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DISSERTATION
GASTRIC CANCER EPIDEMIOLOGY AND THE PATTERNS OF MEDICATION CONSUMPTION IN UKRAINE: CONTRIBUTIONS AND IMPLICATIONS

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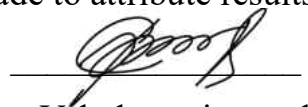
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SUMMARY

Protas Y. Gastric cancer epidemiology and the patterns of medication consumption in Ukraine: contributions and implications. – Degree awarding scientific manuscript is under copyright.

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Gastric cancer is one the leading cause of the mortality, in general as well as due to oncological diseases. It was the fifth most common form of cancer and the fourth leading cause of the death due to oncologic diseases. Despite the fact that incidence rate of gastric cancer is decreasing worldwide, researchers and medical practitioners keep on working on the prevention measure against gastric cancer because of poor prognose of the survival rate for the patients with the diagnosis. Modifiable (such as high salt intake, consumption of processed red meat, smoked food and alcohol, smoking, *Helicobacter pylori* and *Eppstein-Barr virus* infections) and unmodifiable (such as male sex, family history of gastric cancer, hereditary cancer syndromes, gastric and general, autoimmune conditions of stomach mucosal lining) are well identified.

Medication consumption is inevitable part of many people's life. The use of medication despite benefits from the treatment of a disease can be associated with some sides, most often harmful effects.

The aim of the research project was to study epidemiological tendencies of gastric cancer, including its main forms, and to investigate possible patterns of the consumption of pharmaceuticals in Ukraine that can impact development of gastric cancer.

Materials for the project includes: (1) the data on gastric cancer incidence rate and its forms, according to International Classification of Diseases for Oncology, 3rd edition (ICD-O-

3) from 2003 till 2021, (2) data on sales of the following group of drugs and individual substances: proton pump inhibitors (PPI), non-steroidal anti-inflammatory drugs (NSAID), including acetylsalicylic acid (ASA), carbocysteine, erdosteine, *N*-acetylcysteine (NAC), statins and metformin. The data on gastric cancer and its form was obtained from the National Cancer Register of Ukraine. The data on sales of the pharmaceuticals were obtained from PharmXplorer, a program product of of Proxima Research Company.

The highest incidence rate of gastric cancer was recorded in 2005, while the lowest was observed in 2020. Between 2003 and 2020, the incidence rate decreased by 30.63%, with a 33.71% reduction compared to 2005 (95% CI, $P < 0.0001$). The most significant drop occurred between 2019 and 2020, reaching 17.97% (95% CI, $P < 0.0001$).

From 2003 to 2020, a total of 30 different types of primary gastric cancer were diagnosed in Ukraine. Among these, eight forms were consistently recorded every year: adenocarcinoma NOS (8140), adenocarcinoma scirrhous (8141), intestinal type adenocarcinoma (8144), diffuse type adenocarcinoma (8145), adenocarcinoma tubular (8211), solid adenocarcinoma (8230), neuroendocrine tumor (8240), and papillary adenocarcinoma (8260). However, four forms of gastric cancer were intermittently absent in certain years: adenomatous polyp (8210) had no cases in 2018, neuroendocrine carcinoma (8246) was not diagnosed between 2003 and 2009, adenocarcinoma in tubulovillous adenoma (8263) was absent in 2014 and 2020, and clear cell adenocarcinoma (8310) was not recorded in 2019.

Among these four forms, neuroendocrine carcinoma was particularly noteworthy, as it was not diagnosed between 2003 and 2009 but appeared in 2010 with an incidence rate of 0.01 per 100,000 people/year, increasing more than sixfold by 2019. Adenocarcinoma NOS remained the most common type, declining slightly from 96.03% of total cases in 2003 to 95.20% in 2020. The highest morbidity rate occurred in 2005, while the lowest was recorded in 2020. Between 2019 and 2020, the morbidity rate dropped by 2.031-fold (95% CI, $P < 0.0001$), with a reliable decreasing trend over the entire study period ($R^2 = 0.7$), mirroring the overall incidence trend of gastric cancer in Ukraine.

The collective incidence rate of all gastric cancer types, excluding adenocarcinoma NOS, remained between 0.34 and 0.55 per 100,000 people/year in 2017 and 2019, respectively, with relatively stable trends. From 2003 to 2014, adenocarcinoma scirrhous was the second most common type of gastric cancer, but from 2015 to 2020, it dropped to the seventh position, decreasing from 1.5% of total cases in 2003 to 0.47% in 2020. The lowest recorded percentage was in 2018, at 0.27% of cases, with a notable 8.45-fold difference between the highest and lowest incidence rates (95% CI, $P < 0.0001$), demonstrating a statistically reliable decreasing trend ($R^2 = 0.8$).

Between 2003 and 2008, solid adenocarcinoma was the third most common type, followed by diffuse type adenocarcinoma in fourth place. However, from 2009 to 2020, diffuse type adenocarcinoma became the third most common form, indicating a gradual increase in its incidence. The incidence of adenocarcinoma tubular also increased over time, peaking in 2019, though the trend was not statistically reliable ($R^2 = 0.048$). Similarly, the incidence of intestinal type adenocarcinoma rose more than 18 times by 2020 compared to 2004, but its trend reliability was moderate ($R^2 = 0.73$). Meanwhile, neuroendocrine tumors (8240) and papillary adenocarcinomas (8260) exhibited stable incidence rates from 2003 to 2020. Hepatocellular adenocarcinoma and linitis plastica were diagnosed only once during the study period, in 2005 and 2007, respectively.

Regarding pharmacological trends, the consumption of PPIs steadily increased in Ukraine from 2014 to 2021, with the daily defined dose (DDD) rate rising by 98.61% ($P < 0.0001$) in 2020 compared to 2014, without any declines or deviations. The consumption of cysteine derivatives followed a similar pattern, with two significant drops: 15.02% in 2015 ($P < 0.0001$) compared to 2014 and 2.44% in 2019 ($P < 0.0001$) compared to 2018. The highest increase occurred in 2016, with a 36.57% rise ($P < 0.0001$) from 2015, culminating in an overall 42.06% increase ($P < 0.0001$) by 2020 compared to 2014.

NSAID consumption in Ukraine also grew from 2014 to 2020, though fluctuations were noted. The DDD rate declined by 9.92% in 2015 ($P < 0.0001$) compared to 2014 and

again by 3.50% in 2020 ($P < 0.0001$) compared to 2019. A peak increase of 26.50% ($P < 0.0001$) was observed in 2019 compared to 2015. Similarly, the consumption of low-dose ASA rose, with minor declines in 2015 (-8.48%, $P < 0.0001$), 2018 (-0.63%, $P < 0.0001$), and 2019 (-1.30%, $P < 0.0001$), while notable increases were recorded in 2017 (+17.72%, $P < 0.0001$) and 2020 (+14.97%, $P < 0.0001$).

The use of statins in Ukraine increased significantly between 2014 and 2020, despite a slight 5.94% decline in 2015 ($P < 0.0001$). By 2020, consumption had risen nearly threefold ($P < 0.0001$) compared to 2014. Similarly, the DDD rate of metformin showed a steady increase throughout the study period, with no observed declines, reaching a 2.41-fold increase in 2021 ($P < 0.0001$) compared to 2014.

The use of combined drugs for *Helicobacter pylori* (*H. pylori*) eradication demonstrated an unstable trend from 2014 to 2020. Three declines were noted: a 19.18% decrease in 2015 compared to 2014 ($P < 0.0001$), a sharp 47.89% drop in 2016 compared to 2015 ($P < 0.0001$), followed by a significant rebound in 2017, which was nearly 2.5 times greater than in 2016 ($P < 0.0001$). The final decrease of 8.02% occurred in 2020 compared to 2019 ($P < 0.0001$).

