

RESEARCH ARTICLE

The Role of Smoking in the Development of Colorectal Cancer

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Introduction. Smoking is an important public health issue nowadays. It causes a lot of diseases and represents also a source of carcinogenic substances. Recent studies showed an increased incidence of colorectal cancer in smokers. The aim of our study is to assess the association between smoking and colorectal cancer and to establish the prevalence of heavy smokers among the patients operated on for colorectal cancer. **Methodology.** We run a retrospective study of the charts belonging to the patients diagnosed with colorectal cancer and operated on in our department between 2004 and 2013. The patients were classified in smokers, former smokers and nonsmokers. The amount of tobacco was evaluated according to the number of smoked cigarettes per day, the smoking period, respectively the pack-years. The data were corroborated with the location of the tumor and analyzed using the online version of Graphpad. **Results.** From 982 patients diagnosed with colorectal cancer, we found 297 smokers (30.24%). Among these, 106 patients (35.69%) have smoked for over 30 years, at least 20 cigarettes per day, more than 30 pack-years. The number of heavy smokers was significantly greater ($p=0.0001$) in the group with rectal cancer compared to the group with colon cancer. The association of smoking with rectal cancer was also important ($p=0.0015$) among the former smokers. **Conclusions.** Smoking is related to higher incidence of colorectal cancer. Our data sustain the hypothesis of increased risk of developing rectal cancer in heavy smokers. We recommend the screening for colorectal cancer among the heavy smoker population.

Keywords: smoking, colorectal cancer, screening

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Introduction

Smoking is a major public health problem. It is an etiologic factor in many diseases and a common source of carcinogenic substances. The data provided by the Romanian Ministry of Health in 2011 (Global Adult Tobacco Survey) shows that 4.85 million people, 26.7% of the Romanian population aged over 15 are smokers, and more than half of them consume daily more than 20 cigarettes [1]. Cigarette consumption increases the risk of lung, laryngeal, pharyngeal, esophageal, stomach, urinary bladder the kidney and pancreas cancer [2,3]. The association between smoking and colorectal cancer (CRC) has not been shown consistently. Some studies showed a positive correlation between smoking and the incidence of CRC, whereas others do not show any relationship between these two [4]. Increased risk of adenomas and CRC was first suggested by Giovanucci et al. [5]. The influence of smoking on the colorectal mucosa can be observed only in studies with a sufficiently long period of reference because of the long induction period [6]. Recent cohort studies show a significantly increased risk of CRC in people who smoke more than 30 years, more than 20 cigarettes per day (30 pack / year) [4-9]. The association between smoking and colorectal cancer has been shown also in ex-smokers. Analysis also shows that men exposed to cigarette smoke are more likely to develop this type of cancer compared to women. The

risk of rectal cancer is greater than colon cancer in both, smokers and ex-smokers [2,4].

Our study aims to assess the association between smoking and CRC. The main objective is to respectively determine the prevalence of heavy smokers among colon and rectum cancer patients in the surgery department.

Material and method

In our study all patients whose data was retrospectively analyzed, between 2004 - 2013 were hospitalized and operated for colorectal cancer in the Mures County Emergency Hospital's 2nd Surgery Clinic. Based on the hospital forms data, patients were classified in smokers, heavy smokers, ex-smokers and nonsmokers. Smokers were patients who smoked at least 1 cigarette per day. Former smokers were patients who quit smoking at least for 1 year after they smoked at least 1 cigarette per day. The amount of tobacco consumed was estimated based on the number of cigarettes smoked per day, period of smoking and number of years smoked (number of packs/year - defined by number of daily cigarette packs smoked multiplied by number of smoking years). Data was divided into groups of smokers with less or more than 20 cigarettes per day and less or more than 30 years smoking. We considered heavy smokers patients who smoked at least 20 cigarettes per day for at least 30 years namely more than 30 pack-years. We excluded patients with negative pathology report and insufficient hospital form data. The obtained data was categorized by gender, age and especially with tumor localization, focus-

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ing on tumor differentiation grade of rectal carcinomas in contrast to the rest of colon tumors. For data processing we used Microsoft Excel. To compare the categorical variables between the groups we used the Fisher's and Chi-square tests in the online version of Graphpad. The significance threshold for *p* value was 0.05.

