

An In-Depth Analysis of Colorectal Cancer in Erbil: Demographic Factors, Regional Disparities, Treatment Approaches and Genetic Studies

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Abstract

Background: This study explores sex, age, histological subtype, cancer stages, treatment methods and genetic studies (mutation and expression) of Adenomatous Polyposis Coli (*APC*), Kirsten Rat Sarcoma Viral Oncogene Homolog (*KRAS*), Tumor Protein 53 (*TP53*) and Deleted in Colorectal Cancer (*DCC*) genes for colorectal cancer (CRC).

Method: In this retrospective research study, 2625 CRC patients were included. The study spanned 11 years, from 2013 to 2023, and revealed fascinating trends and patterns within each category. GraphPad Prism version 9.0. (GraphPad Software, Inc.) was used to analyze acquired data. T test was used for the comparison between two groups. A *P*-value of 0.05 or below was considered statistically significant.

Results: The data demonstrate a considerable rise in CRC incidences throughout the study's period, peaking in 2021 and men outnumbered women annually. The age-based analysis showed individuals of all ages were vulnerable to CRC, with the number of cases rising until peaking at 60. Histologically, colon cancer was more common than rectal cancer, and adenocarcinoma was the most common subtype. Most cases were grade 2 based on tumor (T), node (N) and metastasis (M) staging system, with T3N1M0 and T3N2M0 being the most prevalent subtypes. The majority CRC patients received curative treatments. Regarding genetic studies of CRC related *APC*, *KRAS*, *TP53* and *DCC* genes in International Cancer Genome Consortium databases, *APC* had the most mutations, with single-base substitutions being predominant. In the Catalogue of Somatic Mutations in Cancer database, *KRAS* had the highest mutations which included 8 missense substitutions. Regarding gene expression, public database Gene Expression Database of Normal and Tumor Tissues 2 showed significant differences between the four selected genes in CRC as compared with the normal tissue.

Conclusion: The study results highlight the complex nature of CRC and its prevalence and treatment. The genetic studies of CRC in databases revealed that *APC* and *KRAS* had the most mutations and gene expression analysis indicated significant differences between CRC and normal tissue for the selected genes.

Keywords: Colorectal neoplasms, *APC* gene, *KRAS* gene, *TP53* gene, *DCC* gene

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Introduction

Colorectal cancer (CRC), the third most common cancer and the second leading cause of death, was responsible for 1.9 million new cases and 0.9 million deaths worldwide in 2020.¹ It is also the third most diagnosed and fatal disease in both sexes in the United States, and it ranks second in cancer-related mortality and is the most common cause among males under the age of 50.² The number of fatalities from rectal and colon cancer is predictable to elevate by 60% and 71.5% by 2035, respectively. These numbers may differ from country to country depending on the level of economic development and considered as an indicator of the country's economic and social development.³ Iraq has the lowest incidence of CRC (6, 12/100,000 population), but its prevalence has been gradually elevating over the past two decades.⁴

The strongest non-modifiable risk factors for

CRC and precancerous polyps are age, male sex, and family history of CRC. Evidence indicates that smoking, obesity, and diet are key modifiable risk factors for sporadic CRC.⁵ CRC may occur in young individuals; however, after the age of 50, there is a 90% increased risk of developing CRC.⁶ Increased physical activity, postmenopausal hormone treatment, nonsteroidal anti-inflammatory medicines, and vegetable and fruit consumption have all been related to a lower risk of CRC.⁷

Several studies on the genome-wide association of CRC have found cancer susceptibility genes (common single-nucleotide polymorphisms) that increase risk, but most heredity factors are still unknown.^{8,9} In CRC, the most common mutation occurs in Adenomatous Polyposis Coli (*APC*) gene followed by Kirsten Rat Sarcoma Viral Oncogene Homolog (*KRAS*), Tumor Protein 53 (*TP53*) and Deleted in Colorectal Cancer (*DCC*)