Concurrently, the incidence rate of gastric cancer in Ukraine decreased by 26.56% between 2014 and 2021 ($P < 0.0001$). Adenocarcinoma remained the predominant form of gastric cancer during this period. Between 2014 and 2022, the total number of cancer cases in Ukraine showed fluctuations, peaking at 138,509 cases in 2019 before declining sharply to 113,368 in 2020. By 2021, cases rebounded to 120,055 but dropped again to 106,151 in 2022, indicating ongoing challenges in cancer detection and control.

Gastric cancer cases followed a steady downward trend, declining from 8,350 cases in 2014 to 5,401 cases in 2022, while the gastric cancer rate remained relatively stable. Gender distribution remained consistent, with men accounting for approximately 61% of cases throughout the period. The proportion of gastric cancer patients over the age of 45 remained above 94% across all study years.

The percentage of gastric cancer among total cancer cases gradually declined from 1.49% in 2014 to 1.46% in 2019. However, a temporary increase was observed in 2020, reaching 1.78%, followed by stabilization at 1.68% in 2021 and another rise to 1.90% in 2022.

Innovative aspects of the research and its findings. This study provides a new long-term assessment of trends in gastric cancer incidence, gender differences, and age-related prevalence from 2003 to 2022, offering a deeper understanding of the evolution of this disease in Ukraine.

Unlike previous studies, this research systematically analyzes the potential protective and risk-enhancing effects of widely used medications, including proton pump inhibitors, statins, nonsteroidal anti-inflammatory drugs (NSAIDs), metformin, and cysteine derivatives, in the development and prevention of gastric cancer.

Additionally, the study presents new data on the efficacy of fixed drug combinations for *H. pylori* eradication and their contribution to reducing gastric cancer incidence in Ukraine.

Particular attention is given to the potential of cysteine derivatives in preventing *H. pylori* adhesion and enhancing eradication efficacy, an underexplored aspect in current gastric cancer prevention strategies.

By comparing national data with global trends, the study identifies critical gaps in screening, early detection of gastric cancer, and pharmacological interventions, proposing strategies to improve the healthcare system.

Furthermore, it provides a new quantitative assessment of the correlation between increased consumption of medications such as statins, NSAIDs, and metformin and the reduction in gastric cancer incidence, suggesting their potential chemopreventive role.

Integrating epidemiological, pharmacological, and public health aspects, this study offers a comprehensive approach to gastric cancer prevention, combining pharmacological interventions with traditional risk reduction strategies.

Theoretical and practical relevance of the study. The study results provide important insights into the impact of widely used pharmacological agents (proton pump inhibitors,

statins, nonsteroidal anti-inflammatory drugs, metformin, and cysteine derivatives) on the incidence of gastric cancer, highlighting their potential preventive or risk-modifying properties. The analysis of epidemiological trends demonstrates a correlation between the consumption levels of these medications and the decline in gastric cancer incidence in Ukraine, aligning with global trends. The findings contribute to the improvement of gastric cancer prevention strategies, particularly by optimizing *H. pylori* eradication protocols and ensuring the rational use of proton pump inhibitors. These conclusions may be valuable for healthcare professionals, policymakers, and researchers in developing targeted measures aimed at reducing gastric cancer incidence and improving public health systems.

Key words: *gastric cancer, medication, PPI, carbocysteine, erdosteine, N-acetylcysteine, NSAID, acetylsalicylic acid, metformin, statins, adenocarcinoma, epidemiology.*

АНОТАЦІЯ

Протас Є. Епідеміологія раку шлунка та моделі споживання лікарських препаратів в Україні: внесок і наслідки. – Кваліфікаційна наукова праця на правах рукопису.

Дисертація подається на здобуття наукового ступеня доктора філософії (PhD) за напрямом підготовки 22 «Охорона здоров'я», спеціальність 229 «Громадське здоров'я». – Дніпровський державний медичний університет, Дніпро, Україна, 2025.

Роботу виконано на кафедрі соціальної медицини, громадського здоров'я та управління охороною здоров'я Дніпровського державного медичного університету, 2021-2024.

Рак шлунка є однією з основних причин смертності, як в цілому, так і внаслідок онкологічних захворювань. Він був п'ятою за поширеністю формою раку і четвертою причиною смертності від онкологічних захворювань. Незважаючи на те, що рівень захворюваності на рак шлунка в усьому світі знижується, дослідники та лікарі продовжують працювати над заходами профілактики раку шлунка через поганий прогноз виживаності пацієнтів з таким діагнозом. Модифікабельні (наприклад, велике споживання солі, споживання обробленого червоного м'яса, копченої їжі та алкоголю, куріння, інфекції, викликані *H. pylori* та вірусом Еппштейн-Барра) і немодифікабельні (наприклад, чоловіча стать, сімейна історія раку шлунка, синдроми спадкового раку, шлунка та загальні автоімунні захворювання слизової оболонки шлунка) добре визначені.

Вживання ліків є невід'ємною частиною життя багатьох людей. Застосування ліків, незважаючи на користь від лікування захворювання, може бути пов'язане з деякими побічними, найчастіше шкідливими наслідками.

Метою наукового проєкту було вивчити епідеміологічні тенденції раку шлунка, в тому числі його основних форм, а також дослідити можливі моделі споживання лікарських засобів в Україні, які можуть впливати на розвиток раку шлунка.

Матеріали для проекту включають: (1) дані про рівень захворюваності на рак шлунка та його форми згідно з Міжнародною класифікацією онкологічних хвороб 3 видання (МКБ-О-3) з 2003 по 2021 рік, (2) дані про продажі наступна група лікарських засобів та окремих речовин: інгібітори протонної помпи (ІПП), нестероїдні протизапальні засоби (НПЗЗ), включаючи ацетилсаліцилову кислоту (АСК), карбоцистеїн, ердостеїн, Н-ацетилцистеїн (НАЦ), статини та метформін. Дані про рак шлунка та його форму отримані з Національного канцер-реєстру України. Дані про продажі ліків були отримані з PharmXplorer, програмного продукту компанії Proxima Research.

Найвищий рівень захворюваності на рак шлунка було зафіксовано у 2005 році, а найнижчий – у 2020 році. У період з 2003 по 2020 рік рівень захворюваності знизився на 30,63%, а у порівнянні з 2005 роком – на 33,71% (95% ДІ, $p < 0,0001$). Найбільше зниження відбулося між 2019 і 2020 роками, досягнувши 17,97% (95% ДІ, $p < 0,0001$).

У період з 2003 по 2020 рік в Україні було діагностовано загалом 30 різних форм первинного раку шлунка. Серед них вісім форм були стабільно зареєстровані щороку: аденокарцинома NOS (8140), скіррозна аденокарцинома (8141), аденокарцинома кишкового типу (8144), дифузна аденокарцинома (8145), трубчаста аденокарцинома (8211), солідна аденокарцинома (8230), нейроендокринна пухлина (8240) та папілярна аденокарцинома (8260). Однак чотири форми раку шлунка були відсутні у певні роки: аденоматозний поліп (8210) не реєструвався у 2018 році, нейроендокринна карцинома (8246) не діагностувалася в період 2003–2009 років, аденокарцинома в тубуло-віллезній аденомі (8263) не була зафіксована у 2014 та 2020 роках, а світлоклітинна аденокарцинома (8310) – у 2019 році.

Серед цих чотирьох форм особливої уваги заслуговує нейроендокринна карцинома, яка не діагностувалася у 2003–2009 роках, але з'явилася у 2010 році з рівнем захворюваності 0,01 на 100 000 осіб/рік, а до 2019 року цей показник зріс у шість разів. Аденокарцинома NOS залишалася найпоширенішим типом, знизившись з 96,03% усіх

випадків у 2003 році до 95,20% у 2020 році. Найвищий рівень захворюваності відзначався у 2005 році, а найнижчий – у 2020 році. Між 2019 і 2020 роками рівень захворюваності знизився у 2,031 рази (95% ДІ, $p < 0,0001$), а загальна тенденція до зменшення була статистично достовірною протягом усього періоду дослідження ($R^2 = 0,7$), що відображає загальну динаміку захворюваності на рак шлунка в Україні.

