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Research article

RESEARCH INTO RISK FACTORS CAUSING MALIGNANT NEOPLASMS OF THE DIGESTIVE ORGANS IN THE ARAL SEA REGION OF UZBEKISTAN: A CASE-CONTROL STUDY

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An alarming trend is observed in recent years involving growing incidence of malignant neoplasms of the gastrointestinal tract. It appears to be associated with a non-hereditary etiology. Behavioral factors, lifestyle, nutrition, microbes, the environment and physiological mechanisms of the host may all play a key role in this. This prompted us to study risk factors causing development of malignant neoplasms.

The aim of this study was to identify risk factors causing malignant neoplasms of the digestive organs in the Aral Sea region of Uzbekistan (the Republic of Karakalpakstan). These risk factors were established by conducting a case-control analytical epidemiological study involving 307 participants; of them, 151 were respondents with malignant neoplasms of the digestive system and 156 relatively healthy respondents. The study was conducted at the Karakalpakstan branch of the Republican Specialized Scientific and Practical Medical Centre for Oncology and Radiology of the Republic of Uzbekistan.

The results of the study have determined that the leading risk factors causing development of digestive cancer are bad habits such as alcohol consumption of 500 ml/week or more (OR = 2.09), smoking 10 or more cigarettes per day (OR = 2.61) and being a current smoker (OR = 2.72). Smoking nasvay, which is common in Central Asia, is also a significant risk factor for digestive cancer in men (OR = 3.587). Dietary habits also play an important role, particularly the consumption of 500 g or more of red meat per week, which creates elevated risks of developing cancer of the digestive organs (OR = 2.08). The physiological balance of the human body determines its health state. Thus, abdominal obesity (OR = 2.24) and a history of being overweight (OR = 2.69) increase the risk of developing malignant neoplasms of the digestive organs. Additionally, the odds ratio (OR) for individuals who prefer hot tea is 1.31 (95 % confidence interval (CI): 0.83–2.07). According to our findings, psycho-emotional states such as stress following the loss of a loved one (OR = 3.25), work involving stressful tasks (OR = 2.84), intense work (OR = 2.17), sleep disorders or insomnia in the last six months (OR = 2.20), and prolonged depression (OR = 2.12) increase the risk of developing digestive cancer.

All examined risk factors are manageable and each of them can be a target for primary prevention of malignant neoplasms of the digestive system.

Keywords: *malignant neoplasms, digestive organs, epidemiology, risk factors, case-control study, prevention, oncology.*

Epidemiologic data indicate a significant increase in the incidence of colorectal cancer in younger populations in the past three decades. Moreover, recent evidence also demonstrates a similar trend in gastric, pancreatic, and biliary tract cancers. A majority of these early-onset cases are sporadic and lack hereditary or familial background, implying a potential key role for behavioral, lifestyle, nutritional, microbial, and environmental factors [1]. According to available data, 5–10 % of all risk factors of malignant neoplasms (MNs) are genetic predispositions whereas approximately 40–45 % of them are associated with physiology, lifestyle (diets, physical activity, smoking, and alcohol intake) and environmental exposures [2].

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The aim of this study was to identify risk factors causing malignant neoplasms of the digestive organs in the Aral Sea region of Uzbekistan (the Republic of Karakalpakstan).

Materials and methods. *The study design.* This study was a part of scientific qualification research on the subject 'Incidence of malignant neoplasms of the digestive system in Aral Sea region of Uzbekistan and substantiation of basic prevention trends'.

The study was approved by the Local Ethics Committee of the I.M. Sechenov First Moscow State Medical University (Sechenov University), the meeting protocol No. 12-24 dated May 16, 2024.

The study object and area. Residents of the Republic of Karakalpakstan aged 35 years and older participated in the case – control study. The following inclusion criteria were applied for Cases: patients with MNs of the digestive system (treated at an oncological inpatient hospital or after treatment); patients with MNs of the digestive system younger than 35 years or with MNs of other locations were excluded from the study. The inclusion criteria for Controls were conditionally healthy people aged 35 years and older (health information provided by the participants); people younger than 35 years were excluded. All respondents were informed about the study aims and methods and provided their voluntary inform consent to participate in it.

To obtain more precise results and make data analysis simpler, the administrative areas in the Republic of Karakalpakstan were distributed into four zones: the Western zone (Muynak District, Kungrad District, Kanlykul District and Shumanay District), the Northern zone (Takhtakupir District, Karauzyak District, Chimbay District, Kegeyli District and Bozatau District), the Southern zone (Amudarya District, Beruniy District, Ellikkala District and Turtkul District) and the Central zone (Nukus City and Nukus District, Khodzheyli District and Takhiatash District) (Figure 1).