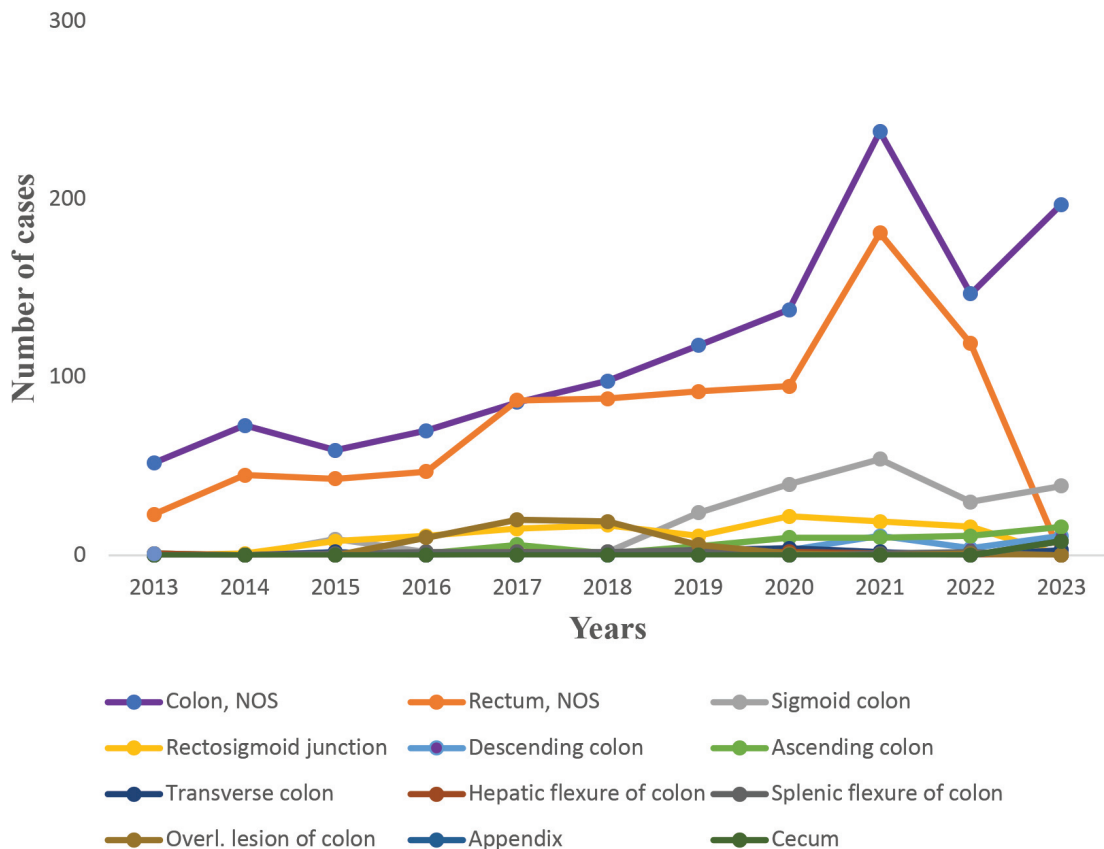


Figure 1. This figure shows the anatomical sites of colorectal cancer cases in Erbil (2013-2023). Colon cancer was greater than rectal cancer in all years in this study. Greatest number of both colon and rectal cancers were observed in 2021.
NOS: Not specified

genes. Mutations in *APC* gene are causing non-malignant adenomas, known as polyps. Approximately 15% of these polyps have a possibility to progress to cancer during the next 10 years.¹⁰ Mutations in the *APC*, *DCC*, *KRAS* and *TP53* genes have been associated with the progression of sporadic CRC, occurring at defined pathological stages of the tumor progression and consequently modulating several genes in the corresponding signaling pathways.¹¹

Despite the rising incidence of CRC, there is little study on how sex, occupation, age, histological subtype, disease stage, and therapy impact CRC. Also, there is a little information on CRC regarding mutation and expression of genes, mainly in Kurdistan region, Iraq. Existing research frequently concentrates on individual elements, obscuring their complex relationships. Therefore, the present study aimed to identify CRC trends, disparities, and associations to inform healthcare professionals, policymakers, and researchers of ways to inhibit, diagnose, and treat

this life-threatening cancer. Also, genetic studies (mutation and expression) of *APC*, *KRAS*, *TP53* and *DCC* genes for CRC were included.

Materials and Methods

Registration of CRC cases in Erbil governorate (2013-2023)

In the present retrospective research, all CRC cases (2625 patients) were diagnosed and registered in Erbil governorate of KRG between 2013 and 2023. The findings were based on information gathered from primary cancer registry centers of Erbil governorate. This research project (No: 4S/311, September 3, 2023) was approved by the Human Ethics Committee of the College of Science at Salahaddin University-Erbil (Erbil, Iraq), meeting the Helsinki Declaration criteria.

