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ORIGINAL ARTICLE

Occurence of Mutation on KRAS, NRAS and BRAF in Patients with Colorectal Cancer

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Highlights:
(1) More than half of colorectal cancer patients had mutations.
(2) Mutations in the KRAS gene are the most frequent in patients of both sexes.
(3) With advancing age, women had a lower risk of BRAF mutations.

ABSTRACT

Study Objective: To investigate the profile of mutations in the KRAS, NRAS and BRAF genes among patients with colorectal cancer in the mid-west of the state of Santa Catarina. *Method*: This is a cross-sectional study that included all the medical records of patients diagnosed with stage IV colorectal cancer in a pathology laboratory between 2016 and 2021. The presence or absence of mutations in the KRAS, NRAS and BRAF genes were analyzed according to patient characteristics and stratified by gender. *Results*: The sample consisted of 244 patients in whom mutations were detected in 58.2%. Of these, 52.3% had a KRAS mutation, 8.1% in the NRAS gene, and 17.1% in BRAF. In males, KRAS mutations were observed in 48.5%, followed by NRAS and BRAF mutations, both with 8.2%. In females, 58.3% were KRAS mutations, 30.0% in the BRAF gene and 7.9% NRAS. The risk of KRAS mutations was higher among women aged 51-60 (PR=1.30; 95%CI:1.07-1.58), the risk of NRAS mutations was lower in men when left-sided (PR=0.94; 95%CI:0.90-0.98). BRAF mutations showed a lower risk among older women (p<0.001). *Conclusion*: There was a higher prevalence of mutations in the KRAS gene in both sexes. The mutations varied according to the sex and age of the patient, and the laterality of the tumor. Furthermore, BRAF gene mutations were more prevalent in women with right-sided tumors, while NRAS gene mutations were less prevalent in men with left-sided tumors.

Keywords: colorectal neoplasia; ras gene; colon adenocarcinoma; statistical interpretation of data.

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INTRODUCTION

Colorectal cancer (CRC) is a gastrointestinal malignancy that encompasses all neoplastic processes related to the subdivisions of the colon, rectosigmoid junction, rectum and anus[1]. It progresses slowly and is usually asymptomatic[2]. Currently, it is the third most common cancer overall[3] and shows increasing morbidity and mortality, resulting in therapeutic challenges in the treatment of this pathology. CRC is considered a common disease affecting the elderly, with most cases diagnosed during the 5th and 6th decades, and a higher prevalence among men, according to the World Health Organization[4].

About 30 to 50% of colorectal and rectum cancers globally are associated with genetic mutations. The RAS oncogene has a well-established role in cell growth as an oncogene, in cell cycle regulation, and in its functions, along with the inactivation of other genes such as tumor suppressors APC, DCC, and P535. Most Ras mutations (86%) are associated with the KRAS gene1. CRC carcinogenesis depends on various factors and pathways, including downregulation of tumor suppressor genes, incompatibility in repair genes, and activation of oncogenes. There are three known human isoforms: NRAS (neuroblastoma RAS viral (v-ras) oncogene homolog), HRAS (Harvey rat sarcoma viral oncogene homolog), and KRAS (Kirsten rat sarcoma 2 viral oncogene homolog). Molecular biology studies offer some advances in understanding the pathophysiology, diagnosis, and treatment of this type of cancer[5]. Molecular pathological analysis that identifies mutations in these genes is crucial for guiding the correct treatment for patients using targeted therapies.

KRAS is a GTPase regulated by a tyrosine kinase receptor EGFR (epidermal growth factor receptor). These receptors are responsible for stimulating the KRAS gene activity by binding to their respective ligands. When the inactive RAS binds to GDP, it allows GDP to be moved in favor of GTP, and the RAS becomes active. Thus, the activated KRAS protein initiates a signaling cascade promoting cell proliferation, as well as activating the NRAS and BRAF proteins (downstream) along the way. BRAF is a protein activated by the KRAS gene and it represents the main element in the RAF-MEK-ERK (MAPK) cascade, which is responsible for proliferation, differentiation, motility and several other cellular aspects, such as cytoskeletal components and transcription factors. The cascade is interrupted when the active RAS hydrolyzes GTP into GDP, converting the RAS to its inactive form. Mutations in the RAS gene that lead to late hydrolysis of GTP (by encoding a defective GTPase), promote increased signaling and consequently proliferation, leading to tumor development[1].

