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# ASSOCIATION BETWEEN SMOKING AND KRAS STATUS IN METASTATIC COLORECTAL CANCER

**Mohammad Ahmad Telfah*, Mohammad Said Alkader, Habeeb Lutfi Etewi, Manar Hasan Hayajneh and Ahmad Taher Alkhladi**

***Corresponding Author: Mohammad Ahmad Telfah**

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## ABSTRACT

**Backgroung**: Colorectal cancer (CRC) is one of the most common cancer worldwide and affecting the mortality, Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation is the most common mutation in CRC, its occurrence may reach 45% of all CRC. Detecting KRAS mutation predicts the response of treatment. Smoking can affect the molecular subtype of CRC such as KRAS wild type, raf murine sarcoma viral oncogene homolog B (BRAF) mutant, microsatellite instability-high (MSI-H), and 5'-C-phosphate-G-3' island methylator phenotype (CIMP) positive tumors. **Material & Methods**: This retrospective study analyzed the medical records of 129 mCRC diagnosed between 2017 and 2022 at the Military Cancer Center (MCAC). The clinical and pathological characteristics of the patients were recorded, including age, gender, primary tumor location, smoking, KRAS status and metastatic site. **Results**: most of the patients had left sided tumor 107 (82.9%), KRAS mutations were detected in 52 patients (40.3%), the most common mutation was gly12asp in 19 patients, and 59 patients (45.7%) were smokers. the most of smoking patients were associated with KRAS wild type (72.9%), while 34 patients (48.8%) were not smoker (P=0.005). the site of tumor is associated with KRAS status, KRAS was wild type in 8 patient (36.4%) in the right side tumor, while 69 patients (64.5%) were KRAS wild type in left side tumor (P=0.01). Left sided colorectal cancer had a more risk to develop KRAS wild type than right sided colorectal cancer (OR= 3.71, 95%CI: 1.36 – 10.2, P=0.01), and smoker patients were at more risk to have wild type colorectal cancer than not smoker patients (OR= 3.16, 95%CI: 1.46 – 6.87, P=0.004). **Conclusion**: smoking and left sided tumor are associated with KRAS wild type CRC, and both of them increase its risk.

**KEYWORDS**: colorectal cancer, metastatic colorectal cancer, KRAS mutant, KRAS wild type, smoking.

## INTRODUCTION

CRC is the 3rd most common malignancy worldwide, and its incidence has increased in Jordan over the past few decades.[1,2] In Jordan, CRC is the most common cancer among men and the second most common cancer among women.[2] KRAS, NRAS, and BRAF mutations have been shown to play an important role in the pathogenesis of CRC, and their detection has become a routine part of the diagnostic workup in many countries.[3] This is because these biomarkers are the primary predictors of how metastatic colorectal cancer (mCRC) patients will respond to targeted therapy with anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (MAbs).[4] However, there is limited data on the prevalence of these mutations in Jordanian patients with colon cancer.

The RAS family of oncogenes comprises; KRAS, NRAS, and HRAS genes, whose proteins are critical for cellular processes such as cell division, differentiation, and apoptosis.[5] These genes experience activating mutations in approximately 85%, 15%, and less than 1% of all RAS mutations found in human tumors. In around 30-40% of CRC, a mutated KRAS gene is considered a crucial genetic change driving the progression from adenoma to CRC.[5]

Smoking is a modifiable risk factor for CRC and smokers have a higher risk for CRC mortality than not smokers, Also smoking can affect the molecular subtype of CRC such as KRAS wild type, BRAF mutant, MSI-H, and CIMP+ tumors.[6]

Our study aimed to assess the association between smoking and KRAS mutation status in CRC patients, and further analysis to assess the site of tumor and KRAS mutation status.

## MATERIALS AND METHODS

### Study Design

This retrospective study analyzed the medical records of 129 mCRC diagnosed between 2017 and 2022 at the Military Cancer Center (MCAC). The tumors were analyzed for KRAS mutations using quantitative polymerase chain reaction from an accredited diagnostic laboratory at Jordan University Hospital. The clinical and pathological characteristics of the patients were also recorded, including age, gender, primary tumor location, smoking, and metastatic site.

The identification of the primary tumor location was based on the following: (1) right-sided tumors were characterized by the primary tumor's location in the cecum, ascending colon, hepatic flexure, and transverse colon; (2) left-sided tumors were classified by the primary tumor's location in the splenic flexure, descending colon, sigmoid colon, and rectum.

### Statistical Analysis

Descriptive statistics were used to summarize the patient's characteristics. Categorical data were expressed using frequencies and percentages. Numerical data were described as the mean and standard deviation or the median and range, as appropriate. The chi-square test was used to assess the association between KRAS mutation and patients' disease characteristics. Binary logistic regression test was used to assess the odd ratio (OR) and 95% confidence interval (CI) for developing wild type colorectal cancer.

### Ethical Considerations

This is an observational retrospective study. All patients were managed under routine clinical practice. The Institutional Review Board (IRB) at the Jordanian Royal Medical Services in Amman, Jordan, approved the current study.

## RESULTS

### Description of study population

Table 1 shows the patients characteristic including the age, gender, site of tumor, smoking status, KRAS status, and site of metastasis. The mean age of population was 52.8 ± 12.4 years, median age was 54, ranging from 19 to 83. Male patients were 78 (60.5%), most of the patients had left sided tumor 107 (82.9%), KRAS mutations were detected in 52 patients (40.3%), the most common mutation was gly12asp in 19 patients, and 59 patients (45.7%) were smokers.