Demographic and clinical data collection for CRC patients in Erbil governorate

The recorded CRC patients involved both sexes, 1428 males and 1197 females. The name, age, place of residence and professionalism of all

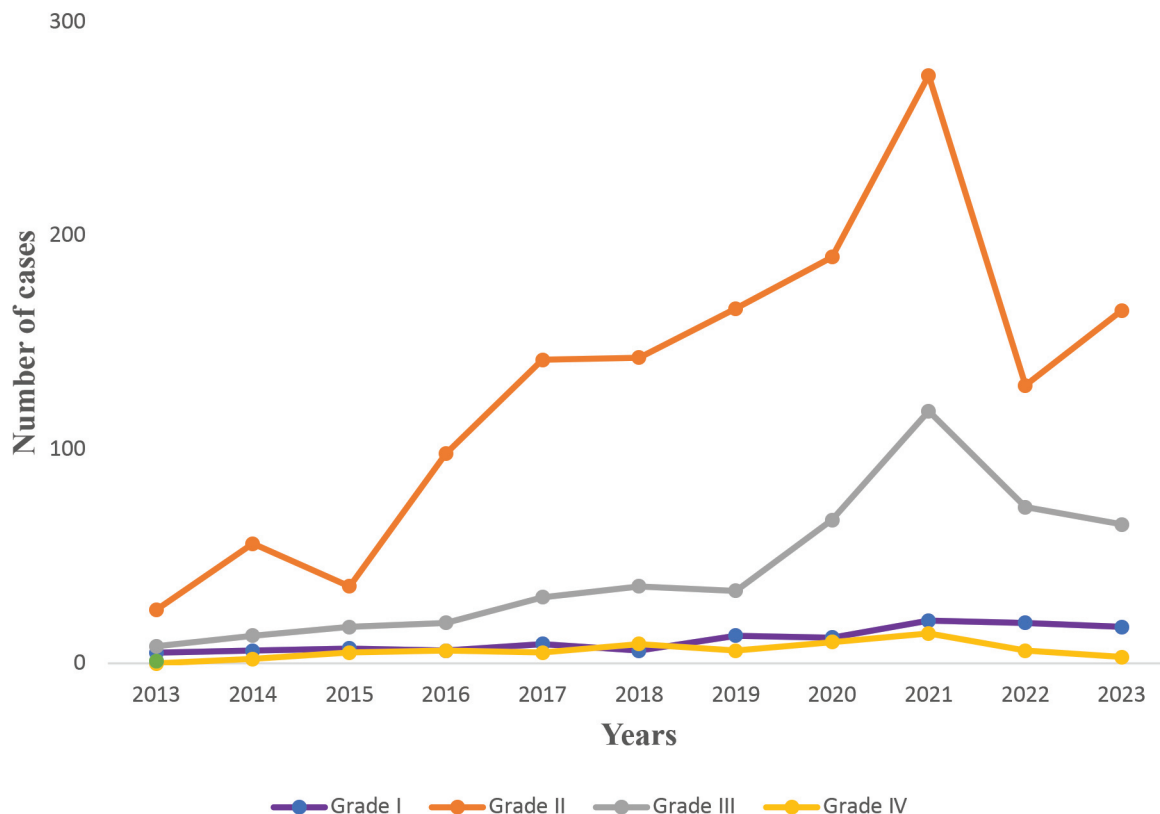


Figure 2. This figure shows the grade of colorectal cancer patients at diagnosis time in Erbil (2013-2023). Most cases were diagnosed at grade 2 each year, more predominantly in 2021

patients were acquired in the present study. In addition, details on each participant's specific cancer site were obtained. The incoming notifications were double-checked against the registered data to prevent duplicate registrations. *Histological assessment and tumor, node, metastasis (TNM) staging of CRC specimens*

The patient's specimen was histologically assessed and the diagnosis for CRC was made based on changes observed in tissue samples and the topography (primary site) was confirmed. Moreover, the TNM staging system was used to describe the cancer's size, indicate whether the lymph nodes contain any cancerous cells and define whether the cancer has spread throughout the body.^{12, 13}

Treatment programs for CRC patients

Based on physician diagnosis and histopathological report, CRC patients were included in a particular treatment program that could involve one of the various therapies such as radiography,

chemotherapy, hormonal therapy and immunotherapy either alone or in combination.