Сукупний рівень захворюваності на всі типи раку шлунка, окрім аденокарциноми NOS, залишався в межах 0,34–0,55 на 100 000 осіб/рік у 2017 та 2019 роках відповідно, демонструючи стабільну динаміку. У 2003–2014 роках скіррозна аденокарцинома була другою за поширеністю формою раку шлунка, але в 2015–2020 роках вона опустилася на сьоме місце, зменшившись з 1,5% загальної кількості випадків у 2003 році до 0,47% у 2020 році. Найнижчий відсоток цього типу раку спостерігався у 2018 році – 0,27% від загальної кількості випадків. Різниця між найвищим та найнижчим рівнем захворюваності становила 8,45 рази (95% ДІ, $p < 0,0001$), а тенденція до зниження була статистично достовірною ($R^2 = 0,8$).

З 2003 по 2008 рік солідна аденокарцинома була третьою за поширеністю, а дифузна аденокарцинома займала четверте місце. Однак у 2009–2020 роках дифузна аденокарцинома стала третьою за частотою, що свідчить про її поступове зростання. Поширеність трубчастої аденокарциноми також збільшувалася, досягнувши піку у 2019 році, хоча загальна тенденція була статистично недостовірною ($R^2 = 0,048$). Аналогічно, захворюваність на аденокарциному кишкового типу зросла більш ніж у 18 разів до 2020 року у порівнянні з 2004 роком, але її тенденція також не була достовірною ($R^2 = 0,73$). У той же час, нейроендокринні пухлини (8240) та папілярна аденокарцинома (8260) демонстрували стабільні рівні захворюваності з 2003 по 2020 рік. Гепатоцелюлярна аденокарцинома та лінітний пластичний рак були діагностовані лише один раз за період дослідження – у 2005 та 2007 роках відповідно.

Щодо фармакологічних тенденцій, споживання інгібіторів протонної помпи стабільно зростало в Україні у 2014–2021 роках, при цьому рівень визначених добових

доз збільшився на 98,61% ($p < 0,0001$) у 2020 році порівняно з 2014 роком без суттєвих спадів. Споживання похідних цистеїну зросло аналогічним чином, хоча спостерігалися два суттєві зниження: 15,02% у 2015 році ($p < 0,0001$) та 2,44% у 2019 році ($p < 0,0001$). Найбільше зростання зафіксовано у 2016 році (+36,57%, $p < 0,0001$), а загальне збільшення у 2020 році становило 42,06% ($P < 0,0001$) у порівнянні з 2014 роком.

Споживання НПЗП у 2014–2020 роках також зросло, хоча спостерігалися коливання. У 2015 році було зафіксовано зниження на 9,92% ($p < 0,0001$), а у 2020 році – на 3,50% ($p < 0,0001$) порівняно з 2019 роком. Пік споживання відзначався у 2019 році, коли рівень визначених добових доз зріс на 26,50% ($p < 0,0001$) у порівнянні з 2015 роком.

Водночас рівень захворюваності на рак шлунка в Україні у 2014–2021 роках знизився на 26,56% ($p < 0,0001$). Загальна кількість онкологічних випадків у країні коливалася, досягнувши піку у 2019 році (138 509 випадків) перед різким падінням до 113 368 у 2020 році. У 2021 році кількість випадків відновилася до 120 055, але знову знизилася до 106 151 у 2022 році.

Кількість випадків раку шлунка знизилася з 8 350 у 2014 році до 5 401 у 2022 році. Чоловіки стабільно складали близько 61% випадків, а понад 94% пацієнтів були старшими за 45 років.

Це дослідження пропонує нову довготривалу оцінку тенденцій захворюваності на рак шлунка, гендерних відмінностей та вікової поширеності у період 2003–2022 років, надаючи глибше розуміння еволюції цього захворювання в Україні.

Новизна дослідження та одержаних результатів. На відміну від попередніх робіт, це дослідження систематично аналізує потенційні захисні та ризикові ефекти широко використовуваних лікарських засобів, зокрема інгібіторів протонної помпи, статинів, нестероїдних протизапальних препаратів (НПЗП), метформіну та похідних цистеїну, у розвитку та профілактиці раку шлунка.

Окрім того, дослідження надає нові дані щодо ефективності фіксованих комбінацій лікарських засобів для ерадикації *H. pylori* та їхнього внеску в зниження рівня захворюваності на рак шлунка в Україні.

Особливу увагу приділено потенціалу похідних цистеїну у запобіганні адгезії *H. pylori* та підвищенні ефективності ерадикації, що є малодослідженим аспектом у сучасних стратегіях профілактики цього виду раку.

Порівнюючи національні показники з глобальними тенденціями, дослідження виявляє ключові прогалини у скринінгу, ранньому виявленні раку шлунка та фармакологічних втручаннях, пропонуючи шляхи вдосконалення системи охорони здоров'я.

Також представлено нову кількісну оцінку взаємозв'язку між збільшенням споживання лікарських засобів, таких як статини, НПЗП та метформін, і зниженням захворюваності на рак шлунка, що може свідчити про їхню потенційну хемопрофілактичну роль.

Узагальнюючи епідеміологічні, фармакологічні та громадсько-оздоровчі аспекти, це дослідження пропонує комплексний підхід до профілактики раку шлунка, поєднуючи фармакологічні втручання з традиційними методами зниження ризику.

Теоретична та практична цінність роботи. Результати дослідження надають важливу інформацію про вплив широко застосовуваних фармакологічних засобів (інгібіторів протонної помпи, статинів, нестероїдних протизапальних препаратів, метформіну та похідних цистеїну) на частоту розвитку раку шлунка, підкреслюючи їхні потенційні профілактичні або ризик-модифікуючі властивості. Аналіз епідеміологічних тенденцій демонструє взаємозв'язок між рівнем використання цих препаратів і зменшенням захворюваності на рак шлунка в Україні, що узгоджується зі світовими тенденціями. Отримані результати сприяють удосконаленню стратегій профілактики раку шлунка, зокрема покращенню схем ерадикації *H. pylori* та раціональному використанню інгібіторів протонної помпи. Ці висновки можуть стати корисними для

медичних фахівців, політиків та науковців у розробці цільових заходів, спрямованих на зниження захворюваності на рак шлунка та покращення системи громадського здоров'я.

Ключові слова: *рак шлунка, ліки, ІПП, карбоцистеїн, ердостеїн, N-ацетилцистеїн, НПЗП, ацетилсаліцилова кислота, метформін, статини, аденокарцинома, епідеміологія*.