Results

Between 2004 and 2013 in our Clinic a total of 1089 patients with CRC were operated. 982 patients had data on smoking and a positive pathology report for CRC. 570 were men (58.04%) and 412 women (41.96%), aged between 28 and 90 years, with an average of 59 years. Analyzing the localization of the tumors, we found 91 (9.26%) in the cecum, 58 (5.90%) in the ascending colon, 36 (3.66%) in the hepatic flexure, 48 (4.89%) in the transverse colon, 32 (3.26%) in the splenic flexure and 28 (2.85%) in the descending colon. In 187 cases (19.04%) the tumor was localized in the sigmoid colon, in 140 cases (14.25%) in the rectosigmoid junction and in 273 cases (27.80%) in the rectum. 72 patients (7.33%) had anorectal tumors and 17 patients (1.73%) presented synchronous tumors (Figure 1).

297 (30.24%) were smokers of a total of 982 patients with CRC (69.36% men and 30.64% women). 164 patients (55.22% of all smokers, 72.56% men and 27.44% women) smoked more than 20 cigarettes per day. The number of heavy smokers was 106 (35.69% of all smokers) of whom 75.47% men and 24.63% women. In 77 patients (72.64% of heavy smokers) the tumor was localized in the rectum. In patients with rectal cancer the number of heavy smokers was significantly higher, $p=0.0001$, compared to other anatomical segments of the large intestine (Figure 2).

From a total of 64 patients (6.52%) who were considered as ex-smokers (81.25% men and 18.75 women) in 26 cases (40.63%) the tumor was located in the rectum. 16 patients with rectum cancer (25% of all patients ex-smokers) smoked more than 30 pack/year. In the other tumor localizations the number of ex-heavy smokers was 8 (12.5%). The association between smoking and rectal cancer was also important in the group of ex-smoker patients, the number of ex heavy smokers was significantly higher in patients with rectal cancer, $p=0.0015$ (Figure 3).

Discussions

Colorectal cancer is the second most frequent malignant disease in women and third most common in men. According to the World Health Organization GLOBOCAN database, in 2008 1.2 million new cases of colorectal cancer were diagnosed and 608 000 people died of this type of neoplasm [10]. Even if many countries have introduced screening programs for early detection of CRC, the incidence of the disease does not seem to decrease [11]. Recently there were discovered many molecular carcinogenic mechanisms of environmental factors, which gives us hope that it will be possible to reduce the incidence of CRC in the near future [12].