Mutation studies and gene interaction analysis

Regarding the mutation studies of *APC*, *KRAS*, *TP53* and *DCC* genes in different types of cancer, the Genome aggregation database (gnomAD) was used for mutation retrieval of mentioned genes. This population referencing database is one of the most powerful tools that provides information about genetic variation and gene interpretation found in the human population. This resource is developed by worldwide investigators who collect and integrate both genome and exome data from massive sequencing programs. The database nowadays is widely used in clinical genetics and genomic research.^{14, 15} In addition, the interaction of *APC*, *KRAS*, *TP53* and *DCC* genes with other genes predicted via GeneMANIA anticipation tool.¹⁶

More importantly, the present investigation examined mutations in *APC*, *KRAS*, *TP53* and

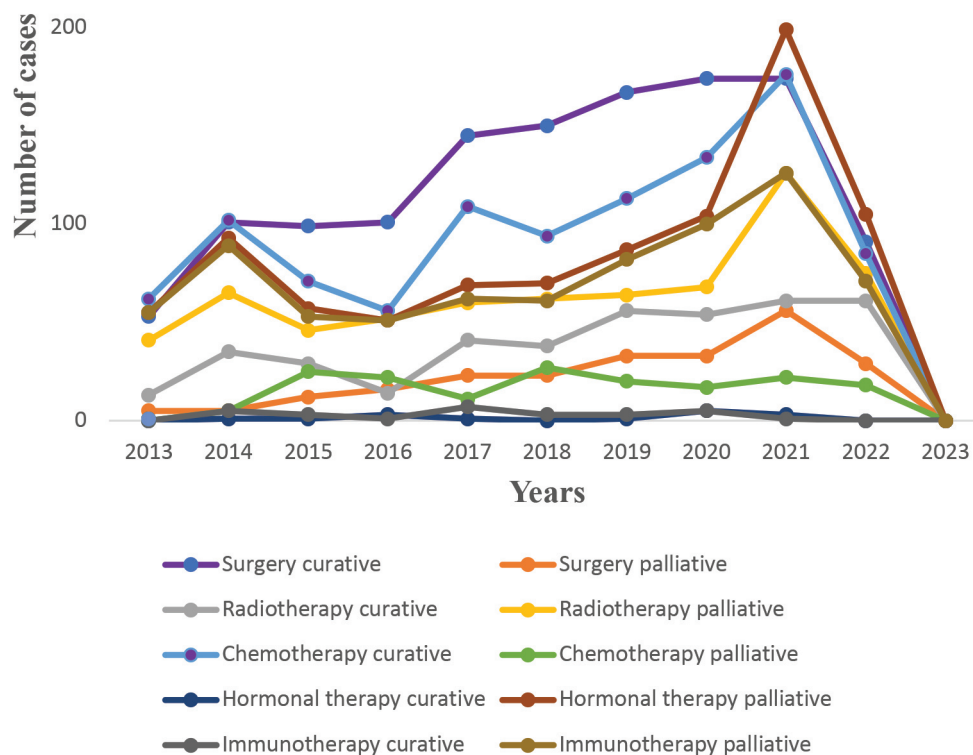


Figure 3. This figure shows the treatment outcomes in colorectal cancer patients across various therapeutic methods in Erbil (2013-2023). In surgical and chemotherapeutic treatments, the colorectal cancer patients have exhibited more curative than palliative type of treatment. However, most patients in alternative therapies received palliative rather than curative treatment

Table 1. Distribution of colorectal cancer patients by gender, age, and occupation in Erbil (2013-2023)

Year	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Gender											
Male	40	62	72	79	131	118	137	159	287	177	166
Female	38	57	51	64	91	111	130	156	230	153	116
Age (Years)											
≤25	7	13	4	5	4	3	3	8	10	8	5
26-35	12	15	11	12	19	26	22	26	53	26	30
36-45	12	20	21	27	35	36	36	37	74	53	42
46-55	13	21	23	32	45	39	56	70	108	77	56
56-65	24	29	40	29	57	61	70	78	115	65	57
66-75	8	13	16	27	43	48	49	63	110	74	73
>76	2	8	8	11	19	16	31	33	47	27	19
Occupation											
Business	10		0		0			19	35	18	
Agriculture related	0					1		1	3	1	
Housewife	12		29	22	33	48	59				
Office worker	1		15	8	20	25	27	41	57	36	
Teaching	3		3	4	7	5	8		30	14	
Blank	26	119	42	90	129	62	129				
Others		30	17	30	44	34	32	55	29		
Manual		2	2	1	1		85	130	65		
Technical		2		1		1	3	0			
Professional					1	1	6		1		
Blank											
Unknown	26		0	0	1	42	3	134	206	167	
Total	78	119	123	143	222	229	267	315	517	330	