LIST OF PUBLICATIONS

The articles in which the main scientific findings are published:

1. Chernov, Y. O. (Protas Y.), Haysanovska, V., & Makarenko, O. V. (2024). Gastric cancer in Ukraine: epidemiologic data and its nosological structure between 2003 and 2020. *Przeglad gastroenterologiczny*, *16*(4), 428–433. https://doi.org/10.5114/pg.2024.134840
2. Протас Є.О., Макаренко О.В., Дука Р.В. Вплив комбінованих препаратів у фіксованих дозах для ерадикації *Helicobacter pylori* на показники захворюваності на рак шлунка в Україні з 2014 до 2021 р. Медичні перспективи. 2025. Т. 30, № 1. С. 202-205. https://doi.org/10.26641/2307-0404.2025.1.325466
3. Protas, Y. O, Makarenko, O. V. (2025). Epidemiology of gastric cancer in Ukraine from 2014–2022: rate, sex and age. *Intermedical journal* 1(2025) C. 121-124. https://doi.org/10.32782/2786-7684/2025-1-21

Scientific publications confirming the validation of the research

4. Protas Y.O., Makarenko O.V. Gastric cancer epidemiologic data in Ukraine in 2003-2020. Materials of the scientific and practical conference with international participation “Ecologic and hygienic issues of the human life activity”, March 13, 2024. P. 25.
5. Protas Y.O., Makarenko O.V. Consumption of proton pump inhibitors in Ukraine from 2014 till 2020. Materials of XI The international scientific and practical distance conference “Management and marketing as parts of modern economy, science, education, practice", March 21, 2024. P. 369.
6. Protas Y.O., Makarenko O.V. Impact of *Helicobacter pylori* eradication and frequently used medications on gastric cancer incidence in Ukraine (2014–2021). Materials of the

all-Ukrainian scientific and practical conference “Public health: from analysing the past to understanding the future”, October 10, 2024. P. 35-39.

CONTENT

LIST OF ABBREVIATIONS

AI	Artificial inteligence
Akt	Protein kinase B
ASA	Acetylsalicylic acid
ATP	Adenosine triphosphate
BabA	Blood group antigen binding adhesin
COX	Cyclooxygenase
CagA	*Cytotoxin associated gene A*
DDD	Daily defined dose
EMT	Epithelial–mesenchymal transition
GERD	Gastroesophageal reflux disease
H. pylori	*Helicobacter pylori*
ICD-O-3	International Classification of Diseases for Oncology, 3rd edition
IGF	Insulin-like growth factor
IL	Interleukin
mTOR	The mammalian target of rapamycin
MUC	Mucin
NAC	*N*-acetylcysteine
NF	Nuclear factor
NOS	Not other specified
NSAID	Non-steroidal anti-inflammatory drugs
PI3K	Phosphoinositide 3-kinases
PPI	Proton pump inhibitors
ROS	Reactive oxygen species
TNF	Tumor necrosis factor
VacA	*Vacuolating cytotoxin gene A*

INTRODUCTION

Ratinale for the chosen topic. Gastric cancer is still one of leading causes of death in general, 4th leading cause of death due to oncologic diseases, and is 5th most common form of cancer. In 2020, around 1,1 million people were diagnosed with gastric cancer and 0,77 million died because of the disease [1].

The disease is more frequently diagnosed in male than in female patients thus the male sex is considered to be an unmodifiable risk factor for gastric cancer [2].

Most of the cases of gastric cancer, more than half of cases, are diagnosed in the developed countries, i.e. countries with high and very high human. The region where most of the cases were diagnosed are Europe (Eastern and Western Europe), Asia (except Western Asia), Latin America [1, 2].

The causative role of many factors were noticed and confirmed by the researchers in the field. The main risk factors of gastric cancer are genetic type (family history of gastric cancer), food habits (salty, smoked, fried food), *H. pylori* and *Eppstein-Barr* infection [3].

Despite the declining trend of gastric cancer, growing population and prolonged life expectance, the prognosis says that the gastric cancer will a burden for the world healthcare and economy even in 2040 [1, 2]

Modern medicine can provide us with a bench of the evidence of the harmful and beneficial use of drugs. In most of the cases of serious adverse effects, neither medical practitioner nor patients were completely aware of the consequences until it was too late, and nothing could be changed [4]. The thalidomide tragedy, rofecoxib discreditation and a happy ending story of pegylated interferon, the side effect of which became a magic stick for the patients suffering from thrombocytosis [4, 5].

Many widely used drugs can influence development of gastric cancer. These drugs may be, either a risk factor or a preventive factor for the gastric cancer [6].

There have been also published several meta-analyses suggesting that use of PPIs is associated with higher risk of gastric cancer. None of the articles has claimed causative or contributing role for this group of drugs [7, 8, 9]. These studies has also been supported be the experimental studies suggesting that use of PPI lead to the promotion of persistent *H. pylori* infection and gastrin upregulation, which cause gastric mucus hyperplasia [10, 11, 12, 13]. Nevertheless, the most recent meta-analysis suggests no meaningful association between use of PPIs and gastric cancer [14]. Another review is implying that the appropriate use, considering the lowest effective dose and the shortest possible regimen, and further studies are needed [15].

Metformin, statins, NSAIDs and cysteine derivatives are considered to protect against gastric cancer [6, 16, 17, 18].

In this study we evaluated the level of consumption of drugs that can play a role in the development of gastric cancer, from 2014 till 2020, and epidemiological indices of gastric cancer Ukraine, from 2003 till 2021.

Considering many previous and ongoing studies in the field of gastric cancer and the implications of the pharmaceuticals in its development, we decided to study level of consumption of the most frequently used drugs in Ukraine, elaborate on the possible explanation of the role of these drugs in the development of gastric cancer. Here we also provide some examples of the future organizational and interventional approaches that can facilitate future studies and in the field of gastric cancer and possible ways of its prevention.

The relevance of the research to scientific programs, plans, and topics. The research work is being carried out within the framework of the research projects of the Department of Social Medicine, Public Health, and Health Care Management: "Scientific justification of organizational and methodological foundations of the system for continuous improvement of the quality of medical care", state registration № 0119U101403, implementation period 01.01.2020 - 31.12.2023 and "Scientific justification of strategies for preserving and restoring

public health through the impact on the determinants of health care system efficiency", state registration № 0123U104849, implementation period 01.01.2024 - 31.12.2027.

Aims of the research project: to investigate the epidemiological trends, key risk factors, and the multifaceted impact of various pharmacological interventions on both the prevention and management of gastric cancer in Ukraine, with a particular emphasis on *H. pylori* eradication strategies and the role of common therapeutic agents such as PPIs, statins, NSAIDs, metformin, and cysteine derivatives in influencing disease propagation and incidence rates.

Objectives of the research:

1. To identify and assess key risk factors for the development of gastric cancer, including *H. pylori* infection, dietary habits, and other lifestyle factors.
2. To investigate the trends in incidence, age distribution, and nosological structure of gastric cancer in Ukraine from 2003 to 2022.
3. To study the role of pharmacological agents, such as proton pump inhibitors, statins, nonsteroidal anti-inflammatory drugs, metformin, and cysteine derivatives, in influencing the risk and prevention of gastric cancer.
4. To evaluate the effectiveness of various pharmacological regimens, particularly fixed-dose combinations, for the eradication of *H. pylori* and their correlation with changes in gastric cancer incidence.
5. To compare the epidemiological trends and treatment strategies for gastric cancer in Ukraine with those in other regions worldwide to identify potential areas for improvement.
6. To develop evidence-based recommendations to enhance early detection, prevention, and treatment strategies for gastric cancer through the optimization of pharmacological and screening protocols.

Subjects of the research: cases of gastric cancer in Ukraine from 2003 to 2022, classified by age, gender, and cancer subtype; pharmacological agents and their role in

influencing the risk and prevention of gastric cancer, including proton pump inhibitors, statins, nonsteroidal anti-inflammatory drugs, metformin, and cysteine derivatives; *H. pylori* eradication strategies, including fixed-dose combination therapies, and their impact on gastric cancer incidence; the role of healthcare policies and medical practices in reducing or maintaining the level of gastric cancer incidence in Ukraine.

Objects of the research: incidence, prevalence, gender and age distribution, and nosological structure of gastric cancer in Ukraine from 2003 to 2022; patterns of drug consumption in Ukraine related to the risk, prevention, and treatment of gastric cancer, including proton pump inhibitors, statins, nonsteroidal anti-inflammatory drugs, metformin, cysteine derivatives, and fixed-dose combinations for *H. pylori* eradication.