The most common site of metastasis was liver, observed in 81 patients (62.8%), followed by lung metastasis in 42 patients (32.6%), peritoneal metastasis was observed in 18 patients (14%).

**Table 1: patients' characteristic.**

| Variables | | Number (%) |
|---|---|---|
| Age | Mean: 52.8 ± 12.4, median: 54, range: 19 – 83 | |
| Gender | Male | 78 (60.5) |
| | Female | 51 (39.5) |
| Site | Right | 22 (17.1) |
| | Left | 107 (82.9) |
| KRAS status | Wild | 77 (59.7) |
| | Mutant | 52 (40.3) |
| Smoking | Not smoker | 70 (54.3) |
| | Smoker | 59 (45.7) |
| Lung metastasis | No | 87 (67.4) |
| | Yes | 42 (32.6) |
| Liver metastasis | No | 48 (37.2) |
| | Yes | 81 (62.8) |
| Peritoneal metastasis | No | 111 (86) |
| | Yes | 18 (14) |
| Other metastasis | No | 121 (93.8) |
| | Yes | 8 (6.2) |

Other metastasis include: brain, ovary, bone, and bone marrow.

### Association between patients' characteristics and KRAS mutation

The Chi-square test revealed statistical significant association between the site of tumor and the KRAS status, KRAS was wild type in 8 patient (36.4%) in the right side tumor, while 69 patients (64.5%) were KRAS wild type in left side tumor (P=0.01). Also smoking status was significantly associated with KRAS status, the most of smoking patients were associated with KRAS wild type (72.9%), while 34 patients (48.8%) were not smoker (P=0.005) while other factors were not associated with KRAS status. Table 2.

**Table 2: The association between patients' characteristics and KRAS mutation.**

| Variable | | KRAS wild type (%) | KRAS mutant (%) | Total number | P-value |
|---|---|---|---|---|---|
| Gender | Male | 45 (57.7) | 33 (42.3) | 78 | 0.56 |
| | Female | 32 (62.7) | 19 (37.3) | 51 | |
| Site | Right | 8 (36.4) | 14 (63.6) | 22 | 0.01 |
| | Left | 69 (64.5) | 38 (35.5) | 107 | |
| Smoking | Not smoker | 34 (48.8) | 36 (51.4) | 70 | 0.005 |
| | Smoker | 43 (72.9) | 16 (27.1) | 59 | |

Binary logistic regression revealed that the risk of developing KRAS wild type colorectal cancer were more in smoker patients and left sided tumor.

Left sided colorectal cancer had a more risk to develop KRAS wild type than right sided colorectal cancer (OR= 3.71, 95%CI: 1.36 – 10.2, P=0.01), and smoker patients were at more risk to have wild type colorectal cancer than not smoker patients (OR= 3.16, 95%CI: 1.46 – 6.87, P=0.004). Table 3.

**Table 3: the risk for KRAS wild type colorectal cancer.**

| | OR | 95% CI | | P-value |
|---|---|---|---|---|
| | | lowest | highest | |
| Left side | 3.71 | 1.36 | 10.2 | 0.01 |
| Smoking | 3.16 | 1.46 | 6.87 | 0.004 |

## DISSCUSSION

In this retrospective study at the Military Cancer Center in Jordan, smoking is strongly associated with KRAS wild type CRC more than KRAS mutant type, and the left side CRC are more prone for developing KRAS wild type than right sided tumors.

A prospective study of 41,836 women patients diagnosed with CRC showed a statistical significant association between smoking and KRAS wild type tumor, further more smoking-related risk like age at initiation of smoking, number of cigarette smoking, and number of pack per year were strongly associated with KRAS wild type CRC more than KRAS mutant type.[7] Another study revealed there is no association between smoker and KRAS status in CRC, but it found smoking of 20 cigarettes per or more associated with increase the risk of KRAS wild type tumor only among men.[8] Similar to our result, smoking is strongly more associated with KRAS wild type tumor than KRAS mutant type tumor. Smoking is also associated with other molecular subtype of CRC, it increase the risk of BRAF mutant type (OR=3.16, 95%CI= 1.80-5.54), and CIMP positive tumor (OR=2.06, 95%CI= 1.43 – 2.97) especially in heavy smokers.[9]

KRAS mutation is commonly associated with the sided of tumor, as known KRAS mutant type commonly presents in the right sided tumor, while left sided often has KRAS wild type, in our study left side tumor had a more risk to develop KRAS wild type tumor than KRAS mutant type (OR=3.71, 95%CI: 1.36 – 10.2, P=0.01). Other studies focus on the association between the right sided tumors and KRAS mutation, representing the right sided tumor is at more risk to develop KRAS mutation than left sided tumor (OR=2.56, 95% CI: 1.90–3.44, P<0001), also KRAS mutations have poor prognostic value on overall survival and disease free survival.[10]

Also a meta-analysis of 16 studies provided that the KRAS mutation is frequently associated with right sided tumor (OR = 1.68, 95%CI = 1.50–1.88, P < 0.01), without any significant heterogeneity across the studies.[11]

## CONCLUSION

This retrospective study demonstrated the effect of smoking in molecular subtype of CRC, focusing on KRAS wild type CRC. It also presented the significance of the site of tumor and its association with KRAS mutation status.

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