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# Influence of helicobacteriosis on the development of pancreatic cancer

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*Helicobacter pylori is considered one of the possible risk factors for the development of digestive system pathology in general and pancreatic cancer in particular. The aim of the work was to investigate the pathogenetic relationship between helicobacteriosis and the risk of pancreatic cancer. The study was based on the results of an examination of 64 people aged 43-83 years, who were divided into two groups: the first group (comparison group, n = 34) – men and women without gastrointestinal pathology at the time of examination and the second group (main group, n = 30) – patients with unresectable, metastatic pancreatic head cancer, stage IV T1-4N0-2M1, complicated by obstructive jaundice. It was found that alcohol consumption in an amount of ≥150 g/week significantly increases the relative risk of developing pancreatic cancer by 2.3 (4.7; 1.5) times, and the presence of type II diabetes mellitus - by 2.5 (5.5; 1.6) times. When screening patients for Helicobacter pylori, the results of the rapid test were positive in the main group in 86.7% of patients, in the comparison group – in 73.5% of patients. Comparison of the results of serological examination revealed a significant difference in the content of immunoglobulin A to Helicobacter pylori in the studied groups, a positive test result was observed in 90% of patients in the main group and in 58.8% of patients in the comparison group. The content of immunoglobulin A to Helicobacter pylori in serum >19 U/ml can be considered as a probable risk factor for pancreatic cancer in patients who consume alcohol ≥150 g/week (sensitivity 85.7%, specificity 50%), or have type II diabetes (sensitivity 85.7%, specificity 53.9%).*
*Key words: pancreatic cancer; lifestyle; microbiota; Helicobacter pylori; risk factors.*

## INTRODUCTION

Pancreatic cancer is the most common cause of death among patients with oncological pathology. The features of the anatomical structure of the pancreas, its location determine the late diagnosis of the disease, the high frequency of complications and explain the low survival rate. The incidence of pancreatic cancer and the mortality rate among these patients increases with age (the highest percentage of deaths among patients over 65 years of age), while factors that increase the risk of developing this pathology include alcohol abuse, nicotine addiction, the presence of diabetes mellitus, acute and chronic inflammatory diseases of the pancreas, and hereditary genetic factors [1].

At the same time, some studies indicate a possible etiological similarity between pancreatic and gastric cancer [2]. At the same time, *Helicobacter pylori* (HP) is considered one of the possible risk factors for the development of digestive system pathology in general and pancreatic cancer in particular [3, 4]. This microorganism was declared one of the Group 1 carcinogens by the International Agency for Research on Cancer (IARC), while HP infection is closely associated with the risk of developing gastrointestinal-associated diseases, such as peptic ulcer disease and gastric cancer [5]. There is also data indicating an increased risk of pancreatic cancer among HP-positive patients due to reduced somatostatin secretion and increased secretin secretion [6]. In addition, it has been proven that HP, as part of the dysbacteriosis of the microbiome and the so-called oncobiome, is associated with the development of pancreatic adenocarcinoma by stimulating cell proliferation [7].

However, other researchers question the role of HP in the development of pancreatic cancer. Thus, when analyzing the data of studies by the Japanese Public Health Center (data on patients with positive results of the HP test and the presence of atrophic gastritis, regarding their influence on the development of pancreatic cancer), it was concluded that there was no statistically significant increase or decrease in the risk of pancreatic cancer for patients infected with HP and/or with atrophic gastritis status, independently or in combination [8].

Therefore, given the global trend towards increasing HP infection among the population, further research into this risk factor for pancreatic cancer is undoubtedly useful, both for assessing the threat and for the prognosis of the disease.

The aim of the work was to investigate the pathogenetic relationship between HP infection and the risk of pancreatic cancer.

## METHODS

The study was conducted at the Department of Surgery No.2 of Bogomolets National Medical University and was approved by the Ethics Committee of Bogomolets National Medical University (18.12.2023). All patients were examined during 2024 and signed informed consent to participate in this study and/or treatment at the institution's clinic.

