.182A > G	p.Gln61Arg	1 (1.08%)
				Q61P	c.182A > C	p.Gln61Pro	1 (1.08%)
				A61T	NA	p.Ala61Thr	1 (1.08%)

(Continued)

Table 4. (Continued)

COUNTRY AUTHOR (REFERENCE)	GENE	EXON	CODON	AMINO ACID	NUCLEOTIDE	PROTEIN	FREQUENCY, NO (%)
Lebanon							
Baba et al.[50]	KRAS	2	12	G12D	c.35G>A	p.Gly12Asp	49 (37.4%)
				G12V	c.35G>T	p.Gly12Val	28 (21.4%)
				G12C	c.34G>T	p.Gly12Cys	15 (11.5%)
				G12A	c.35G>C	p.Gly12Ala	7 (5.3%)
				G12S	c.34G>A	p.Gly12Ser	6 (4.6%)
				G12R	c.34G>C	p.Gly12Arg	2 (1.5%)
			13	G13C	c.37G>T	p.Gly13Cys	1 (0.8%)
				G13D	c.38G>A	p.Gly13Asp	16 (12.9%)
		3	61	Q61H	c.183A>T	p.Gln61His	1 (0.8%)
		4	117	K117N	c.351A>T	p.Lys117Asn	1 (0.8%)
			146	A146T	c.436G>A	p.Ala146Thr	1 (0.8%)
				A146V	c.437C>T	p.Ala146Val	1 (0.8%)
	NRAS	2	12	G12D	c.35G>A	p.Gly12Asp	6 (37.5%)
			13	G13R	c.37G>C	p.Gly13Arg	2 (12.5%)
		3	61	Q61R	c.182A>G	p.Gln61Arg	3 (18.75%)
				Q61L	c.182A>T	p.Gln61Leu	3 (18.75%)
	BRAF	15	600	V600E	1799T>A	p.Val600Glu	2 (1.2%)
Saudi Arabia							
Bader et al.[42]	KRAS	2	12	G12D	c.35G>A	p.Gly12Asp	16 (45.7%)
				G12V	c.35G>T	p.Gly12Val	11 (31.4%)
				G12C	c.34G>T	p.Gly12Cys	3 (8.5%)
				G12S	c.34G>A	p.Gly12Ser	1 (2.8%)
			13	G13D	c.38G>A	p.Gly13Asp	4 (11.4%)
Zekri et al.[43]	KRAS	2	12	NA	NA	NA	NA
			13	NA	NA	NA	NA
Zahrani et al.[44]	KRAS	2	12	G12V	c.35G>T	p.Gly12Val	26 (35.6%)
				G12D	c.35G>A	p.Gly12Asp	26 (35.6%)
				G12S	c.34G>A	p.Gly12Ser	10 (13.7%)
				G12C	c.34G>T	p.Gly12Cys	6 (8.2%)
				G12R	c.34G>C	p.Gly12Arg	3 (4.2%)
				G12A	c.35G>C	p.Gly12Ala	2 (2.7%)
			13	G13D	c.38G>A	p.Gly13Asp	10 (90.9%)
				G13R	c.37G>C	p.Gly13Arg	1 (9.1%)

(Continued)

Table 4. (Continued)

COUNTRY AUTHOR (REFERENCE)	GENE	EXON	CODON	AMINO ACID	NUCLEOTIDE	PROTEIN	FREQUENCY, NO (%)
Mulla et al.[47]	KRAS	2	12	G12A	c.35G>C	p.Gly12Ala	1 (6.7%)
				G12C	c.34G>T	p.Gly12Cys	1 (6.7%)
				G12D	c.35G>A	p.Gly12Asp	8 (53.3%)
				G12S	c.34G>A	p.Gly12Ser	2 (13.3%)
				G12V	c.35G>T	p.Gly12Val	3 (20%)
	NRAS	2	12	G12D	c.35G>A	p.Gly12Asp	1 (50%)
		3	61	Q61L	c.182A>T	p.Gln61Leu	1 (50%)
Saharti[51]	KRAS	2	12	G12D	c.35G>A	p.Gly12Asp	17 (18.3%)
				G12V	c.35G>T	p.Gly12Val	6 (6.5%)
				G12S	c.34G>A	p.Gly12Ser	4 (4.3%)
				G12A	c.35G>C	p.Gly12Ala	3 (3.2%)
				G12R	c.34G>C	p.Gly12Arg	1 (1.1%)
				G12C	c.34G>T	p.Gly12Cys	1 (1.1%)
			13	G13D	c.38G>A	p.Gly13Asp	3 (3.2%)
		3	61	Q61H	c.183A>T	p.Gln61His	2 (2.2%)
		4	117	K117N	c.351A>T	p.Lys117Asn	2 (2.2%)
			146	A146T	c.436G>A	p.Ala146Thr	2 (2.2%)
	NRAS	3	61	Q61K	c.181C>A	p.Gln61Lys	1 (1.1%)
				Q61L	c.182A>T	p.Gln61Leu	1 (1.1%)
	BRAF	15	600	V600E	1799T>A	p.Val600Glu	2 (2.2%)

Abbreviation: NA, not available.