Innovative aspects of the research findings. This research provides a novel longitudinal assessment of gastric cancer incidence trends, nosological structure, gender disparities, and age-related prevalence from 2003 to 2022, offering a deeper understanding of the disease's evolution in Ukraine.

Unlike previous studies, this work systematically evaluates the potential protective and risk-enhancing roles of frequently used drugs such as PPIs, statins, NSAIDs, metformin, and cysteine derivatives in gastric cancer development and prevention.

The study introduces new insights into the effectiveness of fixed-dose combination therapies for *H. pylori* eradication and their contribution to the observed decline in gastric cancer cases in Ukraine.

This research highlights the potential of cysteine derivatives in inhibiting *H. pylori* adhesion and improving eradication success, an aspect underexplored in the context of gastric cancer prevention strategies.

By comparing national data with global trends, the study identifies critical gaps in gastric cancer screening, early detection, and pharmacological interventions, proposing strategies for healthcare improvement.

The study provides a novel quantitative assessment of how increasing drug consumption trends, particularly of statin, NSAIDs and metformin align with the decline in gastric cancer incidence, suggesting a possible chemopreventive role.

This research integrates epidemiology, pharmacology, and public health perspectives to propose a more holistic approach to gastric cancer prevention, focusing on pharmacological intervention alongside traditional risk-reduction measures.

Practical significance of the study results. The study results provide valuable insights into the impact of commonly used pharmacological agents (PPIs, statins, NSAIDs, metformin, and cysteine derivatives) on gastric cancer incidence, highlighting their potential preventive or risk-modifying roles. By analysing epidemiological trends, the research identifies correlations between drug consumption patterns and the declining incidence of gastric cancer in Ukraine, aligning with global trends. These findings support the optimization of gastric cancer prevention strategies, particularly through improved *H. pylori* eradication protocols and the cautious use of PPIs. The results can guide healthcare professionals, policymakers, and researchers in developing targeted interventions to reduce gastric cancer incidence and improve public health outcomes.

Personal contribution of the PhD-candidate. The dissertation is an independent and completed scientific work of the candidate. The research objectives and tasks were determined by the candidate in collaboration with the research supervisor (Professor O.V. Makarenko). Together, they developed the general research methodology and outlined the subjects and objects of the study.

The candidate personally conducted the patent and literature search, performed experimental research, summarized, analysed, and systematized the obtained results, provided their scientific interpretation, and formulated the conclusions and practical recommendations. In the dissertation, only those findings that result from the candidate's personal research are included from co-authored scientific publications.

Presentations of the dissertation results. The main results obtained during the dissertation work were presented at the scientific and practical conference with international participation “Ecologic and hygienic issues of the human life activity” (Kyiv, March 13, 2024); the XI international scientific and practical distance conference “Management and marketing as parts of modern economy, science, education, practice", (Kharkiv, March 21, 2024); the all-Ukrainian scientific and practical conference “Public health: from analysing the past to understanding the future” (Dnipro, October 10, 2024); the scientific and practical internet-conference with international participation “Topical issues of clinical pharmacology and clinical pharmacy” (Kharkiv October 29-30, 2024).

Structure and scope of the dissertation. The dissertation comprises 142 pages and includes an introduction, a literature review, a section detailing the research materials and methods, three chapters presenting the results of the original research, an analysis and synthesis of the findings, conclusions, practical recommendations, and a bibliography containing 236 references. Additionally, the dissertation includes supplements and is illustrated with 9 tables and 10 figures.

CHAPTER 1

STOMACH CANCER: THROUGH MORPHOLOGY TO EPIDEMIOLOGY

1.1. Gastric cancer epidemiology

Gastric cancer is an oncologic disease. It is the fifth most common form of cancer and the fourth leading cause of cancer-related deat [3, 19]. Yearly, around 1000000 new cases of gastric cancer are diagnosed and around 700000-800000 deaths are registered due to gastric cancer [1, 19, 20].

Risk factors for gastric cancer can be divided in two groups: environmental and host-related [21]. Environmental (modifiable) risk factors are infections with *H. pylori* and *Epstein-Barr virus*, smoking, consumption of salt, smoked food, red meat and alcohol. Host-related (unmodifiable) risk factors are male sex, family history of gastric cancer, hereditary gastric cancer syndromes, hereditary cancer syndromes, autoimmune gastritis and pernicious anaemia [3, 21]. Type II diabetes and obesity are also factors that requires more detailed studies [22, 23].

The most common form of gastric cancer is adenocarcinoma, not other specified (adenocarcinoma NOS) [24].

Gastric cancer can be caused by *H. pylori* and its role in the development of gastric cancer was studied extensively. In this light, molecular genetic characteristics defining individual strains phenotype and properties plays crucial role. Some phenotypes were identified as those associated with higher risk of gastric cancer [3, 10, 24, 25].

Considering the role of *H. pylori* in the development of gastric cancer a pathogenetic model was proposed. The progression towards gastric cancer begins with non-atrophic gastritis triggered by cagA+/vacAs1m1 *H. pylori* isolates [10].

Type 2 diabetes mellitus is associated with an increased risk of various cancers, including gastric cancer. Hyperglycaemia, hyperinsulinemia, and insulin resistance, which are

characteristic features of diabetes, have been linked to the development and progression of gastric cancer. These metabolic abnormalities can create a pro-inflammatory and pro-tumorigenic environment, contributing to cancer initiation and progression [26].

A study examining the prevalence of different types of cancer among type II diabetes mellites patients found a significant association between diabetes and the incidence of colorectal carcinoma, breast cancer, uterine carcinoma, and haematological malignancies. Interestingly, the study also noted that non-diabetic patients had higher rates of prostate, lung, and gastric carcinomas [27].

Obesity is a major risk factor for various cancers, including gastric cancer. Adipose tissue in obese individuals secretes various adipokines and inflammatory cytokines, which can promote a pro-inflammatory state and contribute to cancer development. Adiponectin, an adipokine, plays a critical role in obesity-driven cancers, including gastric cancer. Lower levels of adiponectin are often observed in obese individuals, which can lead to increased inflammation and tumorigenesis [28].

Good health-promoting lifestyle behaviours, such as regular physical activity, healthy eating, and stress management, are crucial in preventing overweight and obesity, which are major risk factors for type II diabetes and certain types of cancer [29].

Stomach: histology and physiology

The stomach, a muscular organ in the gastrointestinal tract, plays a crucial role in generating and secreting hydrochloric acid into its lumen. The intricate control of acid secretion involves a complex process influenced by various humoral and neuronal pathways. Nervous stimuli trigger increased parietal acid secretion through a cascade involving the assembly and activation of proton pumps, as outlined in Schubert and Peura's review [10, 30].

Histologically, two distinct types of glands are found in the gastric mucosa – oxyntic glands and pyloric glands. Oxyntic glands, prevalent in the stomach corpus, house parietal cells responsible for hydrochloric acid secretion. Pyloric glands, on the other hand, are primarily associated with G cells that release gastrin into the bloodstream upon activation.

Gastrin, in turn, stimulates histamine release from enterochromaffin cells, contributing to the activation of H+K+-ATPase, a proton pump. The dynamics of gastrin secretion are altered during *H. pylori* infection, with decreased levels during acute infection and elevated levels in cases of antral gastritis. Progressive infection can lead to irreversible achlorhydria in the stomach due to oxyntic gland atrophy, as explained in the review by Schubert and Peura [10, 30].

The gastric epithelium is shielded by a thick mucus layer, buffered by bicarbonate to protect underlying cells from the highly acidic gastric juice. Composed mainly of mucins like MUC1, MUC5AC and MUC6, mucins are large molecules linked by disulfide bonds. Surface epithelial cells express MUC5AC, while glands express MUC6 [10, 31].