DCC genes in CRC. We retrieved data on mutations of selected genes from ICGC and COSMIC.¹⁷

Gene expression and prognostic analysis of selected genes in CRC

To observe the expression level of *APC*, *KRAS*, *TP53* and *DCC* genes in CRC compared with normal tissue, GENT2 was used that provided gene expression profile in large number of samples using two different platforms the Affymetrix U133Plus2 and the Affymetrix U133A to contrast the two outcomes. Furthermore, GENT2 also afforded meta-survival analysis of the selected genes in CRC, that evaluate the prognostic potential of these genes in many independent studies.¹⁸

Statistical analysis

GraphPad Prism version 9.0. (GraphPad Software, Inc.) was used for data analysis and presentation. Unpaired t-test was used for the comparison between two groups. A *P*-value of 0.05 or below was considered statistically significant.

Results

Incidence of CRC sorted by sex, age and profession

The present study found that the total number of CRC patients increased noticeably each year from 2013 to 2023, to more than threefold in 2023, and peaking in 2021. Based on sex, the recorded male patients with CRC between 2013 and 2023 was higher than the number of female patients each year. In our study, patients of all ages were susceptible to develop CRC. In addition, with advancing age, the number of cases increased progressively until it peaked at about 60 years of age. Among the recorded 2625 patients, 625 (around one fourth) of cases were between 56-65 years.

Over the 11-year study period, there was an increase in the number of cases across all occupational categories by the end of the study compared with the beginning.

Moreover, the professions associated to agriculture had the lowest rate of CRC patients and the majority of instances in male and female genders involved office employees and housewives, respectively (Table 1).

Table 2. Mutations in the *TP53*, *KRAS*, *APC* and *DCC* genes in CRC retrieved from the ICGC database

Genes	No. of mutations	Types of mutation	Consequences	Clinical significance
<i>APC</i>	18	17 single base substitution 1 Insertion	1 Missense, 16 Stop Gained and 1 Frameshift	3 Likely pathogenic 5 Pathogenic 0 Pathogenic/Likely pathogenic
<i>KRAS</i>	17	17 single base substitution	17 Missense	1 Likely pathogenic 10 Pathogenic 6 Pathogenic/Likely pathogenic
<i>TP53</i>	16	16 single base substitution	15 Missense, 1 Stop Gained	5 Likely pathogenic 7 Pathogenic 4 Pathogenic/Likely pathogenic
<i>DCC</i>	8	8 single base substitution	2 Missense and 6 Stop Gained	0 Likely pathogenic 0 Pathogenic 0 Pathogenic/Likely pathogenic

APC: Adenomatous Polyposis Coli; *KRAS*: Kirsten Rat Sarcoma Viral Oncogene Homolog; *TP53*: Tumor Protein 53; *DCC*: Deleted in Colorectal Cancer; CRC: Colorectal cancer; ICGC: International Cancer Genome Consortium; No.: Number

Adenocarcinoma prevalence and regional disparities in colon versus rectal cases

Different methods of diagnosis for CRC were used and most of the CRC patients were diagnosed based on histology of primary. It appeared that approximately all the expected patients had malignant CRC status every year during the study. Then, based on histological classification, most of the patients were diagnosed with adenocarcinoma. Furthermore, our data showed that colon cancer cases outnumbered rectal cancer cases in each study year and the greatest number of both colon and rectal cancer were recorded in 2021 (Figure 1).

Assessment of CRC grades

The study results displayed that more than half of diagnosed CRC patients were in grade 2 at the time of diagnosis. Additionally, most grade 2 CRC patients have T3N1M0 (295 patients) and T3N2M0 (203 patients) for the 11 years of study period. Furthermore, our data showed that most grade 1 CRC patients are at an advanced stage of their disease and the highest number (7 patients) were classified in T4N0M0 in 2021. However, in grade 2, the bulk of CRC patients were in T3N1M0 and T3N2M0 involving 164 and 105 patients detected in 2022, respectively. Regarding grades 3 and 4 of CRC progress, most of the cases were diagnosed in 2021 (Figure 2).

Treatment approaches for CRC

The majority of CRC patients with different treatment methods (surgical treatment, radiotherapy, chemotherapy, hormonal therapy and immunotherapy either alone or in

combination) received mainly curative or palliative type of treatment. In surgical and chemotherapeutic treatment, CRC patients exhibited more curative than palliative type of treatment. However, most patients in alternative therapies received palliative rather than curative treatment (Figure 3).