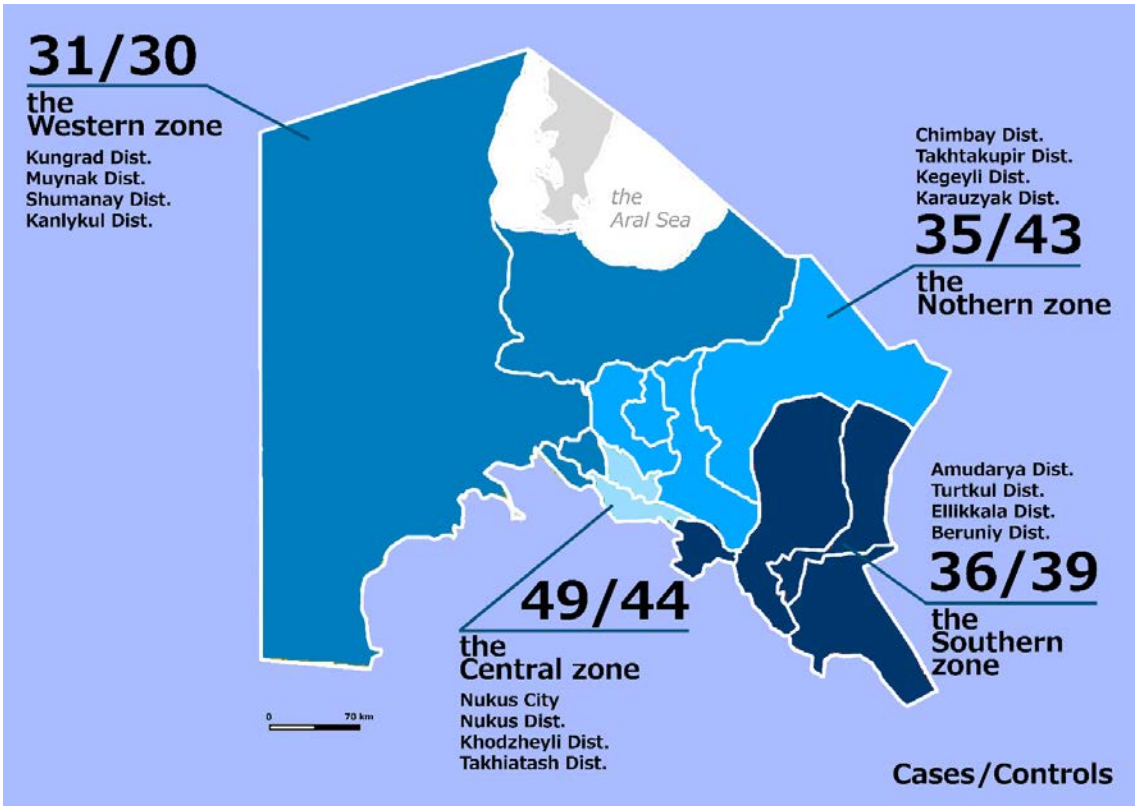

Figure 1. Conditional zoning and number of respondents by administrative territories of the Republic of Karakalpakstan

Survey. Data on lifestyles, bad habits and diets were collected by using an original questionnaire created by the authors. It consisted of 9 sections, namely, General Information (5), Diet (32), Smoking (9), Nasway Smoking (7) Hookah Smoking (5), Alcohol Intake (8), Overweight and Obesity (10), Water (7), and Special Section (13). The latter included questions about either present or absent digestive disorders, stomatitis, pathology of head and neck lymph nodes, gastritis, ulcer, and psychoemotional state. Overall, the questionnaire contained 96 questions; we highlighted 21 of them namely 5 from General Information about sex, age, residence (urban or rural), height and body mass; 14 questions were selected as those with the most significant results; 14 of them included "Yes" or "No" answers. Answers to the remaining questions did not exceed threshold values, which we had set for statistical analysis, and were later excluded from the present study.

The 'Cases' participants were questioned in the Karakalpakstan Branch of the Republican Specialized Scientific and Practical Medical Oncology and Radiology Centre of the Republic of Uzbekistan.

Statistical analysis. A relationship was investigated between risk factors and cancer by assessing it per OR with 95 % confidence interval (95 % CI). It is worth noting that OR not lower than 2.0 was taken as the threshold value for the relationship between a risk factor and the disease.