In addition to mucins, another protective component against acidity in the gastric mucosa is cyclooxygenase 1 (COX 1). COX 1 converts arachidonic acid into prostaglandins, which stimulate bicarbonate release and regulate proton pump activity, providing an additional mechanism of defence against aggressive acidic content of the gastric lumen [32].

Most common diseases of stomach are: functional dyspepsia, gastritis, peptic ulcer disease, acute gastric bleeding, gastric cancer [25, 33, 34].

1.2. *Helicobacter pylori*

Microbiology and epidemiology

H. pylori, a spiral- and rod-shaped Gram-negative bacterium with multiple flagella located at one end, thrives in microaerophilic and microcapnophilic environments. Correspondence to the classical Kochs postulate was difficult to confirm because the reliance of the bacteria on the human host and challenges in creating an animal model led to its identification through a "self-experiment," confirming its role in causing gastritis and gastric ulcer disease. Professors Barry Marshall and Robin Warren were honoured with the Nobel Prize in 2005 for their groundbreaking discovery, establishing peptic ulcer disease as an infectious condition [35, 36].

The precise route of transmission is still not established. But fecal-oral and oral-oral route is still considered to be as possible one and transmission normally occurs within a family. Other routes, such water transmission were studied but the results don't provide strong evidence in their favour [35, 36, 37]. It is difficult to establish the way of transmission due to number and time of genetic events occurs during infection. Virulence factors associated genes are very mutable thus displaying their high genetic diversity. Only conservative housekeeping, vital, genes don't undergo many genetic events remaining intact. Multilocus sequence typing, a genetic typing technique, based on the sequencing of housekeeping genes, provides possibility to at least group the bacteria by the region of origine and understanding of the evolutionary prospectives of the bacteria, but gives almost no information about the possible route of transmission [38, 39].

Nevertheless, it was confirmed recently that in fact *H. pylori* can have a reservoir in the oral cavity. The bacteria attach to the surface of the epithelial cells of mouth mucosa. These cells are capable to express many glycoproteins on their surface. Many of these glycoproteins serve as receptors for the receptors for the bacteria [40, 41].

H. pylori is a very unique pathogen, especially in the sense of the niche it can colonize. The bacteria can survive in the gastric mucosa that is quite a challenge itself when it comes to primary colonization and keeping itself viable through the physiological cycle in the stomach lining and response of the body to the *H. pylori* infection [42, 43, 44, 45].

Virulence factors: acid-suppression

Colonization of stomach mucosa by *H. pylori* occurs with the help of acid-suppressing mechanism. The mechanism is involving production of urease and release of nickel ions in acid-responsive manner [46].

Urease is a protein which consists of two subunits, UreA and UreB. The active complex of the enzyme is located in UreB subunit. The complex contains essential bi-nickel metallic complex. Urease converts urea to carbon dioxide and ammonia which neutralizes hydrochloric acid and buffers cytosolic environment under acidification [46].

Nickel ions, being released from their depot, neutralizes hydrochloric acid directly. So far, only one efflux mechanism has been described and this is cadmium, zinc, nickel metal export pump of Resistance-Nodulation-Division. Activity of the pump and thus realise of nickel ions is pH-dependent [46].

Virulence factors: adhesion

Another interesting moment, which makes *H. pylori* a very interesting pathogen, is its ability to bind gastric mucosa in a very sophisticated way. The binding properties of *H. pylori* are mediated by the number of adhesins that assure its biding to gastric mucosa without being pretty much detected by the host immunity and not being killed by the gastric acid. The most studied adhesins are blood group antigen binding adhesin (BabA) and sialic acid binding adhesin are two best characterized adhesins. LacdiNAc-binding adhesin, helicobacter outer membrane protein Q and Z are identified and characterised quite recently [42].

BabA is one of those adhesin it binds to Le^b-antigen expressed on the surface of epithelial cells [17]. The recent studies have shown that the individuals who can secrete blood group antigen on the surface of epithelial cells are more prone to be infected with certain microorganisms [47, 48, 49]. This also relevant for *H. pylori* that can firmly binds buccal epithelial cells expressing Le^b on their surface and by so doing make a reservoir for further infection [40].

The binding of the adhesin to its ligand is acid-sensitive i.e. under acidification the adhesin can detach its ligand. This mechanism is very clever. The mechanism of detachment from its ligand under acidification makes it possible for *H. pylori* to be released from the epithelial cells shedding to the acidic lumen during it natural turnover cycle [10].

Host-modifying virulence factors

Cytotoxin associated gene A (cagA) is encoded by the gene located in the end of *cagA* pathogenicity island which, in addition, encodes type IV secretion system (T4SS). CagA

protein is very immunogenic protein which activates hosts immune response and is involved in inflammation promotion [44, 45].

CagA protein is delivered to the host gastric epithelial cells via T4SS. Inside the cell cagA protein undergoes phosphorylation in the site of EPIYA motif. Phosphorylated and unphosphorylated cagA proteins affects transcription and expression of the proteins involved in cell-cell interaction of gastric mucosa, such as tight junction and adherence, cell polarity, mobility, proliferation and differentiation [44].

VacA gene encodes vacA protein which is secreted by type V autotransport secretion system and delivered into the host cell by endocytosis. VacA protein is an 88 kDa mature protein. The immature vacA protein is secreted as 96 kDa protein being cleaved off passenger domain [44].

On having bound to epithelial cell vacA protein oligomerises and incorporates, by forming anion-selective channels in endosomal membranes. This leads to swelling of the endosomes. In the lamina propria by interacting with immunocompetent cells (T cells, B cells, Dendritic cells and microphages), vacA attenuates immune response [44].

H. pylori strains that are positive for *babA*, *cagA, vacA* were shown to be associated with follicular form of gastritis and chronic gastritis. Chronic gastritis can progress to intestinal metaplasia. All these morphological changes in the gastric mucus can play importantrole in the development of gastric cancer [50].

1.3. Use of drugs and their role in the development of gastric cancer

PPIs and gastric cancer

PPIs inhibit the H+/K+ ATPase enzyme (proton pump) in gastric parietal cells, significantly reducing gastric acid production and increasing gastric pH. This mechanism provides relief from acid-related symptoms and promotes healing of gastric mucosa [51]. Common PPIs include omeprazole, esomeprazole, lansoprazole, pantoprazole, and

rabeprazole, available both over-the-counter and by prescription, contributing to their widespread use [52].

Several meta-analyses since 2019 have investigated the link between long-term PPI use and gastric cancer risk, offering a comprehensive overview of existing evidence.

A meta-analysis of 18 studies involving 4348905 participants found some association between long-term PPI use and an increased risk of gastric cancer, especially for those using PPIs [53]. Another meta-analysis of 7 studies with 943070 participants suggested an increased risk of gastric cancer among PPI users compared to non-users [54]. This meta-analysis and another one reinforced the association between PPI use and gastric cancer, emphasizing that the risk was particularly pronounced in populations with *H. pylori* infection [12, 54].

The mechanisms through which PPIs contribute to gastric cancer development are diverse and often linked to the duration of treatment. A study showed that chronic PPI use in animal models resulted in hypergastrinemia and an increased incidence of gastric tumours. This study highlighted gastrin's role in promoting gastric epithelial proliferation, suggesting that PPI-induced hypergastrinemia could be a key mechanism driving the increased cancer risk observed in epidemiological studies [55].

Long-term PPI use can alter the gastric microbiome by reducing the acidic barrier that normally controls bacterial populations. One mechanism is bacterial overgrowth; reduced gastric acidity allows for the overgrowth of bacteria, including nitrosating bacteria that convert dietary nitrates into carcinogenic nitrosamines [56, 57]. Another mechanism involves promoting *H. pylori* infection and modulating the immune response. In the presence of *H. pylori* infection, the altered gastric environment can exacerbate inflammation and increase the risk of gastric atrophy and carcinoma [58, 59].