Approximately 15%-30% of patients with CRC present with metastases, and 20%-50% of patients with initially located disease will develop metastases[7]. Genetic analysis of mutations in patients with stage IV (metastatic) colorectal cancer is justified because targeted therapy with Epidermal Growth Factor Receptor (EGFR) inhibitors is ineffective in patients with mutations in the KRAS, NRAS or BRAF genes[8]. Molecular analysis for mutations in KRAS, NRAS, as well as BRAF mutations, is highly advised in all patients at the time of diagnosis of metastatic CRC, due to its relevance in selecting first-line therapy[9]. Since these mutations are negative predictors for the use of anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs), RAS testing is mandatory before starting this treatment[7].

In this sense, this study aims to investigate the mutation profiles in the KRAS, NRAS, and BRAF genes among patients with colorectal cancer in the Midwest region of the state of Santa Catarina from 2016 to 2021.

MATHERIALS AND METHOD

The method employed to conduct this study consisted of a cross-sectional survey based on secondary data. All the medical records of patients diagnosed with stage IV colorectal cancer at a pathology laboratory in the Midwest of Santa Catarina between 2016 and 2021 were included.

The laboratory that provided the medical records for the study receives patients referred from oncology services that treat patients from the Unified Health System (SUS) in all the municipalities belonging to the mid-western region of Santa Catarina, as it is a reference service in oncology within the Health Care Networks (RAS).

After selecting the medical records that met the inclusion criteria (histology of adenocarcinoma of the colon or rectum), the relevant information was entered onto a standard form. This information included the following characteristics: the patient's age group (in complete years), gender (female/male), laterality of the primary lesion (right, left, both sides), site of the lesion and the presence or absence of mutations in the KRAS, NRAS and BRAF genes.

The data collected was scanned into an Excel spreadsheet and then transferred to the statistical program Stata 13 for the following analyses.

Initially, a descriptive analysis of the study variables was carried out. Pearson's chi-square test and Fisher's exact test were used. The percentages of mutations detected and their classification according to type: NRAS, KRAS and BRAF according to gender were presented in graphs.

Finally, the factors associated with each type of mutation (NRAS, KRAS and BRAF) were assessed using Poisson Regression with robust variance adjustment. The measure of effect used was the prevalence ratio, followed by the 95% confidence interval. In the adjusted analysis, the variables were controlled for patient age and tumor laterality. The level of statistical significance adopted was 5% for two-tailed tests.

This study was submitted to and approved by the Human Research Ethics Committee of the Universidade do Oeste de Santa Catarina, under protocol no. 5.080.642

RESULTS

A total of 254 patients were identified during the study period. After excluding 09 medical records with cases of signet ring carcinoma and 01 patient with a primary lung site, the final study sample consisted of 244 patients. The majority were male (58.2%) and aged between 51 and 60 years (32.2%). Molecular analysis revealed a mutation in 58.2% of patients. Regarding laterality, 71.6% of the primary cancer sites were located on the left side, while 28.4% were located on the right side. Among patients who underwent genetic mutation analysis, 52.3% had a mutation in the K-RAS gene, 8.1% in the NRAS gene, and 17.1% in the BRAF gene (Table 1).

Table 1 – Description of the main characteristics of the sample stratified by the patient's sex. Joaçaba, SC, 2022. (n=244)

Characteristic	Total (%)	Male (%)	Female (%)	P-value
Age (Years)				0,915*
26-50	56 (22,9)	33 (58,9)	23 (41,1)	
51-60	79 (32,2)	45 (57,0)	34 (43,0)	
61-70	53 (21,6)	33 (62,3)	20 (37,7)	
≥71	57 (23,3)	32 (56,1)	25 (43,9)	
Presence of mutation				0,044*
Detected	142 (58,2)	75 (58,2)	67 (47,2)	
Not detected	102 (41,8)	67 (65,7)	35 (34,3)	
K-RAS Mutation	112 (52,3)	63 (56,2)	49 (43,8)	0,158*
N-RAS Mutation	09 (8,1)	6 (66,7)	3 (33,3)	0,631#

BRAF Mutation	21 (17,1)	6 (28,6)	15 (71,4)	0,002#
Laterality				0,001#
Right	65 (26,6)	29 (44,6)	36 (55,4)	
Left	164 (67,2)	108 (65,8)	56 (34,2)	
No data	14 (5,7)	04 (28,6)	10 (71,4)	
Both sides	01 (0,4)	01 (100,0)	0 (0,0)	
Total	**244 (100,0)**	**142 (58,2)**	**102 (41,8)**	

*Chi-squared test; # Fisher's exact test

The prevalence of mutations according to the patient's sex is shown on Figure 1. Among the male patients who underwent molecular analysis, mutations in the KRAS gene were observed in 48,5% of them, followed by NRAS gene mutation and BRAF genes, both with 8,3%. In females, the prevalence was 58,3% in the K-RAS gene, 30,0% in the BRAF gene and 7,9% in the N-RAS gene.

