International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319-6718, ISSN (Print): 2319- 670X
www.ijpsi.org Volume 12 Issue 5 ǁ Sep. –Oct., 2023 ǁ PP. 14-23

Colon Cancer in Republic of North Macedonia – Status, Trends, and Geographic Distribution

Sanja Sazdovska, PhD

ABSTRACT
Globally, colorectal cancer (CRC) is one of the most common types of cancer. According to the Global Cancer Statistic in 2020, CRC ranks third, representing 10,0 % of newly diagnosed cases (6.0 % for colon cancer and 3.8 % for rectum cancer), and occupies the second position in terms of mortality with 9.4% (5.8 %for colon cancer and 3.44 for rectum cancer). More than half of the cases manifest in developed countries. To be more specific, regions in the world with the highest Human Development Index (HDI) exhibit, for both genders, CRC incidence and CRC-related mortality rates, that are at least twice as high as those observed in regions with a lower HDI. Globally, colorectal cancer (CRC) is the third most common cancer and the second deadliest cancer, causing 1.9 million incidents and 0.9 million deaths in 2020. The incidence of CRC is elevated in highly developed countries and is increasing in middle and low-income countries due to the influence of Western countries. The primary objective of this paper is to present the status, trend, and geographical distribution of CRC in the Republic of North Macedonia (RNM) during the period 2014-2021. The national study on CRC in the Republic of North Macedonia is a cross-sectional analytical study. The analysis refers to the period 2014-2021, coinciding with the establishment of the National System for Electronic Records in Healthcare - My term. The data source for the national CRC study consist of the comprehensive healthcare databases within the National System for Electronic Records in Healthcare - My term, and mortality statistic provided by the State Statistics Office of the Republic of North Macedonia in the period 2014-2021. Selection criteria and sample size. For the CRC study, the research sample comprises all individuals who, during the implementation period, were documented in the electronic system (e-system) My Term by their attending physician, in relation to healthcare services or interventions associated with a CRC diagnosis. This paper demonstrates an upward linear trend in the incidence of colon cancer in the Republic of North Macedonia from 2014 to 2021. The incidence increased from 9.24 per 100,000 in 2016 to 37.98 per 100,000 in 2018. In terms of CRC incidence, the highest rates were observed in 2021 in the Vardar region (42.56 per 100,000), followed by the Skopje region (37.84 per 100,000), while the lowest incidence occurred in the Polog region (14 per 100,000). Over the entire period (2014-2021), the highest prevalence was recorded in the Pelagonian region (217.4 per 100,000). In conclusion, the study showed that the incidence of CRC in RNM in the period 2014-2021 shows an upward linear growth trend with a predominance of patients over 65 years of age, a greater number of male patients as well as a more frequent occurrence among those living in urban areas.

Keywords: *colorectal cancer, mortality, morbidity, incidence, prevalence*

Date of Submission: 15-10-2023 Date of acceptance: 31-10-2023

I. INTRODUCTION

Globally, colorectal cancer (CRC) is one of the most common types of cancer. According to the Global Cancer Statistic in 2020, CRC ranks third, representing 10,0 % of newly diagnosed cases (6.0 % for colon cancer and 3.8 % for rectum cancer), and occupies the second position in terms of mortality with 9.4% (5.8 % for colon cancer and 3.4 % for rectum cancer). [1] More than half of the cases manifest in developed countries. [2] To be more specific, regions in the world with the highest Human Development Index (HDI) exhibit, for both genders, CRC incidence and CRC-related mortality rates, that are at least twice as high as those observed in regions with a lower HDI.[3] In 2020, colorectal cancer (CRC) is anticipated to be the third most common and second-deadliest cancer worldwide. It will cause 1.9 million new cases of the disease and 0.9 million deaths.[4] The incidence of CRC is elevated in highly developed countries and is increasing in middle and low-income countries due to the influence of Western countries. Furthermore, it is imperative to note that there is an increased incidence of early stage of CRC. As the number of cases of CRC increases, public health concerns are escalating worldwide. Thus, emphasizing the significance of raising awareness regarding CRC becomes pivotal in advocating for healthier lifestyles, devising novel strategies for the management of CRC, and establishing comprehensive global screening initiatives. These endeavors are instrumental in the prospective mitigation of morbidity and mortality associated with CRC.[5] The incidence, prevalence, and mortality rates of the colorectal