There were 64 people aged 43–83 years examined, who were divided into two groups: the first group (comparison group, n = 34) – men and women without gastrointestinal pathology at the time of examination and the second group (main group, n = 30) – patients with unresectable, metastatic pancreatic head cancer stage IV T1-4N0-2M1, complicated by obstructive jaundice. Patients in the comparison group were examined in outpatient settings, all patients in the main group were hospitalized. Patients in the two groups did not significantly differ in age, gender, body mass index and comorbidity (Table 1).

Pancreatic head cancer was diagnosed and staged according to the National Comprehensive Cancer Network (NCCN) guidelines, 2015-2024, the European Society for Medical Oncology (ESMO 2019, 2023), and the American Joint Committee on Cancer (AJCC) classification, VII-VIII editions (2016-2022) [9]. Histologically, the tumors in all patients were identified as ductal adenocarcinomas. The

**Table 1. Comparative characteristics of patients in the study groups**

| Indicators | Main group (n = 30) | Comparison group (n = 34) | P |
|---|---|---|---|
| Age, years | 63.1±8.3 | 63.7±7.9 | 0.76 |
| Sex | | | |
| Men | 18 (60%) | 18 (52.9%) | 0.57 |
| Women | 12 (40%) | 16 (47.1%) | 0.57 |
| Body-mass index | | | |
| <25 kg/m² | 15 (50%) | 17(50%) | 1.0 |
| ≥25–<27 kg/m² | 10 (33.3%) | 10 (29.4%) | 0.73 |
| ≥27 kg/m² | 5 (14.7%) | 7 (20.6%) | 0.54 |
| Comorbidities | | | |
| Ischemic heart disease | 27 (90%) | 31 (91.2%) | 0.87 |
| Arterial hypertension | 19 (63.3%) | 20 (58.8%) | 0.71 |
| Cerebrovascular accident | 9 (30%) | 14 (41.2%) | 0.35 |
| Chronic obstructive pulmonary disease | 9 (30%) | 12 (35.3%) | 0.65 |

extent and resectability of pancreatic tumors were determined according to the NCCN (2015-2024) and ESMO (2019-2023) guidelines based on a comparison of clinical, laboratory, and radiological findings. Exclusion criteria for both groups were: any erosive-ulcerative lesions of the stomach and/or duodenum at the time of examination, mental illness, and the patient's refusal to participate in the study.

To analyze lifestyle factors that could increase the risk of pancreatic cancer, patients filled out a developed questionnaire. Patients also underwent a screening study for HP in feces using the «Cito test *HP* Ag» and a serological examination to detect antibodies, namely immunoglobulin A (negative result <18 U/ml) and G (negative result <15 U/ml) to HP.

Statistical analysis. Statistical analysis was performed with MedCalc® (Version 23.1.7–64-bit, open access online resource, https://www.medcalc.org). Normality of data distribution was determined by the Shapiro-Wilk test. Differences between groups were determined using the Student's t test for independent samples. Differences in sample distribution were assessed using the $\chi 2$ test. Correlation analysis was performed using Spearman's correlation for nonparametric data distribution. The relationship between the indicators was determined using ROC analysis. The results are presented as mean values and their standard deviation (M ± SD) in the case of parametric distribution and as median and quartile (Me (Q1;Q3)) in the case of nonparametric data distribution. Differences between indicators were considered significant at $P < 0.05$.

## RESULTS

The results of the analysis of lifestyle factors that increase the risk of developing pancreatic cancer are presented in Table 2.

The results of the study revealed that among patients with pancreatic cancer, alcohol consumption ≥150 g/week and type II diabetes mellitus were significantly more common. At the same time, alcohol consumption in an amount of ≥150 g/week significantly increased the relative risk of developing pancreatic cancer by 2.3