Results and discussion. ***General Information.*** Three hundred and seven respondents took part in the survey; of them, 151 were Cases and 156 were Controls. All respondents lived in the Republic of Karakalpakstan (Uzbekistan). Cases were made of 77 (51 %) women and 74 (49 %) men. Controls were quite similar with 83 (53.2 %) women and 73 (46.8 %) men. Thirty-seven point seven percent (57) of Cases lived in urban areas and 62.3 % (94) in rural ones. Among Controls, 40.4 % (63) lived in urban areas and 59.6 % (93) in rural ones. The average age of Cases was 64.4 years [63.1–65.7]; Controls, 62.2 years [61.4–62.9]. Distribution of the respondents in each group per the specific zones is shown in Figure 1. Cancer locations in the respondents are shown in Figure 2.

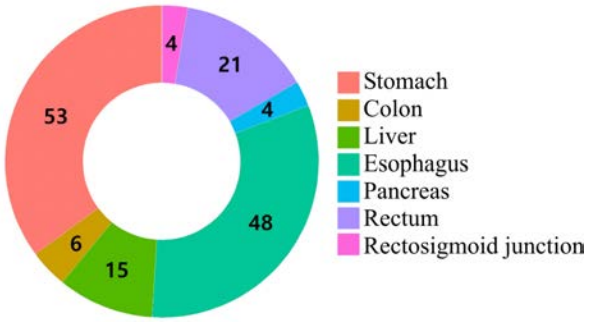

Figure 2. Cancer locations in Cases

Bad habits. ***Alcohol intake.*** Globally, estimated 741,300 (95 % CI: 558 500–951 200), or 4.1 % (3.1–5.3), of all new cases of cancer in 2020 were attributable to alcohol consumption [3]. In our survey, 19 respondents (12.18 %) from Controls gave the positive answer to the question "Do you drink 500 ml or more alcohol per week?". Among Cases, the positive answer was given by 34 (22.52 %) respondents. OR equaled 2.09 [CI 95 %: 1.136–3.922; p = 0.017]. When stratified per sex, OR was 2.661 [95 % CI: 1.012–7.241; p = 0.047] for women and 1.749 [95 % CI: 0.77–4.034; p = 0.089] for men.

Smoking. Smokeless tobacco consumed orally or by inhalation has been used just as long as any other tobacco type. Studies that have been conducted for many years have established a relationship between smokeless tobacco consumption and potentially malignant neoplasms in the oral cavity, oral cavity cancer, esophageal cancer and pancreatic cancer as well as its possible contribution to cardiovascular diseases, hypertension, ulcer, and fetus morbidity and mortality [4].

In our survey, the question "Do you or have you smoked Nasway?" was answered positively by only men in both groups. Accordingly, the data were stratified per the male sex only. Among Cases, 27 men smoke Nasway or used to do it; among Controls, 10 men. OR equaled 3.587 [95 % CI: 1.6–8.461; p = 0.001].

Some studies have reported an evidenced relationship between tobacco smoking and esophageal cancer [5]. In particular, smoking-

related health risk can grow from twofold to tenfold depending on a study design and a sample size. Esophageal cancer risk depends both on smoking intensity and duration; however, empirical data give evidence of exposure duration having more considerable effects than its intensity [6].

The questionnaire included questions about smoking at present and smoking 10 cigarettes or more a day in the past. The first question was answered positively by 34 Cases and 13 Controls, OR equaled 2.723 [95 % CI: 1.426–5.371; $p = 0.002$]. Twenty-nine people from the first group and 13 from the second one gave the positive answer to the second question. It is noteworthy that there was only one female respondent among those who answered *Yes* to this question. OR equaled 2.6 [95 % CI: 1.31–5.39; $p = 0.006$].

Eating habits. ***Drinking hot tea.*** Tea is a globally popular beverage. Green tea is rich with polyphenols, which have been widely examined as chemical cancer prevention means. Epigallocatechin-3-gallat, the most prevalent and active substance in tea, is reported to suppress cancer progression [7, 8]. In epidemiological research, an association between tea consumption and reduced cancer risks was also confirmed by several Case – Control studies[1] [9], prospective cohort studies [10] and meta-analyses [11–13]. In our survey, the question was "Do you like drinking hot tea?" Positive answers were given by 44.4 % (67) Cases and 37.8 % (59) Controls. OR equaled 1.31 [95 % CI: 0.83–2.07; $p = 0.2466$].