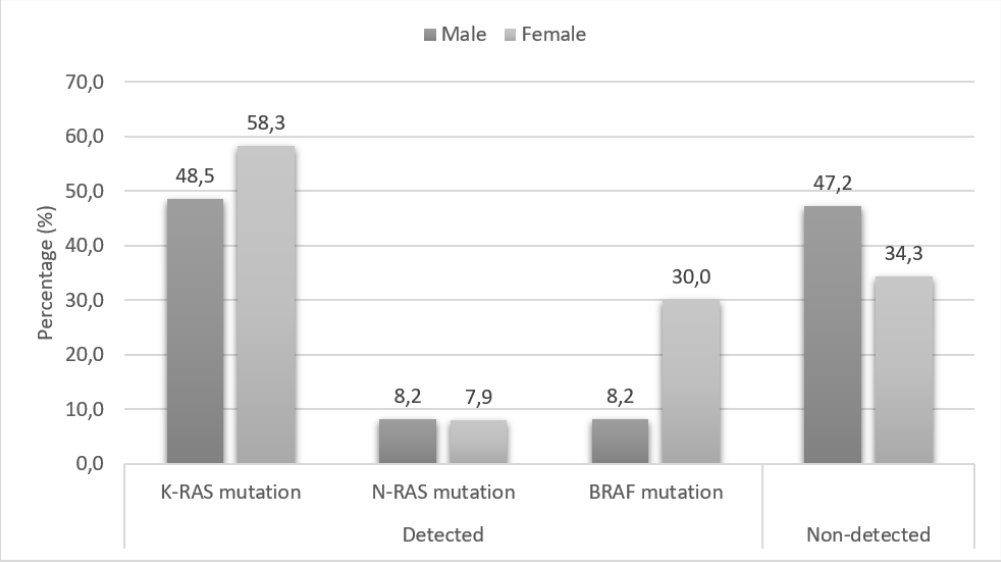

Figure 1 – Prevalence of mutations according to the sex of the patient who underwent the test.

Finally, the factors associated to each of the mutations and their behavior according to the patient's sex were analyzed (Table 2). Regarding the K-RAS gene mutation, after adjustment for confounding factors, it was found to be associated with the patient age solely in female patients, demonstrating that women between the ages of 51 and 60 had a higher risk of having this mutation (PR=1.30; 95% CI: 1.07-1.58). N-RAS gene mutation is associated with the laterality only in males, indicating lower risk of mutation on left-sided laterality (PR=0,94; CI95%: 0,90-0,98). As for the BRAF gene mutation, there was a trend with increasing age, with a lower risk of this type of mutation in older women (p<0.001).

Tabela 2 – Crude and adjusted analysis of factors associated with the occurrence of K-RAS, N-RAS and BRAF mutations according to the patient's sex. Joaçaba, SC, 2022

	K-RAS Mutation PR (CI95%)		N-RAS Mutation PR (CI95%)		BRAF Mutation PR (CI95%)	
	MALE	**FEMALE**	**MALE**	**FEMALE**	**MALE**	**FEMALE**
Age (years)	p=0,572	p=0,025	p=0,892	p=0,322	p=0,233	p<0,001*
26-50	1,00	1,00	1,00	1,00	1,00	1,00
51-60	0,94 (0,79-1,11)	1,30 (1,07-1,58)	1,01 (0,92-1,10)	1,06 (0,89-1,26)	0,95 (0,85-10,6)	0,86 (0,75-0,98)
61-70	0,92 (0,77-1,09)	1,24 (0,98-1,57)	0,97 (0,86-1,10)	1,15 (0,96-1,38)	1,02 (0,96-1,08)	0,70 (0,58-0,85)
≥71	0,87 (0,72-1,04)	1,09 (0,86-1,39)	0,97 (0,86-1,09)	1,16 (0,95-1,37)	1,03 0,97-1,10)	0,62 (0,51-0,77)
Laterality	p=0,060	p=0,246	p=0,013	p=0,831	p=0,066	p=0,978
Right	1,00	1,00	1,00	1,00	1,00	1,00
Left	1,15 (0,99-1,34)	1,10 (0,93-1,39)	0,94 (0,90-0,98)	0,99 (0,93-1,06)	0,97 (0,94-1,00)	0,99 (0,93-1,20)

PR: Adjusted prevalence ratio, CI95%: Confidence Interval of 95%

DISCUSSION

Most of the results of this study support the current literature on the behavior of colorectal cancer in patients with genetic mutations in the KRAS, NRAS and BRAF genes. In accordance with the CRC screening guidelines established by the Brazilian Ministry of Health, the data analysis of this study showed a predominance of individuals over 50 years of age[10] with the disease, reaffirming the prevention and early detection measures included in these guidelines. The literature shows that the risk of colorectal cancer increases with age and is common in people over the age of 50, and in people over the age of 60, the most common malignancies are lung cancer (21%), colorectal cancer (9%), stomach cancer (9%), and liver cancer (9%)3 respectively. It has also been shown that the median age at diagnosis of CRC is 72 years for women and 68 years for men.