PPIs also affect immune function and inflammatory responses. They can impair immune response by modulating immune cell’s function, potentially reducing the body's ability to detect and eliminate precancerous and cancerous cells in the gastric mucosa [60, 61].

Additionally, PPIs contribute to chronic inflammation, a known risk factor for gastric cancer development [62].

The increasing global use of PPIs, both prescribed and over-the-counter, refers to the need for awareness and caution regarding their long-term use. Overprescription and misuse are concerning, as studies indicate that a significant proportion of PPI prescriptions may be inappropriate, with many individuals using PPIs longer than clinically necessary [63].

The impact of PPIs on gastric cancer risk may vary across different populations due to genetic, environmental, and lifestyle factors. In East Asia, regions like Japan, China, and South Korea have high rates of gastric cancer and *H. pylori* infection, making the potential risks associated with long-term PPI use warrant careful consideration and monitoring (Miftahussurur et al., 2020). In Western countries, where gastric cancer rates are generally lower, the widespread use of PPIs for gastroesophageal reflux disease (GERD) and other acid-related disorders necessitates vigilance regarding long-term use and potential cancer risks [64].

Some epidemiological studies have provided mixed results regarding the association between long-term PPI use and gastric cancer risk. A large cohort study investigated the risk of gastric cancer among long-term PPI users compared to those using histamine-2 receptor antagonists. This study, which included 122118 participants, found that long-term PPI and histamine-2 receptor antagonists use was associated with an increased risk of gastric cancer, particularly among those who used the medication for more than three years and those with a history of *H. pylori* infection [65]. Controversially, other authors did not find a significant association between PPI use and gastric cancer risk. These studies imply that on the limitations of many meta-analysis, suggesting that factors such as genetic predisposition, dietary habits, and the prevalence of *H. pylori* infection might influence the risk differently in various populations [66, 67].

Combined fixed dose drugs for *H. pylori* eradication

H. pylori eradication is one of the main approaches to prevent gastric cancer. There are several main regimens to treat *H. pylori* infection that were mentioned above. These

approaches involve 3-4 medications. Some of the schemes were developed into combined fixed dose drugs [68].

Unfortunately, in Ukraine, it is quite difficult to trace the implementation and prescriptions of the medication for *H. pylori* eradication, because still there is no unified system of digital medical journals, where it would be stated that the patient was recommended eradication therapy. A system of digital prescription was adopted quite recently. At the same time presence of combined fixed dose drugs for *H. pylori* eradication gives us possibility to evaluate how widely eradication therapy applied and somehow understand the trends [69].

Combined fixed-dose drug regimens involve the use of multiple antimicrobial agents and a PPI combined into a single pack. This approach simplifies the treatment regimen, improves patient compliance, and enhances the eradication rates of *H. pylori*. This approach has one main advantage. Simplified regimen because the form of the drug and clear indication for the pills. with instruction that is improving adherence [70].

The effectiveness of combined fixed-dose drug regimens has been demonstrated in numerous studies, especially for the treatment of some cardiological and pulmonological diseases such as, high blood pressure, heart failure, chronic obstructive pulmonary disease [71, 72]. The results of the studies are leading to their widespread adoption in many countries as well as to development and implementation of combined fixed dose drugs into other fields of medicine [73].

Different regions have adopted various fixed-dose combinations based on local resistance patterns, availability of drugs, and healthcare infrastructure [68].

In Asia and North America, high prevalence of clarithromycin resistance has led to the preference for bismuth quadruple therapy in countries like those of Asia Pasific while in Europe still triple therapy is preferable [70, 74]. Concomitant therapy is widely used in many European countries, including Spain and Italy, due to its high eradication rates and favourable safety profile [75].

The role of cysteine derivatives in gastric cancer prevention

Acetylcysteine, carbocysteine, and erdosteine are derivatives of cysteine known for their ability to break covalent disulfide bonds in biomolecules. These drugs are renowned for their antioxidant properties. Oxidative stress plays a significant role in gastric cancer pathogenesis by promoting inflammation and genetic mutations that lead to carcinogenesis. By neutralizing reactive oxygen species (ROS), these agents reduce oxidative stress and related cellular damage [76].

NAC, carbocysteine and erdostein are also precursors to glutathione, a potent intracellular antioxidant. Elevated glutathione levels help detoxify harmful substances and protect cells from oxidative damage. Additionally, NAC, carbocysteine and erdosteine can directly scavenge free radicals, reducing oxidative stress within the gastric mucosa [76].

These cysteine derivatives also have mucolytic effects, reducing mucus viscosity and facilitating its clearance, potentially aiding in the removal of carcinogenic substances from the gastric mucosa. Their mucolytic activity helps clear mucus, and their anti-inflammatory properties further reduce gastric inflammation, a known risk factor for gastric cancer. These derivatives are generally well-tolerated and considered safe for most patients with a low incidence of side effects [76].

A study investigated the chemopreventive effects of NAC in a rodent model of gastric cancer. The findings indicated that NAC supplementation reduced the signs of gastrointestinal tumour initiation and progression by decreasing oxidative stress and inflammation in the gastric mucosa [77, 78]. It was also shown in i*n vivo* that NAC's use had prevented development of gastritis caused by *H. pylori* infection, a precursor to gastric cancer. Results from these studies suggest that NAC can reduce gastric inflammation and improve mucosal health, potentially lowering the risk of progression to gastric cancer [78, 79].

Laboratory studies have shown that carbocysteine can be used potentially for the treatment of ulcerative colitis and inhibit proliferation of cancerous lesions of the airways, suggesting its potential role in cancer prevention [80]. Preclinical studies using *in vitro* and *in*

vivo models have shown that erdosteine can prevent colonic inflammation and inflammation in general by reducing free radical formations due to its antioxidant properties [81].

A study evaluated erdosteine's effect on oxidative stress and inflammation in patients with chronic bronchitis. The results showed that erdosteine significantly reduced markers of oxidative stress and inflammation, suggesting its protective role against bronchial mucosal damage and subsequent cancer risk [82]. These properties may also be of great use in the treatment of inflammatory and oncological disease originating form gastric mucosa since the respiratory and gastric mucosa shares many common properties [83].

Cysteine derivatives can also attenuate *H. pylori* infection. These drugs can reduce mucus viscosity, potentially altering the mucosal environment, and disrupt the biofilm matrix, reducing the protective environment for *H. pylori* [82, 84]. Erdosteine's anti-inflammatory properties help reduce gastric mucosal inflammation, enhancing mucosal healing and reducing bacterial adhesion sites. NAC was shown to interfere with BabA to Leb mediated binding to the gastric mucosa by disrupting loops in the binding pocket of BabA through breaking disulfide bonds crucial for loop formation [84, 85].

Adding NAC to a standard eradication therapy modestly increased *H. pylori* eradication rate. This study suggests that NAC might influence bacterial adhesion mechanisms, including those mediated by gastric mucus irrigation [86]. Also, addition of mucolytic agents in *H. pylori* eradication was investigated, having found that carbocysteine helped reduce mucosal inflammation and bacterial load, indirectly suggesting an impact on bacterial adhesion [87]. It was found in several studies that mucolytic agents such as NAC, carbocysteine and erdosteine effectively enhanced H. *pylori* eradication. The reduction in bacterial load and biofilm disruption implies a potential impact on BabA function [17, 85].

NSAIDs and gastric cancer prevention

NSAIDs, including ASA and ibuprofen, have been studied for cancer prevention, particularly gastric cancer. COX enzymes, especially COX 2, reducing inflammation and modulating cellular processes linked to cancer development. COX 2 inhibition by NSAIDs

reduces inflammation, angiogenesis, and cellular proliferation, while promoting apoptosis, thereby potentially lowering cancer risk [88, 89].