cancer (CRC) exhibit considerable variation, exceeding a tenfold difference across various regions worldwide. Data concerning CRC in the year 2020 for both genders, reveal that Japan is the country with the most elevated incidence rate of 117.4 per 100,000 inhabitants, coupled with a mortality rate of 47.4 per 100,000 inhabitants.[6] Portugal and Hungary occupy the second and the third positions in this regard, with incidence of 103 and 101.4 cases per 100,000 inhabitants, accompanied by mortality rates of 42.4 and 50.5 per 100,000 inhabitanst, respectively.[7] On a global scale, CRC ranks as the third most prevalent cancer among men and the second most prevalent among woman. Notably, in ten out of the 191 countries worldwide, CRC stands as the most frequently diagnosed malignancy in males. According to data from the World Health Organization (WHO) in 2018, there were over 1.8 million new cases of CRC diagnosed globally, constituting approximately 11 % of all newly diagnosed malignancies, with a total of 861.000 deaths.[8] It is pertinent to underscore that the rates are significantly higher among men in comparision to woman.[9] Preventing colorectal cancer is feasible through achieving a substantial rate of early detection, which in turn leads to successful treatment. Analyzing epidemiological factors, including gender, age, family predisposition, obesity, physical activity, and other parameters, plays a pivotal role in accurately portraying the scope of this issue in our country.[10] It should be noted that malignant neoplasms are the second most common cause of death in the Republic of North Macedonia (RNM), ranking just behind circulatory diseases. Within the framework of the International Classification of Diseases, Injuries and Causes of Death – ICD10 (International Classification of Diseases 10th Revision), the morbidity and mortality associated with CRC are categorized under the following specific diagnostic codes: C18 (for colon carcinoma), C19 (for recto-sigmoid carcinoma), C20 (for rectum carcinoma), and C21 (for anus carcinoma).

RESEARCH SUBJECT

The focus of this paper is to provide an overview of the status, emerging trends and geographic distribution related to morbidity and mortality of CRC in the Rebulic of North Macedonia.

II. MATERIALS AND METHODS

The national study on CRC in the Republic of North Macedonia is a cross-sectional analytical study. The analysis refers to the period 2014-2021.

The data source for the national CRC study consist of the comprehensive healthcare databases within the National System for Electronic Records in Healthcare - My term, and mortality statistic provided by the State Statistics Office of the Republic of North Macedonia in the period 2014-2021.

For the CRC study, the research sample comprises all individuals who, during the implementation period, were documented in the electronic system (e-system) My Term by their attending physician, in relation to healthcare services or interventions associated with a CRC diagnosis.

III. RESULTS AND DISCUSSION

It has been determined that the data on colon cancer have been analyzed using ICD C18, which identifies the situational analysis of colon cancer during the research phase of this study. It is intended that further research in this field will focus on the situation when it comes to rectosigmoid cancer, rectal cancer, and anal cancer, which are all part of ICD 19 and 20.

The analysis of the colon cancer morbidity encompasses data sourced from the National System for Electronic Records in Healthcare – My Term, spanning the period from 2014 to 2021. As the My Term program commenced in 2014, the numbers recorded for this specific year (Table 1) encompass both the newly diagnosed cases and all other instances of colon cancer entered the system for various purposes, including monitoring or interventions.

For the eight-year period (2014–2021), the analyses revaled that a total of 3.685 (100%) cases of colon cancer were documented. Further examination of the entire period, 20214–2021, indicated that the lowest number, 191 cases (5.2%), was recorded in 2015, followed by 222 cases (6.0%) in 2016. The number of newly reported colon cancer cases escalated notably in 2018 and 2019, reaching 788 cases (21.4%) and 721 cases (19.6%), respectively, nearly doubling the cumulative count of 392 cases (14.9%) documented in 2014. A marked decrease in the number of colon cancer cases was observed in 2020, with 400 cases (10.85%), likely attributed to the impact of the COVID-19 pandemic. Subsequently, in 2021, the number of new cases increases significantly once more to 648, approaching the highest levels recorded since 2018/2019. This upswing in the colon cancer incidence in 2021 can be attributed to the intermittent relaxation of COVID-19 measures and the intend to restore the healthcare services to pre-pandemic levels. Thus, in turn, led to increased patient mobility and the number of medical visits and examinations (Table 1).

Table 1. Rate of change, incidence, and period prevalence of colon cancer (2014-2021) in RNM

ICD10 - C18				
Years	**N (%)**	**Change rate**	**Incidence/ 100,000**	**Prevalence period/ 2014-2021**
2014	392 (10,64%)	-	18,99*	177,79 / 100,000
2015	191 (5,18%)	↓51,3%	9,24	
2016	222 (6,02%)	↑16.2%	10,72	
2017	323 (8,76%)	↑45.5%	15,58	
2018	788 (21,38%)	↑143,9%	37,98	
2019	721 (19,57%)	↓8,50%	34,73	
2020	400 (10,85%)	↓44,52%	19,33	
2021	648 (17,58%)	↑62,0%	31,32	
Total	**3685**		*cumulative	

The rate of change (increase/decrease) in the number of colon cancer cases in the current year compared to the previous one is detailed in Table 1 as follows:

- A rate of decline of ↓51.3% in 2015 compared to 2014 (as anticipated due to the cumulative number of cases in 2014);
- A growth rate of ↑16.2% in 2016 compared to 2014;
- A growth rate of ↑45.5% in 2017 compared to 2016;
- A supstantial growth rate of ↑143.9% in 2018 compared to 2017;
- A decline of ↓8.5% in 2019 compared to 2018;
- A decline of ↓44.5% in 2020 compared to 2019;
- A noteworthy increase of ↑62% in 2021 compared to 2020.

During the period from 2015 to 2018, each successive year exhibited an increasing rate of change in comparison to the preceding year. This trend is particularly noticeable in 2018, where the growth rate of newly registered cases of colon cancer, in contrast to 2017, soared to 143.9% (Table 1). However, in 2019, a modest decline of 8.5% was observed compared to 2018. This decrease may not be considered as an absolute optimistic sign, it is essential to acknowledge the possibility of fluctuations influenced by various factors, including administrative ones.