When analyzing the "sex" variable, this study found a higher prevalence of CRC in men, in agreement with the data of the 2020 Estimation of the José Alencar Gomes da Silva National Cancer Institute (Inca)2, which, excluding non-melanoma skin cancer, lists CRC in men as the second most common cancer in the Southeast (28.62/100,000) and Midwest (15.40/100,000) regions. These regions have similar cultural practices to the southern region of Brazil, where CRC is the third most common tumor (25.11/100,000), serving as an epidemiological indicator for the state of Santa Catarina. Thus, according to Mattiuzzi et al. (2019)[3], men in Brazil have a 50% increased risk of developing colorectal cancer compared to women (risk from 0 to 74 years is 2.75% for men and 1.83% for women, respectively). In addition, according to INCA[2] data, the distribution of incidence by geographic region indicates that the South and Southeast concentrate 70% of cancer incidence, and the pattern of cancers is similar to that of developed countries, in which prostate, female breast, lung, colon and rectum predominate. Among the female population, CRC is the second most common in the Southeast (26.18/100,000) and South (23.65/100,000) regions, but still shows a predominance of incidence in men compared to women[6]. In some countries, such as Iran, women have a higher prevalence of CRC compared to men[11], contrary to the data found in this study in an analysis of the profile of the population of the Midwest of Santa Catarina, indicating that other factors may be associated with the development of such tumors, including lifestyle issues, specifically an inadequate

diet, a low intake of calcium and vitamin D12, physical inactivity, smoking and alcohol consumption[13], ethnicity, cultural practices and purchasing power, which supports Caló et al. (2022)14, who described that the mesoregions with the best socioeconomic development are associated with higher CRC mortality rates.

Some national studies claim that Brazilian women have a predominant prevalence of CRC in the right colon to the detriment of the left, contrary to the results of this study in which most primary sites in women were on the left. In addition, in an analysis of gender and laterality, Tsai (2018)15 cited a higher incidence of right colon cancer in women than in men. This may be related to the fact that BRAF mutations are frequently observed in right colon cancer, in agreement with what was observed in this study, and these mutations are more frequent in women than in men. However, in the analysis performed on the sample studied in this article, there is no evidence of increased risk of mutation associated with right-sidedness between men and women. Regarding the location of the tumors in the patients studied, the left colon is most affected, with an emphasis on the sigmoid colon. There is disagreement in the literature regarding the prevalence of laterality of colon and rectal tumors. While some Brazilian studies show a higher overall prevalence of right-sided CRC[16], others confirm what was observed in this study, with a prevalence of 5 left colon tumors to 1 right colon tumor[10].

The data showed a gender difference in the presence of mutations in the BRAF gene and in the laterality of the tumor, with a prevalence of BRAF mutations in women and an incidence on the right side. This finding occured in other studies reviewed in the national literature. Consistent with the statistical information presented in this study, Tsai et al (2018)15 found significant differences between male and female patients in terms of tumor location ($p<0.0001$) and pathological stage ($p=0.011$). Female patients had significantly more BRAF gene mutations (6.4VS. 3.3%, OR 1.985. $p= 0.006$), as well as a higher prevalence of right-sidedness and diagnosis at more advanced stages. Studies show that the laterality of colorectal cancer affects the patient's quality of life, with right-sided tumors having worse symptoms, thus affecting survival, and being associated with advanced age and BRAF mutations.16 From the molecular perspective, right-sided colon neoplasms have a greater number of mutations in intracellular signaling pathways and carry more microsatellite instabilities resulting from genetic and epigenetic inactivation of DNA repair enzymes. The explanation for the different behavior in laterality comes from embryological differentiation, while the right colon is derived from the middle intestine, the left colon is derived from the posterior section of the intestine. Thus, each of these structures has its own genetic microenvironment, making them phenotypically different[8]. When studying the relationship between women with mutations in the BRAF gene and increasing age, there was a decrease in the risk of mutations with age, contrary to the literature, since cancers associated with BRAF mutations are associated with microsatellite instability, and these are associated with advanced age (women over 70) according to Tsai (2018)15, in relation to the protection offered by estrogen in younger women cited by Lindblom.