Mutations and genes interactions of selected genes

Based on gnomAD database, that reports all mutations in all types of cancer, there are more types of variant present in *APC* compared with *KRAS*, *TP53* and *DCC* genes. In addition, data from the GeneMANIA predicting tool displayed that *APC*, *KRAS*, *TP53* and *DCC* have interaction with other genes mainly through physical interaction.

More importantly, mutations retrieved from the ICGC database in CRC for *APC*, *KRAS*, *TP53* and *DCC* genes. Mutations were more in *APC* gene (18 mutations) present as compared with other selected genes in our study. Most mutations in all selected genes were composed of single-base substitutions. In addition, 16 stop gained for *APC* gene and 17 missenses for *KRAS* gene as the highest among selected genes were observed. Remarkably, in ICGC dataset, no clinically significant mutations were observed for *DCC* gene (Table 2).

While based on COSMIC database, *APC* and *TP53* genes had a total of 7 mutations in CRC and most were substitution missense mutation. Regarding *KRAS* gene, the highest mutations were recorded in COSMIC database among

Table 3. Mutations in the *APC*, *KRAS*, *TP53* and *DCC* genes in CRC retrieved from the COSMIC database

Genes	Total	Insertion - Frameshift	Substitution - Missense	Substitution - Nonsense	Deletion - In frame	Unknown
<i>APC</i>	7	1	4	2	-	-
<i>KRAS</i>	10	-	8	-	1	1
<i>TP53</i>	7	1	4	2	-	-
<i>DCC</i>	-	-	-	-	-	-

APC: Adenomatous Polyposis Coli; *KRAS*: Kirsten Rat Sarcoma Viral Oncogene Homolog; *TP53*: Tumor Protein 53; *DCC*: Deleted in Colorectal Cancer; CRC: Colorectal cancer; COSMIC: Catalogue of Somatic Mutations in Cancer

selected genes in this study which include 10 mutations as a total with 8 substitution missense mutations. Markedly, the COSMIC database did not contain mutations in *DCC* gene (Table 3).

The expression of genes in CRC and their subtypes and meta-survival data

In our study, the unpaired t-test demonstrated significant differences ($P < 0.001$) in gene expression in *KRAS*, *APC*, and *TP53* between tumor tissues as compared with normal tissue using U133-plus 2 platform. However, the average expression level was not significant between the colon cancer and normal tissue for *DCC* gene. Using U133A platform the data showed significant difference between CRC and normal tissue in all four selected genes (Table 4).

The meta-survival analysis exhibited that there is significant difference ($P < 0.02$) in overall survival (OS) and *APC* gene in CRC, while not statistically significant difference was observed between OS and *KRAS*, *TP53* and *DCC*. Furthermore, there was significant difference ($P < 0.01$) between *TP53* and recurrence free survival (RFS), while no significant difference was noted in other selected genes in CRC (Table 5).

Gene expression across CRC subtype showed there is no significant difference between colorectal subtypes including moderately-differentiated, well-differentiated and poorly-differentiated in *APC*, *KRAS*, *TP53* and *DCC* genes (Table 6).

Discussion

Many people are affected by CRC, which is a major global health concern. The incidence of CRC has been progressively rising in recent years, and the Kurdistan region of Iraq is not an exception. The present study reported a gradually

increased CRC incidence rate which peaked in 2021. A convincing justification for increase in cancer cases might be due to the demographic shifts in the Erbil population that are brought by instability in neighboring countries in 2020 and thereafter that led to migration of thousands of Syrian and Lebanese immigrants to Erbil. This is in alignment with previous study that predicted a significant increase in cancer burden between 2013 and 2019 in Erbil governate.¹⁹ It is also in line with global data wherein CRC incidence is increasing and accounts for 11% of all cancer diagnoses.²⁰ In term of gender, our data showed slightly higher incidence rate of CRC in men than women. As compared with female patients, male patients with CRC have a worse prognosis and a mortality rate that is around 40% higher.^{21, 22} While the causes of sex discrepancy are not fully known, it is believed that they may be linked to differences in the exposure to risk factors such as drinking alcohol, tobacco use, dietary habits, physical inactivity, and sex hormones.²³

Age is regarded as one of the most important factors determining the risk of developing CRC. Globally, there is a significant rise in the incidence and mortality of CRC recorded after age 50.¹ Although the prevalence of CRC has decreased or stabilized in certain countries, younger generations are now more likely to develop early-onset CRC, particularly rectal cancer.^{24, 25} Our findings tie well with previous studies wherein the majority of CRC patients were older than 50 years old in Erbil governate with increase in younger age group (25 to 45 years). Researchers highlight the need for better screening guidelines and greater awareness in younger patients.^{26, 27}