The analysis of the rate of change in 2018 and 2019, which coincided with the period of the highest number of registered cases, when compared to 2015, which had the lowest number of registered cases, revealed a significant increase in new cases of colon cancer. Specifically, there was a substantial rise of ↑312.6% in 2018 and ↑277.5%. in 2019.

In 2020, the impact of the COVID-19 pandemic led to a 44.5 % reduction in the rate of new colon cancer cases compared to 2019. However, in 2021, there was a 62% increase in new cases compared to 2020. It is still important to note that, while there was an icrease in 2021, it was still 10.1% lower than the number cases in 2019.

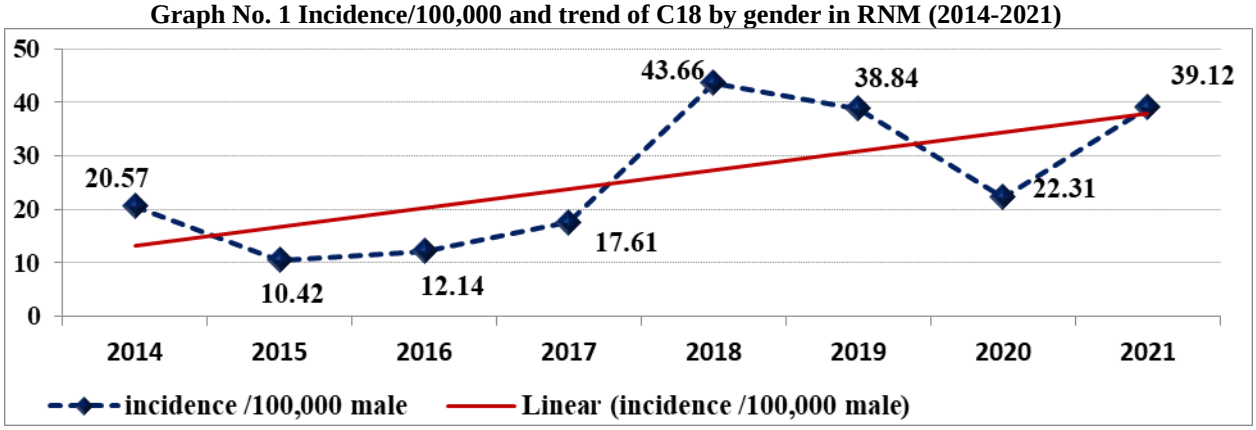
For each year within the period from 2014 to 2021, the calculated rates of the incidence of colon cancer showed the lowest occurrence in 2015, followed by 2016 (9.24 cases per 100,000 individuals and 10.7 cases per 100,000 inhabitants, respectively). Thereafter, there was a continuous increase in incidence, reaching its peak in 2018 at 37.98 cases per 100,000 inhabitants. There was a slight decrease in the incidence of colon cancer in 2019 (34.7 cases per 100,000 inhabitants). Notably, in 2020, there was a sharp decrease in the incidence, dropping to 19.3 cases per 100,000 inhabitants, which raises a valid suspicion that this decline might be attributable to the effects of the COVID-19 pandemic. In 2021, the incidence of colon cancer increased significantly, reaching 31.32 cases per 100,000 inhabitants, coming close to the highest values observed in the years 2018 and 2019.

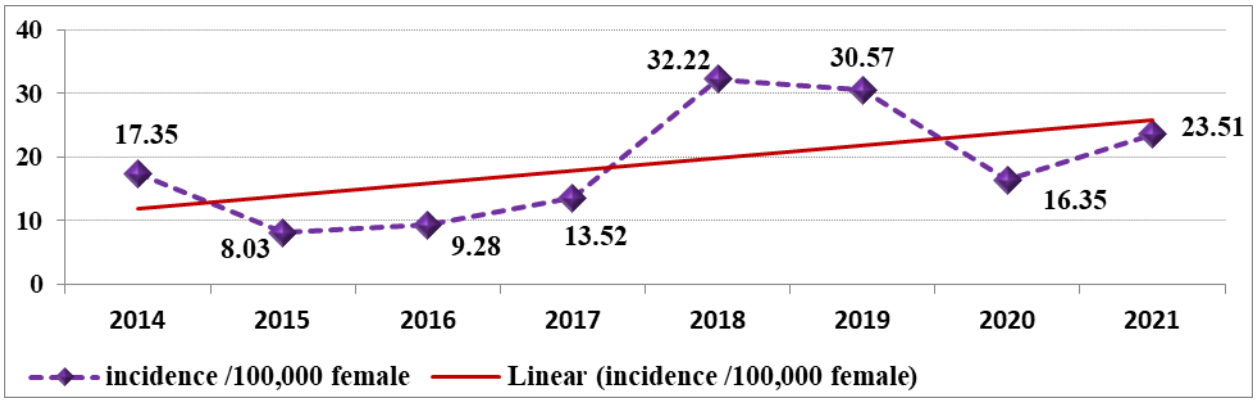
The calculated linear trend over this eight-year period suggests a potential tendency for the prevalence of this issue to continue increasing in the forthcoming years. Consequently, there is a pressing need to enhance or adapt current preventive measures and incorporate mechanisms for identifying at-risk population groups, facilitating targeted research, and enabling timely prevention strategies.