**Table 2. Analysis of risk factors for pancreatic cancer development in the study groups**

| Indicators | Main group (n = 30) | Comparison group (n = 34) | P |
|---|---|---|---|
| Alcohol consumption | | | |
| Never | 1(3.3%) | 4 (11.8%) | 0.2 |
| Past | 2 (6.7%) | 5 (14.7%) | 0.31 |
| Occasional | 3 (10%) | 7 (20.6%) | 0.24 |
| <150 g/week | 3 (10%) | 9 (26.5%) | 0.09 |
| ≥150 g/week | 21 (70%) | 9 (26.5%) | 0.0006 |
| Smoking status | | | |
| Never | 8 (26.7%) | 9 (26.5%) | 0.98 |
| Former | 7 (23.3%) | 9 (26.5%) | 0.76 |
| Current | 15 (50%) | 16 (47.1%) | 0.81 |
| History of diabetes mellitus type II | | | |
| Yes | 21 (70%) | 10 (29.4%) | 0.001 |
| No | 9 (30%) | 24 (70.6) | 0.001 |
| Familial history of cancers | | | |
| Yes | 8 (26.7%) | 5 (14.7%) | 0.23 |
| No | 22 (73.3%) | 29 (85.3%) | 0.23 |

(4.7; 1.5) times ($\chi 2$ = 3.13, 95% CI 1.44-4.85, P = 0.0017), and the presence of type II diabetes mellitus - by 2.5 (5.5; 1.6) times ($\chi 2$ = 2.93, 95% CI 1.35-4.56, P = 0.0033).

When screening patients for HP, the results of the rapid test were positive in 79.7% (51/64) of patients, namely in the main group in 26 (86.7%) patients, in the comparison group – in 25 (73.5%) patients ($\chi 2$ = 1.68, 95% CI-7.0-31.67, P = 0.19). When comparing the results of the serological examination, a significant difference in the content of immunoglobulin G to HP in the studied groups was not obtained, a positive result was obtained in the main group in 76.7% (23/30) patients and in 64.7% (22/34) patients in the comparison group ($\chi 2$ = 1.08, 95% CI -10.36-32.36, P = 0.29). However, a significant difference in the content of immunoglobulin A to HP was observed, a positive test result was observed in 90% (27/30) of patients in the main group and in 58.8% (20/34) of patients in the comparison group ($\chi 2$ = 7.82, 95% CI 9.67-40.04, P = 0.005).

Further, an analysis was conducted to determine the presence of an associative relationship between the content of immunoglobulin A to HP in patients who consumed alcohol ≥150 g/week (Fig. 1) and had type II diabetes mellitus (Fig. 2) with the risk of developing pancreatic cancer.

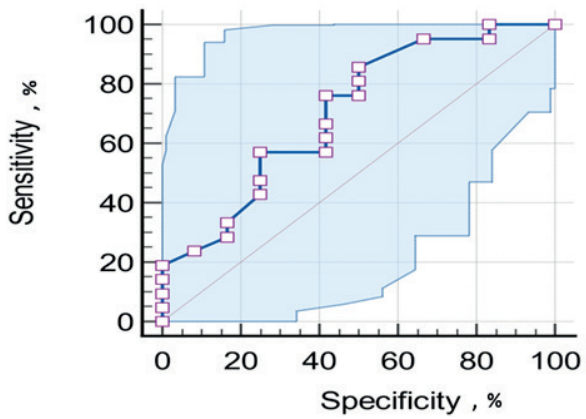


Fig. 1. ROC curve of immunoglobulin A to *Helicobacter pylori* in patients consuming alcohol ≥150 g/week and at risk of developing pancreatic cancer

According to the results of the analysis of immunoglobulin A to HP, the area under the ROC curve (AUROC) is 0.706 (P = 0.037), the cut-off point corresponds to 19 U/ml, the Yoden index is 0.357, i.e. for patients who consume alcohol ≥150 g/week, the content of immunoglobulin A to HP in the blood serum >19 U/ml can be considered as a probable risk factor for the occurrence of pancreatic cancer (sensitivity 85.7%, specificity 50%).

According to the results of the analysis of immunoglobulin A to HP, the area under the ROC curve (AUROC) is 0.718 (P = 0.028), the cut-off point corresponds to 19 U/ml, the Yoden index is 0.395, i.e. for patients with type II diabetes mellitus, the content of immunoglobulin A to HP in the blood serum >19 U/ml can be considered as a probable risk factor for the occurrence of pancreatic cancer (sensitivity 85.7%, specificity 53.9%).