Although lifestyle-related factors mentioned previously are associated to a higher risk of

Table 4. This table illustrates the tissue-wide gene expression profile of *APC*, *KRAS*, *TP53* and *DCC* genes in CRC

Significant Gene expression (Two sample T-test)								
Colon	GPL570 platform (HG-U133_Plus_2)				GPL96 platform (HG-U133A)			
	P-value	Log2FC	Average Expression level (397 Normal samples)	Average Expression level (3775 Colon cancer samples)	P-value	Log2FC	Average Expression level (127 Normal colon samples)	Average Expression level (1112 Colon cancer samples)
<i>APC</i>	<0.001	-0.59	7.61	7.01	<0.001	-0.52	6.81	6.78
<i>KRAS</i>	<0.001	-0.68	10.56	9.88	0.002	-0.21	9.38	9.16
<i>TP53</i>	<0.001	0.38	8.30	8.68	<0.001	0.45	7.58	7.57
<i>DCC</i>	0.12	0.09	3.81	3.89	<0.001	-0.48	5.81	5.81

APC: Adenomatous Polyposis Coli; *KRAS*: Kirsten Rat Sarcoma Viral Oncogene Homolog; *TP53*: Tumor Protein 53; *DCC*: Deleted in Colorectal Cancer; CRC: Colorectal cancer

developing colon cancer,²⁸ our results demonstrate that most diagnosed CRC female patients were housewife while most men were office employees. This is in line with the study that indicates individuals with low socioeconomic level are more likely to develop cancer than those with high socioeconomic level.²⁹ It has also been reported that occupation has influenced the diagnosis and treatment of cancer patients.^{28, 30} This may be partially clarified by the low socioeconomic class population's restricted access to high-quality treatment resources and healthcare facilities as well as their poor eating, sedentary lifestyles, and smoking habits as well as the poor level of awareness about cancer signs might contribute to higher incidence numbers.^{3, 31}

Most CRC cases are found to be in grade 2 at diagnosis time, according to the results of the present study. For CRC, it is known that the grade of cancer is the most crucial prognostic factor. The prognosis is better, if the tumor remains localized in colon or rectum rather than spreading to other regions of the body.¹ Early identification can significantly improve prognosis and quality of life by reducing death, preventing metastasis, and enhancing prognosis and future quality of life.³² Additionally, it has been demonstrated that individuals with metastatic CRC have a low percentage of survival because of their resistance to chemotherapy and greater pathological grade.³³

Essential knowledge about the molecular basis of cancer is provided by mutations retrieved from various databases. Important genes, including

APC, *KRAS*, *TP53* and *DCC* are highlighted. Variations in the spreading of mutations across mentioned genes were found in the gnomAD database. Numerous mutations, involving missense, were discovered in all of the chosen genes, revealing the complicated sequence of alterations in these gene responsible for suppressing tumor growth. Also, in our study, *APC*, *KRAS*, *TP53* and *DCC* showed interactions with other genes mainly through physical interaction. In addition, numerous noteworthy mutations in *APC*, *KRAS*, *TP53* and *DCC* genes were discovered by the ICGC database, highlighting their significance in the development of CRC. While in COSMIC database, *APC* and *TP53* genes are exhibiting same number of mutations in CRC and *APC* gene is showing a range of types of mutation such as insertion frameshift, substitution missense and substitution nonsense. However, *KRAS* gene mutations were very common in the COSMIC database. Moreover, in the present study, data showed significant difference between CRC and normal tissue in *APC*, *KRAS*, *TP53* and *DCC* genes using U133A platform. The meta-survival analysis displayed that there is significant difference only in OS and *APC* gene in CRC. Furthermore, there was significant difference between *TP53* and RFS, while no significant difference was noted in other selected genes in CRC. In general, these results give significant information about the genetic mutations in CRC-related genes and could direct future research on targeted therapies and

Table 5. The meta-survival analysis of *APC*, *KRAS*, *TP53* and *DCC* genes in CRC