Abdominal obesity. Obesity can induce onset of many chronic diseases such as diabetes, atherosclerosis, MNs and hypertension. In recent years, obesity is becoming a more and more serious global public health challenge. Epidemiological studies show that obesity increases risks of various MNs, most of them being MNs of the digestive system [14]. According to the results of meta-analyses, abdominal obesity also increases risks of pancreatic, liver, stomach, esophageal and colorectal cancer [15–18]. In our survey, we established whether the respondents had abdominal obesity. Among Cases, this state was found in 72 (47.8 %) respondents; among Controls, in 45 (28.8 %). OR equaled 2.242 [95 % CI: 1.4–3.61; $p \leq 0.001$]. After sex-related data stratification, 39 (52.7 %) men were found to be obese in the first group and 16 (21.9 %) in the second one with OR = 3.93 [95 % CI: 1.93–8.23; $p \leq 0.001$].

Overweight in the past. Obesity is a risk factor of many diseases, primarily, hypertension, dyslipidemia, type 2 diabetes mellitus (DM), cardiovascular diseases (CVD), non-alcoholic fatty liver disease (NAFLD), Alzheimer disease, and cancer [19, 20]. We decided to find out whether the respondents had had any issues with overweight in the past. According to the study results, OR of MNs of the digestive system was higher in those respondents who had had overweight in the past against those without it, OR = 2.7 [95 % CI: 1.627–4.5, $p \leq 0.01$].

Red meat consumption. In the report issued by the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) in 2007 and entitled Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective, the international expert group made an extensive review of available literature data and concluded that a substantial amount of data from cohort and case-control studies showed a dose-response relationship, supported by evidence for plausible mechanisms operating in humans. Red meat is a convincing cause of colorectal cancer [21]. A meta-analysis that covered 148 articles gave evidence that red and processed meat consumption was significantly associated with greater risk of colorectal cancer (RR = 1.17; 95 % CI: 1.08–1.26), colon cancer (RR = 1.21; 95 % CI: 1.09–1.34), and rectal cancer (RR = 1.26; 95 % CI: 1.09–1.45) [22]. In our survey, the positive answer to the question "Do you consume

[1] Gao Y.T., McLaughlin J.K., Blot W.J., Ji B.T., Dai Q., Fraumeni J.F. Jr Reduced Risk of Esophageal Cancer Associated With Green Tea Consumption. *J. Natl Cancer Inst.*, 1994, vol. 86, no. 11, pp. 855–858. DOI: 10.1093/jnci/86.11.855

500 grams or more of red meat weekly?" was given by 23 (14.7 %) respondents in the first group and 40 (26.5 %) in the second, OR = 2.079 [95 % CI: 1.177–3.727; $p = 0.01$].

Psychoemotional / psychosocial state. Psychosocial factors (for example, psychological stress, drastic events in life, long depression and social isolation) can affect the energy balance thereby promoting obesity [23]. A meta-analysis reported a considerable contribution made by chronic everyday stress, drastic life events, depression and social isolation to cancer growth and metastasis [24]. Questions about psychoemotional state were also included in our survey.

The questionnaire included the following questions in this sub-group: "Have you ever experienced severe stress (death of a spouse, divorce, severe disease etc.)?" "Do you have many responsibilities at work?" "Have you ever had a long depression?" "Does your work involve nervous strain?" "Does your work involve stress?" "Do you feel excessive responsibility at your workplace?" We established a positive correlation with MNs in each case, except the last one. People who were suffering from severe stress due to loss of a loved one or an accident turned out to be close to MN onset (OR = 3.25 [95 % CI: 1.748–6.239; $p \leq 0.001$]). Also, people with too stressful work (OR = 2.837 [95 % CI: 1.7–4.788; $p = 0.001$]) or with elevated work intensity (OR = 2.17 [95 % CI: 1.315–3.614; $p = 0.002$]) were exposed to greater MN risks.

More evidence is being accumulated about the relationship between depression and cancer incidence and progression. Depression not only makes it difficult to overcome cancer and stick to treatment requirements but also affects components of endocrine and immune function that may affect cancer surveillance [25]. Our study established that OR of MNs of the digestive system was higher for people in depression against those who did not have it (OR = 2.124 [95 % CI: 0.9927–4.733, $p = 0.053$]).

Stress and depression directly affect sleep. Sleep, especially at night, is very significant for a healthy life. Our survey included the following question: "Have you ever had long sleep disorders or insomnia in the last six months?" As a result, OR was found to be equal to 2.2 (95 % CI: 1.31–3.74, $p = 0 > 002$) (Figure 3).