The period prevalence, which represents the rate of individuals diagnosed with colon cancer in our country for the period 2014–2021, is documented at 177.79 cases per 100,000 inhabitants (Table 1).

Simultaneously, data from the literature indicates that the five-year survival rate for colorectal cancer (CRC) ranges between 63% and 90%. This variance is influenced by factors such as the stage of disease development, the presence of risk factors at the time of diagnosis, and the effectiveness of treatment, encompassing factors such as treatment acceptance, speed of implementation, and treatment quality, among others.

Graph No. 1 Incidence/100,000 and trend of C18 by gender in RNM (2014-2021)

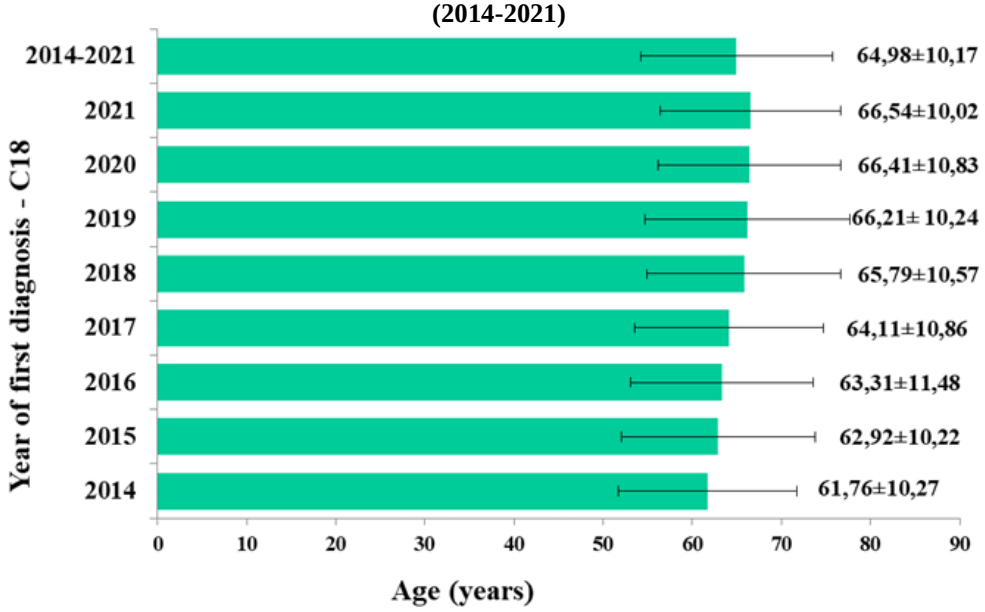




The highest incidence of colon cancer cases in both genders occurred in 2018, with a rate of 43.7 cases per 100,000 in men and 32.2 cases per 100,000 in women, followed by 2019, which saw rates of 38.8 cases per 100,000 in men and 30.6 cases per 100,000 in women. In contrast, the lowest incidence was recorded in 2015 and 2016, with rates ranging from 10.4 to 12.1 cases per 100,000 in men and 8.0 to 9.3 cases per 100,000 in women. It's noteworthy that in 2018 and 2019, the incidence of colon cancer in both genders was more than three times higher when compared to the rates in 2015 and 2016, as illustrated in Graph 1.

The linear trend analysis of the development tendency of colon cancer in the Republic of North Macedonia from 2014 to 2021 suggests, that there is a prevailing tendency for an increase in the occurrence of colon cancer in both genders in the upcoming years.

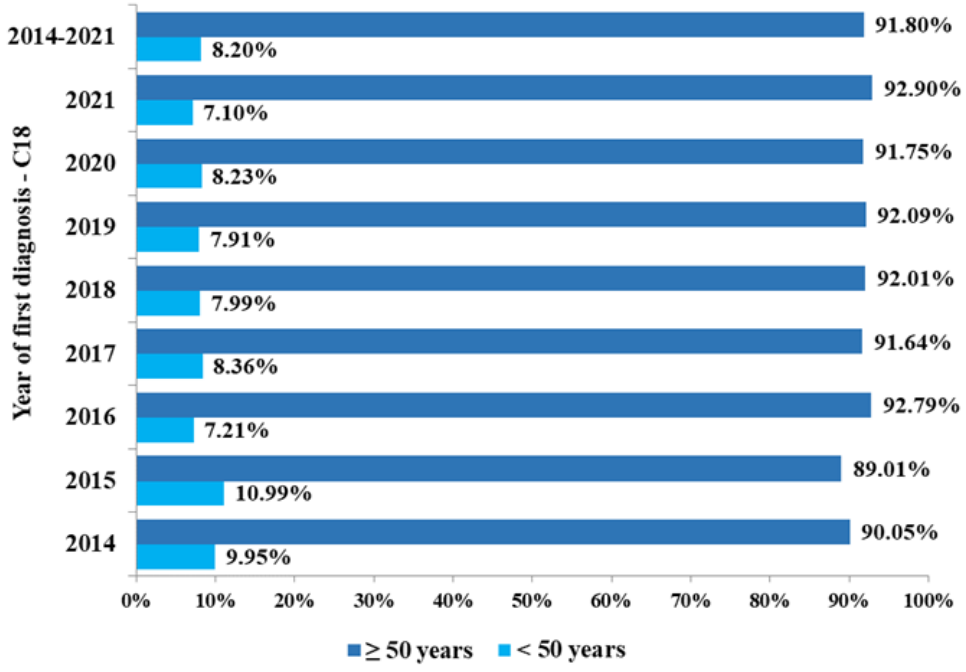
Graph no. 2 Average age of persons diagnosed with C18 according to years of first diagnosis in RNM (2014-2021)