## DISCUSSION

The increase in the incidence of pancreatic cancer is due to both an aging population and an increase in the prevalence of modifiable risk factors for the disease. Population-based interventions aimed at smoking cessation, reducing alcohol consumption, preventing obesity, and reducing weight reduce the risk of developing a number of diseases, including pancreatic cancer. Inherited genetic changes also play a key role in the occurrence of this pathology, and the identification of high-risk individuals, together with improved screening technology, may provide opportunities for early diagnosis of the cause of increasing cancer mortality. We confirmed that alcohol consumption ≥150 g/week significantly increases the relative risk of developing pancreatic cancer by 2.3 (4.7; 1.5) times (P = 0.0017), and the presence of type II diabetes mellitus by 2.5 (5.5; 1.6) times (P = 0.0033).

Recently, new data have been published indicating a possible link between HP and an increased risk of developing acute and chronic

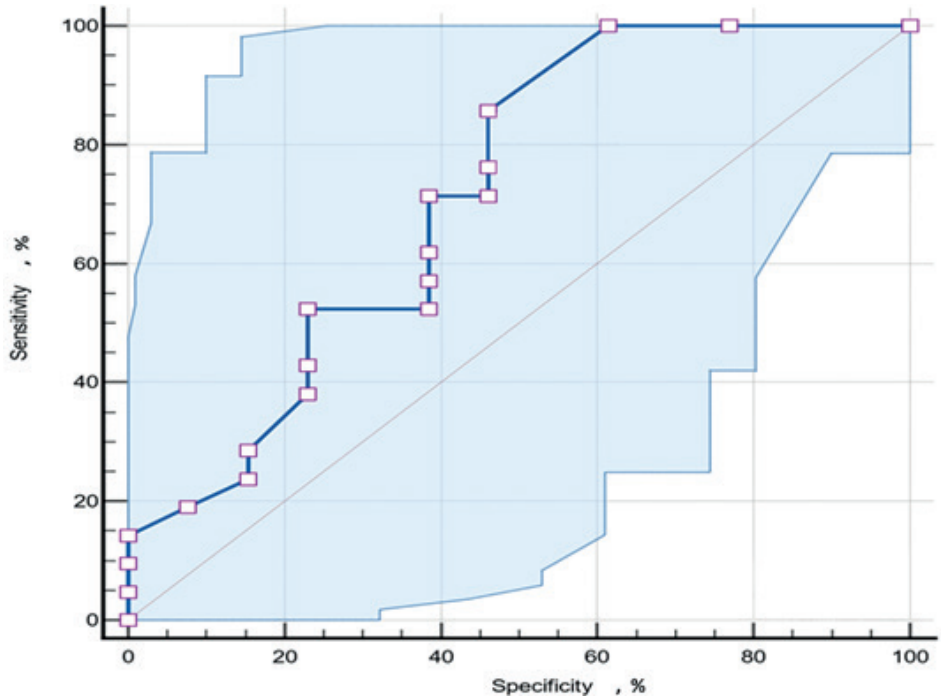


Fig. 2. ROC curve of immunoglobulin A levels to *Helicobacter pylori* in patients with type II diabetes mellitus and at risk of developing pancreatic cancer

pancreatic diseases, but only a few studies have been found linking this bacterium to pancreatic cancer, which, at present, do not contain reliable evidence of such a link [10, 11]. Thus, there is an assumption that some aggressive factors produced by this microorganism (ammonia and lipopolysaccharides), as well as the production of inflammatory cytokines, can induce pancreatic damage [12]. In addition, attention is drawn to the role of HP in inflammation that occurs in autoimmune pancreatitis and is explained by the mechanism of molecular mimicry between several proteins (mainly enzymes) of HP and pancreatic tissue [13].

According to the results of the rapid test for HP, we detected infection with this microorganism in 86.7% of patients with pancreatic cancer, however, such infection was also observed in completely healthy individuals (73.5%), which cannot be considered reliable ($P = 0.19$).

Also, significantly more frequent increase in the content of immunoglobulin A to HP was determined in patients with pancreatic cancer, alcohol abuse and type II diabetes mellitus. However, when comparing the content of immunoglobulin G to HP in the studied groups, no significant difference was obtained (the main group had a positive result in 76.7% of patients, the comparison group - in 64.7% of patients ($P = 0.29$)).