Colon	OS						PFS						RFS					
	Fixed			Random			Fixed			Random			Fixed			Random		
	HR	z-value	P-value	HR	z-value	P-value	HR	z-value	P-value	HR	z-value	P-value	HR	z-value	P-value	HR	z-value	P-value
<i>APC</i>	1.00		0.02	1.00		0.02	NA			NA			1.00	0.84	0.40	1.00	0.84	0.40
<i>KRAS</i>	1.00	1.69	0.09	1.00	0.99	0.33	NA			NA			1.00	1.92	0.05	1.00	1.34	0.18
<i>TP53</i>	1.00	-1.10	0.27	1.00	-0.90	0.37	NA			NA			1.00	-2.58	0.01	1.00	-2.58	0.01
<i>DCC</i>	1.00	0.68	0.50	1.00	0.24	0.81	NA			NA			1.00	1.31	0.19	1.00	1.31	0.19

APC: Adenomatous Polyposis Coli; *KRAS*: Kirsten Rat Sarcoma Viral Oncogene Homolog; *TP53*: Tumor Protein 53; *DCC*: Deleted in Colorectal Cancer; CRC: Colorectal cancer; OS: Overall survival; PFS: Progression-free survival, RFS: Recurrence-free survival

diagnostic approaches. The available databases were widely used nowadays to study the mutations and expression of genes in cell lines,¹⁸ lung adenocarcinoma³⁴, clear cell renal cell carcinoma¹⁵ and CRC.³⁵ CRC increases through a steady series of histological alterations, each of which is supplemented by a particular genetic change. The *APC* gene is a tumor suppressor gene that has a valuable responsibility in regulating cell growth and maintaining genomic stability. Mutations in the *APC* gene has been associated with the progression of sporadic CRC.¹¹ Mutation and inactivation of the *APC* gene is a key and early event almost uniquely remarked in colorectal tumorigenesis.³⁶ Regarding *KRAS* gene, it is a mutated oncogene in CRC, with mutations in approximately 40% of all CRC cases; its mutations result in constitutive activation of the *KRAS* protein, which acts as a molecular switch to persistently excite downstream signaling pathways, including cell division and survival, thereby leading to tumorigenesis.³⁷ Concerning *TP53* gene in CRC, the *TP53* gene is mutated in 43% of tumors, and the other rest tumors often have compromised p53 functioning because of changes in the genes encoding proteins concerned in p53 regulation. The mutation of *TP53* in CRC are usually missense mutations that impair wild-type p53 function.³⁸ Given the *DCC* gene, *DCC* rs2229080 variants play a significant role in colorectal cancer development.³⁹

Conclusion

The findings of the present study emphasize the need for comprehensive initiatives to reduce

CRC rates, especially in certain demographic and occupational groups. Early diagnosis and screening should give priority to high-risk groups including men and certain occupations. To understand these differences and develop better prevention and treatment methods, further study is necessary. These measures may minimize CRC incidence, improve outcomes, and reduce its burden on both individuals and society. In addition, our analysis reveals valuable information about genetic mutations in CRC-associated genes, highlighting numerous missense variants in *APC*, *KRAS*, *TP53* and *DCC* genes from the gnomAD and ICGC databases, and showcasing their interactions and mutation types. *APC* and *TP53* genes exhibit a variety of mutations, while *DCC* gene shows fewer clinically significant variations. Gene expression analysis and meta-survival data further indicate the importance of *APC* and *TP53* genes in CRC prognosis, underscoring the potential for these findings to guide future targeted therapies and diagnostic approaches.

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Authors' Contributions

BB collected data and supervised the project. BH designed the study and organized data. ZJH

Table 6. The expressions of *APC*, *KRAS*, *TP53* and *DCC* genes across CRC subtype

Tissue	<i>APC</i>		<i>KRAS</i>		<i>TP53</i>		<i>DCC</i>	
	P-value	Log2FC	P-value	Log2FC	P-value	Log2FC	P-value	Log2FC
Moderately-differentiated vs. well-differentiated	0.96	0.00	0.99	0.00	0.79	0.07	0.64	0.08
Moderately-differentiated vs. poorly-differentiated	0.52	-0.04	0.66	0.03	-0.98	0.01	0.10	-0.25
Well differentiated vs. poorly-differentiated	0.68	-0.04	0.73	0.03	-0.83	-0.06	0.11	-0.33

APC: Adenomatous Polyposis Coli, *KRAS*: Kirsten Rat Sarcoma Viral Oncogene Homolog, *TP53*: Tumor Protein 53, *DCC*: Deleted in Colorectal Cancer, CRC: Colorectal cancer

analyzed the data and wrote the manuscript. KHR wrote and submitted the manuscript. AS participated in the interpretation of data and editing the manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

None declared.

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