In the total sample of 3.685 individuals diagnosed with colon cancer over the eight-year period from 2014 to 2021, the distribution by age was as follows (Graph 2):

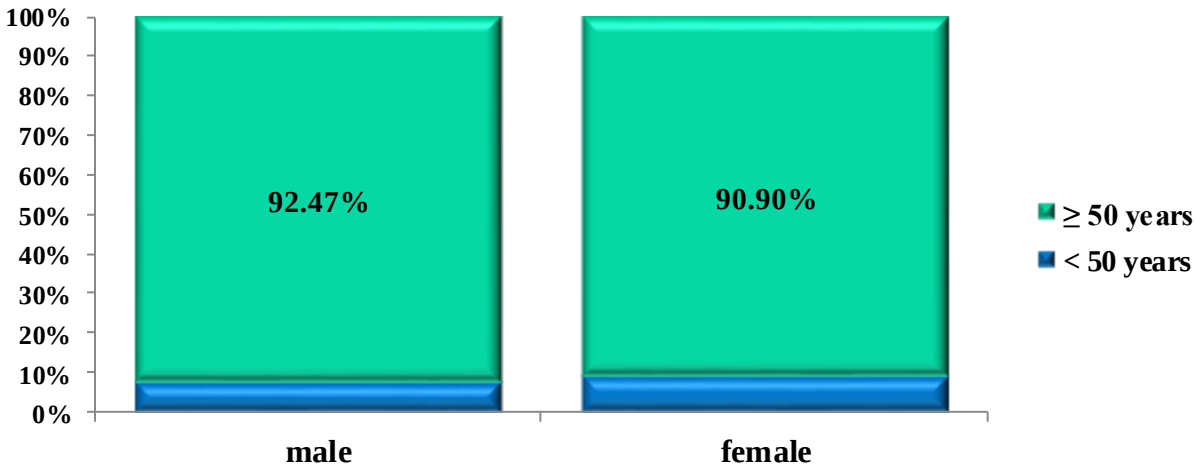
- 4 cases (0.1%) under 20 years old;
- Individuals less than 30 years old comprised 22 cases (0.6%);
- A total of 92 cases (2.5%) were aged 40 or below;
- The proportion of newly diagnosed individuals in the age group of 40-49 was 210 cases (5.7%)
- The largest number of newly diagnosed cases was found in the age group of 64, with 160 cases (4.3%), followed closely by the age group of 67, with 148 cases (4.0%)
- 263 cases (7.1%) pertained to individuals aged 80 and above.
- Only 5 cases (0.1%) were in the age group of 90 or older.

Graph no. 3 Structure of C18 conclusions by years of first diagnosis and age under/over 50 years (2014-2021)



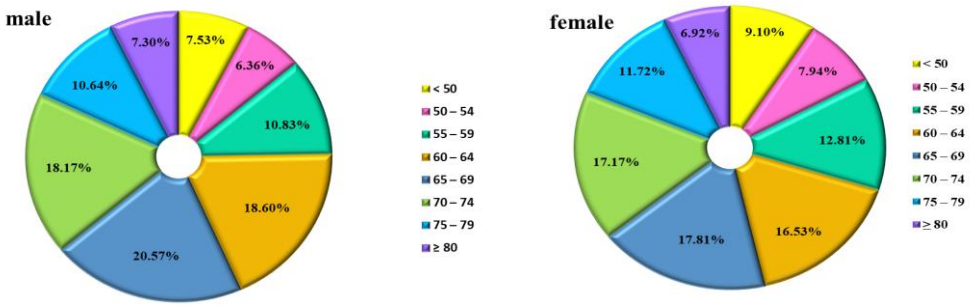
The highest average age at which the first diagnosis was made in both genders occurred in 2019. For men, the average age was 66,5±10,9 years, while for women, it was 65.8±12.2. This was followed by the year 2021, where the average age for men was 66.4±9.8, and for women, it was 66.7±10.7 (Graph 3).
For each of the examined eight years, no significant difference was noted between men and women in terms of the age at which they received their first diagnosis of colon cancer (Graph 4).