We found an associative relationship between the content of immunoglobulin A to HP in patients who consumed alcohol ≥150 g/week/or had type II diabetes mellitus and the risk of developing pancreatic cancer. It was found that the content of immunoglobulin A to HP in serum >19 U/ml can be considered as a probable risk factor for the occurrence of pancreatic cancer in patients who consumed alcohol ≥150 g/week (sensitivity 85.7%, specificity 50%), or had type II diabetes mellitus (sensitivity 85.7%, specificity 53.9%).

Thus, an increase in the content of immunoglobulin A to HP is one of the risk factors for pancreatic cancer, which requires early

diagnosis and treatment in patients who abuse alcohol or have type II diabetes. In addition, the data obtained indicate the need for antibacterial therapy as part of the complex treatment of patients with pancreatic cancer, the selection of which should be carried out not only taking into account the results of bacterial cultures of bile, but also the sensitivity of HP.

## CONCLUSIONS

1. Alcohol consumption ≥150 g/week significantly increases the relative risk of developing pancreatic cancer by 2.3 (4.7; 1.5) times and the presence of type II diabetes mellitus by 2.5 (5.5; 1.6) times (p=0.0033).

2. When screening patients for *Helicobacter pylori*, the results of the rapid test were positive in the main group in 86.7% of patients, in the comparison group – in 73.5% of patients.

3. Comparison of serological examination results revealed a significant difference in the content of immunoglobulin A to *Helicobacter pylori* in the studied groups, a positive test result was observed in 90% of patients in the main group and in 58.8% of patients in the comparison group.

4. The content of immunoglobulin A to *Helicobacter pylori* in serum >19 U/ml can be considered as a probable risk factor for pancreatic cancer in patients who consume alcohol ≥150 g/week (sensitivity 85.7%, specificity 50%), or have type II diabetes (sensitivity 85.7%, specificity 53.9%).

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## ВПЛИВ ХЕЛІКОБАКТЕРІОЗУ НА РОЗВИТОК РАКУ ПІДШЛУНКОВОЇ ЗАЛОЗИ

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*Helicobacter pylori* розглядається як один з можливих факторів ризику розвитку патології травної системи в цілому та раку підшлункової залози зокрема. Метою нашої роботи було дослідити патогенетичний зв'язок між хелікобактеріозом та ризиком виникнення раку підшлункової залози. Дослідження базувалося на результатах обстеження 64 осіб віком від 43 до 83 років, які були розділені на дві групи: перша група (група порівняння, n = 34) – чоловіки та жінки без патології шлунково-кишкового тракту на момент огляду та друга група (основна група, n = 30) – хворі на нерезектабельний, метастатичний рак головки підшлункової залози IV стадії T1-4N0-2M1, ускладнений обструктивною жовтяницею. Було виявлено, що вживання алкоголю в кількості ≥150 г/тиж вірогідно збільшує відносний ризик розвитку раку підшлункової залози у 2,3 (4,7; 1,5) раза, а наявність цукрового діабету 2-го типу – у 2,5 (5,5; 1,6) рази. При проведенні скринінгового обстеження пацієнтів на *Helicobacter pylori* результати експрес-тесту були позитивними в основній групі у 86,7% хворих, в першій групі – у 73,5% хворих. Порівняння результатів серологічного обстеження виявило вірогідну різниця вмісту імуноглобуліну А до *Helicobacter pylori* у досліджуваних групах, позитивний результат тесту відмічався у 90% пацієнтів основної групи та у 58,8% хворих групи порівняння. Вміст імуноглобуліну А до *Helicobacter pylori* у сироватці крові >19 Од/мл можна розглядати, як вірогідний фактор ризику виникнення раку підшлункової залози у пацієнтів, що вживають алкоголь ≥150 г/тиж (чутливість 85,7%, специфічність 50%), або хворіють на цукровий діабет 2-го типу (чутливість 85,7%, специфічність 53,9%).

Ключові слова: рак підшлункової залози; спосіб життя; мікробіота; *Helicobacter pylori*; фактори ризику.

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