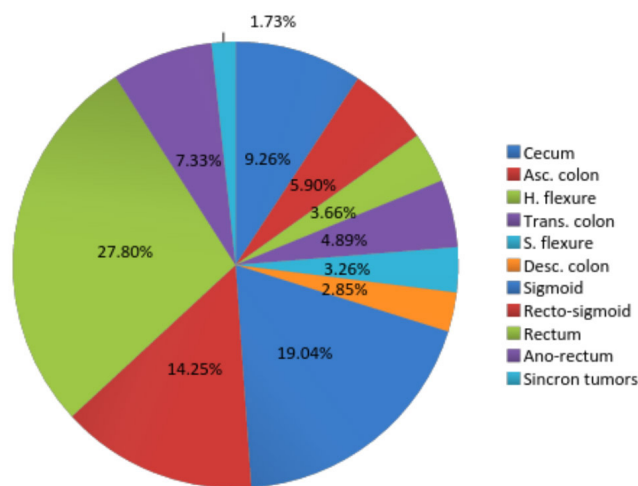


Fig. 1. Tumor localization in all patients with CRC

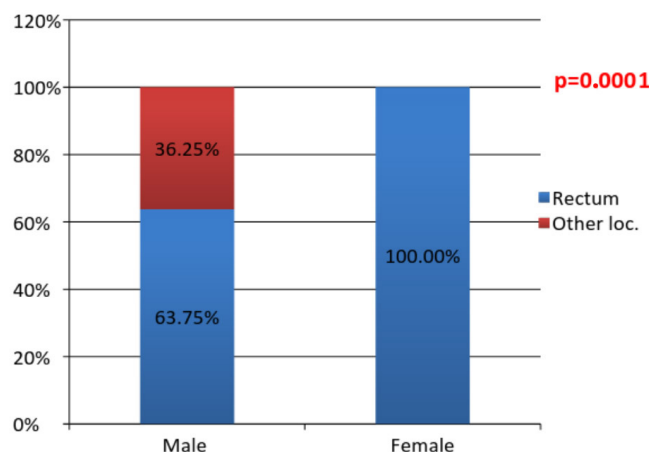


Fig. 2. Ratio of rectal cancer compared to other localisations in heavy smokers

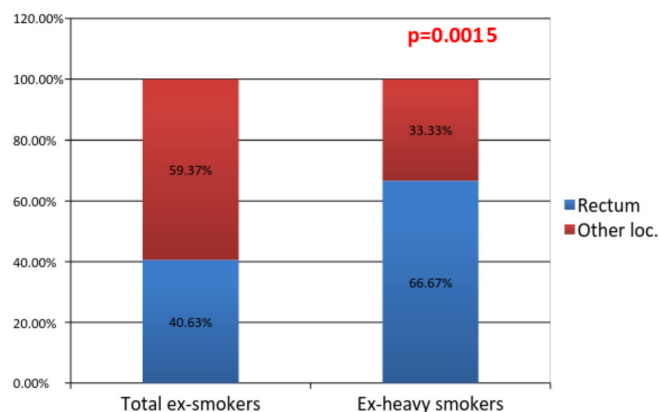


Fig. 3. Ratio of rectal cancer in ex-heavy smokers compared to total ex smokers

A number of recent cohort studies have shown that smoking has an important role in the development of this type of neoplasm, so we can say that about 12% of all colorectal neoplasms can be attributed to smoking [13]. The

carcinogenic effect of cigarette smoke on colorectal mucosa is lower than in the respiratory system or gastro-esophageal level, but the relationship between smoking and CRC has been shown consistently in cohort studies regardless of the country of origin [4].

The main carcinogenic substances found in cigarette smoke are aromatic amines, nitrosamines, heterocyclic amines and polycyclic aromatic hydrocarbons. The metabolism of these substances via cytochrome P450 leads to the formation of aberrant DNA and further gene mutations (KRAS, BRAF, MYC). Nitrosamines can activate and bind nicotine-acetylcholine receptors, which result in an increase of intracellular reactive oxygen species concentration. The oxidative stress leads to activation of the NF- κ B and COX-2 inflammatory pathways and also promotes the MAPK proliferative signaling cascade [12]. Recent research shows an increased incidence of CRC in smokers who smoked for more than 20 years, but a significantly increased incidence is demonstrated in studies with a follow-up of over 30 years. In addition, the effect of cigarette smoke on the large intestine's mucosa is dose-dependent. The risk of developing CRC increases in people who smoke more than 20 cigarettes/day [12]. We can state that people who smoke more than 20 cigarettes a day for at least 30 years (30 pack/years) have a significantly increased risk of CRC [9]. These alarm signals in the relationship between colorectal cancer and tobacco are not widely known, mainly because these studies have emerged just recently. Most people know that smoking can cause lung and heart diseases, but few of them know that it can also lead to CRC. Other studied risk factors were alcohol consumption, family history and obesity. They proved to have an important role in the development of CRC and for this reason they can be considered confounding variables. But after adjusting these variables results show that no change was found in the relationship between smoking and this type of CRC [4]. In both smoker and ex-smoker groups the risk of developing CRC is much higher in men than in women [4]. This difference between genders is explained by various chromosomal mutations, through interaction of smoking with protective endo- and exogenous estrogens, or by the abdominal adiposity or body mass dependent effect of smoking [14,15]. Both smokers and ex-smokers present a greater risk of developing rectal cancer than colon cancer, although it is unclear whether there is a difference in the pathogenetic mechanism. However, distal colon cancer is

more common than proximal, therefore it is easier to demonstrate a significant association [4].

Conclusions

Our data supports the hypothesis of increased risk of developing rectal cancer in heavy smokers. Men who smoke more than 20 cigarettes for more than 30 years are the most affected. We recommend the introduction of colorectal cancer screening especially among heavy smokers.

Conflict of Interest

Nothing to declare.

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