Graph no. 4 Persons with C18 in RNM according to gender and age under/over 50 years (2014-2021)



Over an eight-year period, a total of 160 cases (7.5%) of colon cancer diagnoses were observed among men under the age of 50, while 142 cases (9.1%) occurred in women of the same age group. Furthermore, the sample consisted of 1.964 men (92.5%) and 1.419 women (90.9%) who were aged 50 years or older. (Graph 4)

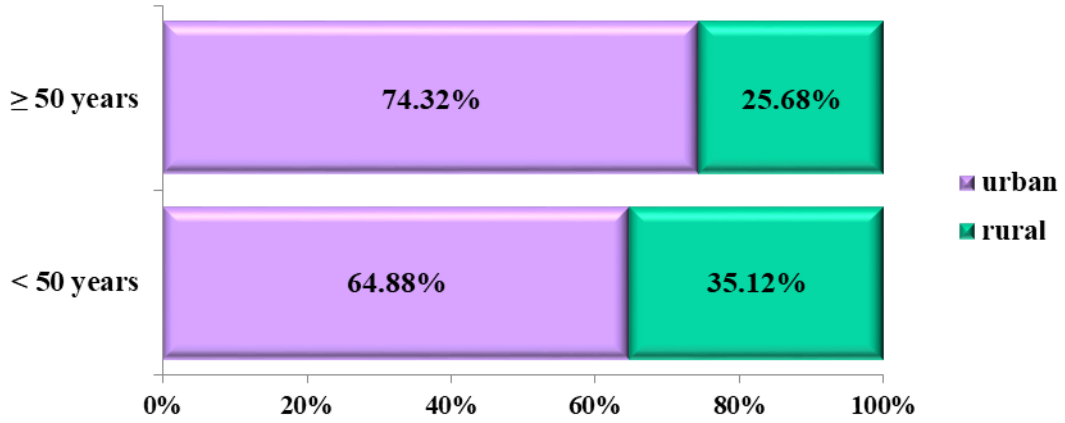
Graph no. 5 Structure of cases diagnosed with C18 in RNM according to gender and eight age groups (2014-2021)



The analysis of the entire sample (2014–2021), categorized into eight age groups of newly diagnosed colon cancer cases, revealed that the age group of 65-69 years was the most prevalent, comprising 715 cases (19.4%). This was followed by the age group of 70-74 years with 654 cases (17.7%) and the age group of 60-64 years with 653 cases (17.7%). Conversely, the age group of 50-54 years had the lowest representation with 259 cases (7%), and those aged 80 years or older had 263 cases (7.1%). The representation of the latter age group was even lower than that of individuals under 50 years old, which accounted for 302 cases (8.2%) (Graph 5).

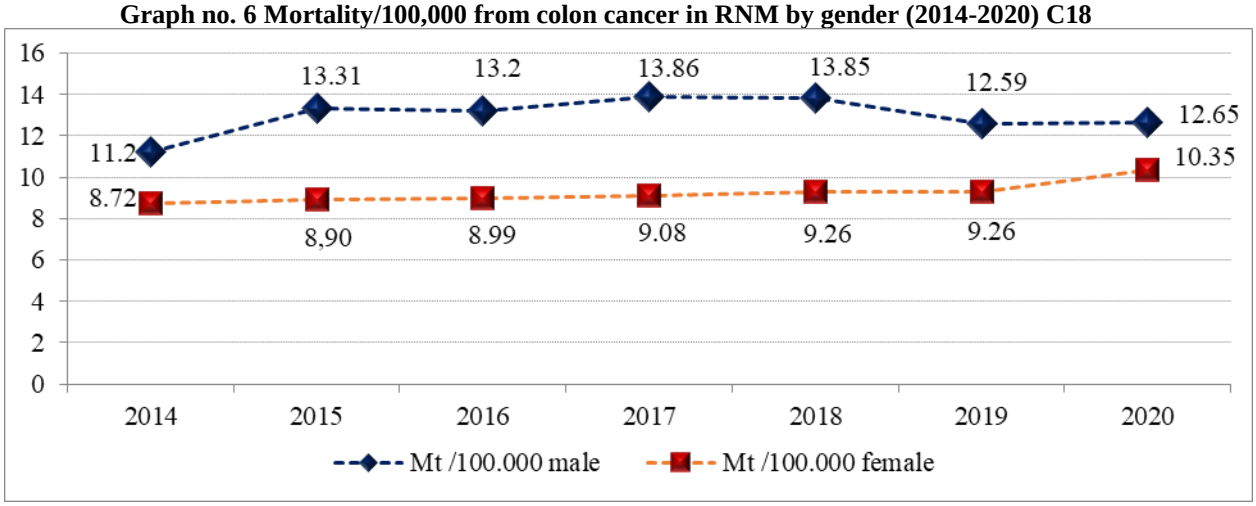
Table 2 and Graph no. 6 Persons diagnosed with C18 in RNM according to place of residence and age under/over 50 years (2014-2021)

Age groups	Residence - C18		Total
	Urban	Rural	
< 50 years	194 64,88%	105 35,12%	299 8,17%
≥ 50 years	2497 74,32%	863 25,68%	3360 91,83%
Total	2691 73,54%	968 26,46%	3659 100%
Pearson Chi-square: 12,556; df=1; p=0,0004*			*significant at p<0.05



Over the eight-year period, patients diagnosed with colon cancer who were under the age of 50 represented 194 (7.2%) of the newly diagnosed patients residing in urban areas and 105 (10.8%) of those residing in rural areas. Furthermore, 2497 (92.8%) of the newly diagnosed cases living in urban areas were aged 50 years or older, while 853 (89.1%) of the newly diagnosed cases living in rural areas fell within the same age group.