All foregoing risk factors are manageable meaning we can influence them. MNs development is a long-term process and this requires developing relevant preventive activities against the examined risk factors to be introduced permanently. In addition, healthcare workers should pay greater attention to any disorders of psychoemotional stability in their patients.

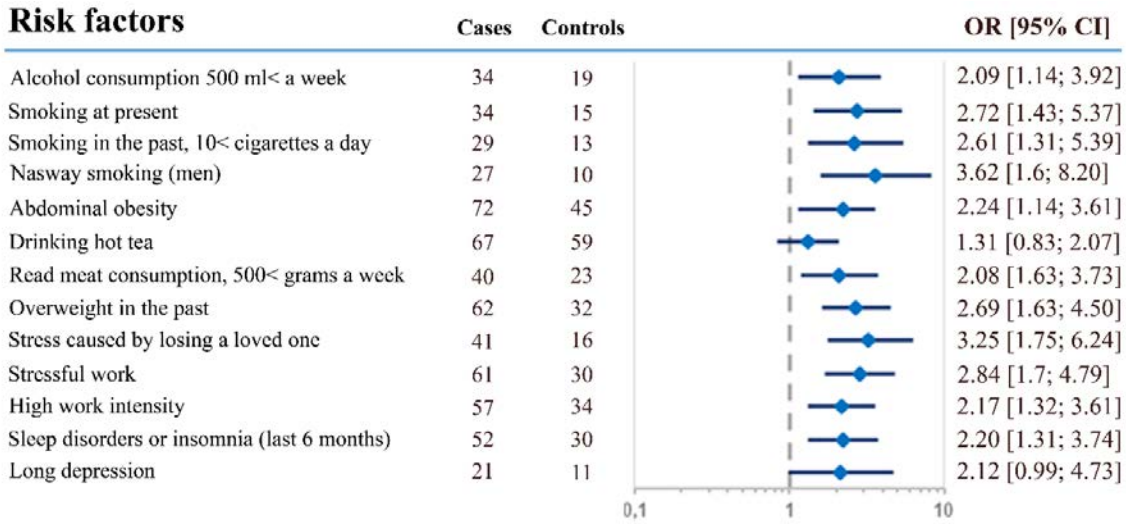

Figure 3. Risk factors causing MNs of the digestive system in the Aral Sea region of Uzbekistan (the Republic of Karakalpakstan)

A systemic review and meta-analysis describes activities aimed at preventing MNs of the gastrointestinal tract where primary prevention is deemed to be the most effective. As regards MNs, this primary prevention includes managing risk factors of the population and this should involve the following: prevention of viral hepatitis (B and C) mostly through vaccination; early risk assessment for Hepatocellular Carcinoma (HCC); modification of risk factors such as alcohol use, obesity and diabetes; positive effects stimulating greater physical activity among the population; and efforts to reduce consumption of red and processed meat. Secondary cancer prevention should include effective clinical methods of population screening using such methods for scheduled check-ups as fecal occult blood testing (FOBT), gastroscopy, colonoscopy, and sigmoidoscopy [26].

Conclusions:

1. Just as on the global scale, such bad habits as smoking (smoking at present with OR = 2.72, 95 % CI: 1.43–5.37; 10 or more cigarettes a day in the past with OR = 2.61, 95 % CI: 1.31–5.39), alcohol intake (OR = 2.09 95 % CI: 1.14–3.92) and Nasway smoking (OR = 3.58 95 % CI: 1.6–8.46) are the leading risk factors able to cause MNs of the digestive system.

2. Consumption of 500 grams or more of red meat a week is a risk factor of MNs of the digestive system (OR = 2.08, 95 % CI: 1.63–3.73).

3. As a rule, overweight and obesity have negative influence on the human body. In our study, abdominal obesity (OR = 2.24, 95 % CI: 1.14–3.61) and overweight in the past (OR = 2.69, 95 % CI: 1.63–4.50) were also proven to be risk factors causing MNs of the digestive system.

4. Psychoemotional states such as stress after losing a loved one (OR = 3.25, 95 % CI: 1.75–6.24), stress at work (OR = 2.84, 95 % CI: 1.7–4.79), intense work (OR = 2.17, 95 % CI: 1.32–3.61), sleep disorders or insomnia in the last six months (OR = 2.20, 95 % CI: 1.31–3.74), and long depression (OR = 2.12, 95 % CI: 0.99–4.73) were proven to be able to contribute to development of MNs of the digestive system.

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Competing interests. The authors declare no competing interests.

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