In addition, the data collected in this study revealed that male patients had a higher prevalence of mutations in the RAS genes compared to females, which was corroborated by Tsai (2018)15, with more mutations in the NRAS gene in men (5.1 vs. 2.3%, OR 2.227, $p=0.012$). However, when associated with laterality in the analysis by Tsai (2018)15, men with tumors on the left had a lower incidence of NRAS gene mutations, in line with what was observed in this study, while tumors on the left were shown to be protective factors for NRAS mutations in men. Based on this information, knowing the location of the tumor increases the chances of improving the patient's quality of life by targeting treatment more specifically. Studies show that anti-EGFR therapy, which targets the epidermal growth factor receptor, has less benefit on the right side, but when other factors are considered, such as mutations in the BRAF and NRAS genes, multivariate analysis shows that these factors predominate, and laterality is insignificant[16]. Therefore, treatment depends on numerous factors, not just laterality,

such as tumor stage, patient age, region within right and left laterality, among others. According to Dr. Michael Lee, right-sided colon tumors have a worse survival rate and are more often associated with advanced age (advanced age was shown to be a protective factor in women with mutated BRAF in the present study) and BRAF mutation, factors that in themselves are poor prognostic factors in multivariate analysis[17]. Other factors, such as low expression of EGFR ligands (EREG and AREG), are also more common in right-sided tumors and may therefore have an impact on the efficacy of anti-EGFR therapy.

Since 1990, it has been proposed that the distal and proximal locations of colon or rectal tumors may have different biological, epidemiological, pathological, and prognostic aspects[16]. Currently, data on the prognosis of right or left colon cancer are conflicting; however, most studies reveal worse survival rate when the primary tumor is located on the right side. The author also cites Benedix et al, who found only a small effect of location[2]. This was corroborated by Weiss et al. who found no difference in prognosis between right and left after adjusting for age, gender, comorbidity, and postoperative adjuvant chemotherapy.

Regarding the KRAS gene, most patients had a mutation in this gene (52.3%), confirming the literature that affirms KRAS has the highest rate of all mutations among the three isoforms of the RAS gene[6]. Additionally, there was a predominance of mutations in KRAS in both sexes, but women over the age of 50 were more likely to have mutations in this gene than men.

The epidemiological profile related to colorectal cancer is crucial for the outcome of this disease, as demonstrated by this study and by Mattiuzzi (2019)[3], when stated that in-depth and accurate knowledge of the epidemiology of cancer provides essential information on the potential causes and population tendencies of these conditions, allowing the establishment of appropriate health interventions for the development of efficient prevention, screening and diagnosis policies.

Furthermore, molecular analysis of the genes that activate cell proliferation is essential for a proper therapeutic process for patients with CRC undergoing clinical treatment, and facilitated access to this test is necessary, given that the global estimate for 2020 was more than 1.9 million new cases of colon and rectal cancer (10.0%), corresponding to the third most incident tumor among all cancers INCA, 202218.

CONCLUSION

We concluded that there is a high prevalence of mutations in the KRAS gene in both sexes of patients with CRC. In addition, the BRAF gene has a higher presence of mutations in women with right-sided tumors and in men, mutations in the NRAS gene on the left side are less prevalent. In conclusion, the analysis of the mutational profile makes it possible to assess the prevalence of risk factors and highlight the attention factors that should be considered when diagnosing patients, covering their cultural aspects, dietary habits and ethnicity, considering each patient individually, with a diet and exposures common to a group living in the area circumscribed in the Midwest of Santa Catarina, given that this population has some particular manifestations in the CRC profile compared to other national and global territories.

There is an increasing tendency of CRC in the Southern Region of Brazil, in both sexes and in the young adult age groups, from the age of 40 years, with a greater increase in mortality from the age of 70 years in men and 80 years in women, given the importance of defining early interventions to reduce mortality from CRC[11]. It is necessary to develop new drugs capable of acting on other receptors or even downstream pathways to treat patients with mutations in the KRAS, NRAS and BRAF genes, since more than half of patients have mutations in one of these genes, especially the KRAS gene, and have a worse response to treatment with targeted drug therapy.

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Nádia Aparecida Lorencette: Conceptualization; Data curation; Methodology; Resources.

Luana Patrícia Marmitt: Formal analysis; Software; Validation; Visualization; Writing – original draft; Writing – review & editing.

Paula Brustolin Xavier: Validation; Writing – review & editing.

Marcelina Mezzomo Debiasi: Data curation; Investigation; Methodology; Project administration; Software; Supervision; Validation; Writing – original draft; Writing – review & editing.

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