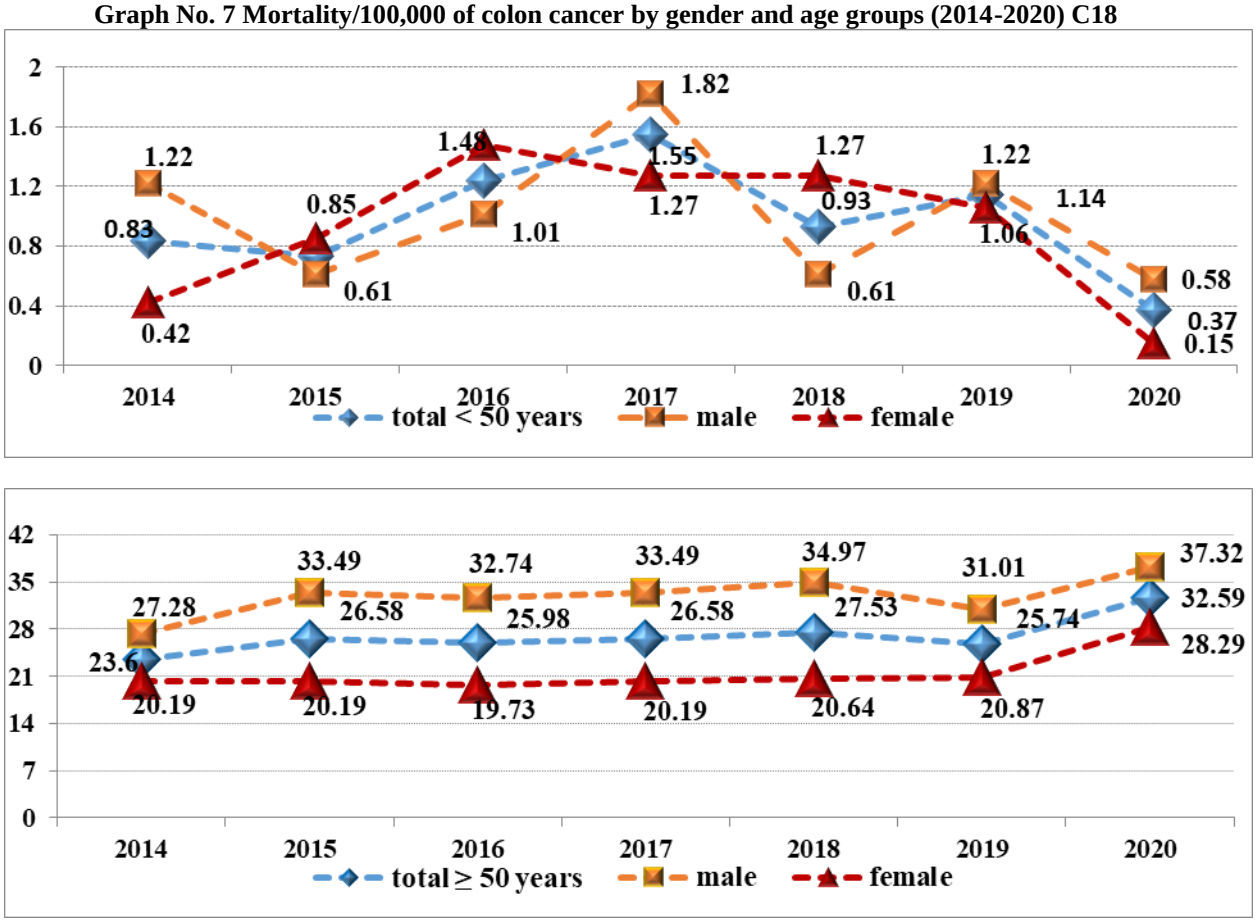
Graph no. 6 Mortality/100,000 from colon cancer in RNM by gender (2014-2020) C18



The highest male mortality rates were recorded in 2017 at 13.86 per 100,000 and in 2018 at 13.85 per 100,000, with a slight decline to 12.59 per 100,000 in 2019. However, there was an increase again in 2020 to 12.65 per 100,000 for males. (Graph 6)

Among women, the highest death rate from colon cancer occurred in 2020, reaching 10.32 per 100,000 women. This was followed by 2018 and 2019, with rates of 9.26 per 100,000 women. The overall increase in mortality from colon cancer in 2020 can be attributed to an increase in female mortality, while male mortality remained stable.

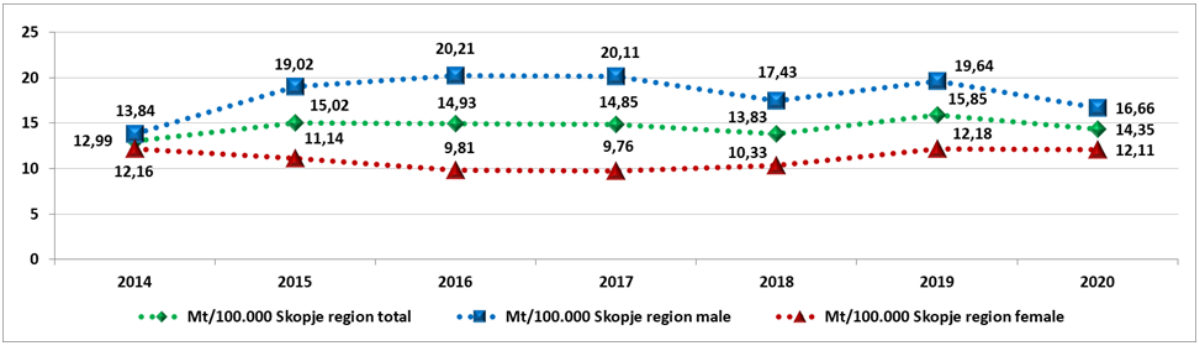
Graph No. 7 Mortality/100,000 of colon cancer by gender and age groups (2014-2020) C18



The mortality rate from colon cancer in the age group of 50 years and older in 2020 reached the highest level compared to all previous years, with a total rate of 32.59 per 100,000, comprising 37.32 per 100,000 for men and 28.29 per 100,000 for women. The next highest mortality rate for the age group of 50 years and older was in 2018, with a total rate of 27.53 per 100,000, consisting of 34.97 per 100,000 for men and 20.64 per 100,000 for women. In 2017, this rate was 26.58 per 100,000 in total, with 33.49 per 100,000 for men and 20.19 per 100,000 for women. (Graph 7)

In terms of geographical distribution, the Skopje region consistently recorded some of the highest death rates from colon cancer throughout the entire period from 2014 to 2020. Despite a slight decrease in 2018, the year 2019 saw the highest mortality rates for both men (19.64 per 100,000) and women (12.18 per 100,000) compared to all other regions. In 2020, this region experienced a reduction in both the overall (14.35 per 100,000 inhabitants) and gender-specific death rates from colon cancer (16.66 per 100,000 for men and 12.11 per 100,000 for women). However, when considering the total mortality rate, the Skopje region in 2020 ranked third, following the Vardar and Pelagonia regions, and placed third in terms of mortality among men and fourth in terms of mortality from colon cancer among women. (Graph 8)

Graph no. 8 Mortality/100,000 from colon cancer by gender - Skopje region (2014-2020)



IV. CONCLUSIONS AND RECOMMENDATIONS

- CRC is one of the most common malignant diseases in the Republic of North Macedonia (12% of all malignant tumors), with an annual incidence of 15 to 30 cases per 100,000 residents.

- During the period 2014-2021, this scientific paper shows a linear increase in colon cancer incidence from 9.24/100,000 in 2016 to 37.98/100,000 in 2018.

- The linear trend of the development tendency of colon cancer in the country (2014-2021) indicated that both genders have a tendency to increase in the coming years.

- The linear trend of the development tendency of colon cancer in the country (2014 - 2021) indicated that both genders tend to increase in the coming years.

- Based on this study results, the specific mortality rate from colon cancer at the national level (2014-2020) ranged from 9.96 per 100,000 in 2014 to 11.56 per 100,000 in 2018.

- Data from private health institutions need to be included in the register for this cancer to produce more accurate and regularly updated statistics on the mortality and morbidity associated with CRC in the Republic of North Macedonia.

- Considering that it is a disease that has serious high proportions and impacts on public health, as well as the economy, a regular epidemiological study is necessary to determine the possible causes of occurrence that are genetic, biochemical, or environmental in nature, encompassing lifestyles, as well as make an economic analysis of the direct and indirect costs associated with morbidity and mortality from this severe malignant disease.

REFERENCES

[1] Yufei Jiang at al. Global pattern and trends of colorectal cancer survival: a systematic review of population-based registration data, 2021, doi: 10.20892/j.issn.2095-3941.2020.0634

[2] Alan.W. et al. 2018, A review of sex-related differences in colorectal cancer incidence, screening uptake, routes to diagnosis, cancer stage and survival in the UK. (DOI: 10.1186/s12885-018-4786-7)

[3] John. M. C. et al. 2021, Racial and Ethnic Disparities in Colorectal Cancer Incidence and Mortality (DOI: 10.1016/bs.acr.2021.02.007)

[4] Deependra.S. et al. 2022. Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO Global Cervical Cancer Elimination Initiative, (DOI: 10.1016/S2214-109X(22)00501-0)

[5] Yue Xi and Pengfei Xu. Global colorectal cancer burden in 2020 and projections to 2040, 2021, doi: 10.1016/j.tranon.2021.101174

[6] The Global Cancer Observatory – Fact sheets Japan - March, 2021. 392-japan-fact-sheets.pdf (iarc.fr) последен преглед 21.10.2022

[7] Bin Lu et al. Colorectal cancer incidence and mortality: the current status, temporal trends and their attributable risk factors in 60 countries in 2000–2019, 2021 (DOI: https://doi.org/10.1097%2FCM9.0000000000001619)

[8] Ferlay J, Ervik M, Lam F, et al. *Global Cancer Observatory: Cancer Today*. Lyon, France: International Agency for Research on Cancer; 2018. Available from: http://gco.iarc.fr/today/data/factsheets/cancers/10_8_9-Colorectum-fact-sheet.pdf, последен преглед ноември 2018.

[9] Firas.B et al. 2021 Colorectal Cancer Epidemiology: Recent Trends and Impact on Outcomes, DOI: 10.2174/1389450121999201117115717

[10] Prashanth. R. et al. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors, 2019, (DOI: 10.5114/pg.2018.81072)