NSAIDs primarily modulate inflammation, a known risk factor for gastric cancer. For example, NSAIDs significantly reduced NF-κB expression and inflammatory cytokines in animal models, leading to fewer gastric tumours [90]. NSAIDs also induce apoptosis in gastric epithelial and cancer cells, as shown by NSAIDs increasing apoptosis markers and reducing tumour growth in mice [91].

Additionally, NSAIDs inhibit the proliferation of gastric cancer cells. NSAIDs reduced cell proliferation by inhibiting the PI3K/Akt pathway, leading to cell cycle arrest and decreased cell viability in gastric cancer cell lines [92]. NSAIDs also inhibit angiogenesis, crucial for tumour growth [89].

Epigenetic modifications play a significant role in cancer development, and NSAIDs can modulate these markers. NSAIDs increased histone acetylation in gastric cancer cells, leading to tumour suppressor gene activation and oncogene downregulation, inhibiting cell proliferation and inducing apoptosis [89, 93].

NSAIDs also modulate immune responses to enhance anti-tumour immunity. NSAIDs reduced regulatory T cells (Tregs) in gastric cancer, enhancing effector T cell activation and anti-tumour cytokine production [59, 89]. Also some other non-NSAIDs were shown to prevent progression of gastric cancer trough COX-pathway. For instance, Curcumin combined with 5-fluorouracil showed greater reductions in cell proliferation and increased apoptosis in gastric cancer cell lines [94].

Meta-analyses support NSAIDs' protective effects against gastric cancer. A meta-analysis reviewed among other use of NSAIDs, has suggested that regular NSAID use, particularly ASA, significantly reduced gastric cancer risk [95]. A meta-analysis focusing on the Asian and North American population also found consistent protective effects across different subpopulations and study designs [6].

Acetylsalicylic acid and gastric cancer prevention

Acetylsalicylic (ASA), a well-known NSAID, has been extensively studied for its role in preventing different types of cancer [89]. Unlike other NSAIDs, ASA irreversibly inhibits COX enzymes, leading to prolonged suppression of COX activity and reduced production of pro-inflammatory prostaglandins. This sustained anti-inflammatory effect contributes to its cancer-preventive properties [96].

ASA also has unique antiplatelet effects by irreversibly inhibiting COX-1 in platelets, preventing thromboxane A2 formation, which reduces platelet aggregation. This not only lowers cardiovascular risks but also has implications for cancer prevention [89, 96].

Preclinical studies show that ASA modulates epigenetic markers such as DNA methylation and histone modifications, reactivating tumour suppressor genes and inhibiting cancer cell growth [97]. Additionally, ASA inhibits the release of growth factors like PDGF from platelets, hindering angiogenesis and tumour [98].

ASA induces apoptosis in cancer cells more effectively than some other NSAIDs by activating multiple apoptotic pathways, including NF-κB and PI3K/Akt. This may enhance apoptotic activity helps eliminate cancer cells and prevent tumour development [99]. Another study in a xenograft mouse model of colon cancer showed that ASA reduced tumour incidence and multiplicity by modulating NF-κB and PI3K/Akt pathways, increasing apoptosis, and preventing DNA damage leading to actiovation tumour suppressor genes [100].

ASA's immunomodulatory effects also contribute to its anti-cancer properties by enhancing the infiltration and activity of immune cells such as T cells and NK cells [101].

A preclinical study on a mouse model of *H. pylori*-induced gastric cancer found that ASA suppressed COX-2 expression and prostaglandin E2 production, reduced inflammation, induced apoptosis, and inhibited angiogenesis by downregulating vascular endothelial growth factor, limiting tumour growth and microvessel density [102].

A comprehensive meta-analysis of 33 studies involving over 1927971 participants found that regular ASA use was associated with a reduction in gastric cancer risk [103]. A population-

based study in the United Kingdom confirmed the protective effect of low-dose ASA on gastrointestinal cancer risk, including gastric cancer. A 54% reduced risk was estimated [104].

Metformin and gastric cancer prevention

Metformin, a well-established drug for type 2 diabetes management, has gained considerable interest for its potential role in cancer prevention, including gastric cancer. Its cancer-preventive effects are attributed to a range of mechanisms involving cellular metabolism modulation, tumour growth inhibition, and interaction with molecular pathways [105].

Metformin shares several anti-cancer mechanisms with other agents, such as inhibiting cell proliferation and inducing apoptosis. However, it also has distinct properties that enhance its cancer-preventive effectiveness [106].

One key mechanism by which metformin exerts its anti-cancer effects is through the activation of the AMP-activated protein kinase (AMPK) pathway. AMPK, an energy sensor that regulates cellular metabolism and growth, is activated by metformin, leading to the inhibition of the mTOR pathway. mTOR is crucial for cell growth and proliferation; thus, its inhibition by metformin reduces protein synthesis and cell proliferation, critical for tumour growth. This metabolic regulation is a quite distinctive feature of metformin's cancer-preventive action, not commonly seen with other agents [107].

Metformin also impacts insulin and insulin-like growth factor-1 (IGF-1) signalling pathways, both important in cancer development. By improving insulin sensitivity and lowering insulin levels, metformin reduces IGF-1 availability—a growth factor that encourages cell proliferation and survival. This reduction in insulin and IGF-1 levels lessens their stimulatory effects on cancer cells, thereby inhibiting tumor growth. This mechanism is especially relevant for diabetic patients who often have elevated insulin and IGF-1 levels, making metformin a valuable preventive agent in this group [108].

Chronic inflammation, a known cancer risk factor, is also addressed by metformin. The drug has demonstrated anti-inflammatory effects by lowering levels of pro-inflammatory

cytokines such as TNF-α, IL-2, and IL-6. These effects are mediated through the inhibition of the NF-κB signalling pathway, which plays a critical role in inflammation and cancer progression. By modulating these inflammatory pathways, metformin helps create a less favourable environment for cancer development [109].

Epithelial–mesenchymal transition (EMT), which involves epithelial cells acquiring mesenchymal traits and thus increased mobility and invasiveness, is another process counteracted by metformin. It reduces mesenchymal markers like vimentin and N-cadherin, while increasing epithelial markers such as E-cadherin, thereb decreasing the invasive potential of cancer cells and hindering metastasis. Additionally, metformin suppresses the STAT3 signalling pathway, known to drive EMT and tumour progression [110]. It also enhances the immune response by increasing CD8+ T cell infiltration in gastric tissue [111].

Metformin's impact on immune modulation includes increasing the infiltration and activity of immune cells like CD8+ T cells and natural killer cells in the tumour microenvironment. It also reduces immunosuppressive cells such as regulatory T cells, thereby boosting the anti-tumor immune response. This immune-enhancing effect is an additional aspect of metformin's cancer-preventive mechanism [111].

These effects of metformin were investigated in different animal models, mostly mice models, of gastric carcinogenesis [108, 112].

A meta-analysis of 5 observational studies evaluated the association between metformin use and gastric cancer risk, including over 1804479 participants, particularly focusing on diabetic patients prescribed metformin. The studies have shown that long-term metformin use is linked to a reduced risk of gastric cancer compared to non-use or the use of other hypoglycemic medications. In diabetic gastric cancer patients who underwent gastrectomy, cumulative metformin use was associated with lower rates of disease recurrence, as well as reduced all-cause and cancer-specific mortality. Although research in this area is limited, current evidence suggests that metformin may decrease the risk of gastric cancer and enhance survival outcomes in individuals with type 2 diabetes [113].

Several meta-analyses of cohort and case-control studies. Patients with abnormal glucose metabolism, especially type 2 diabetes mellitus, may have a high risk of gastric cancer in terms of incidence or mortality. The association between diabetes mellitus and gastric cancer is more remarkable in women and in Asian populations. The link between type 2 diabetes mellitus and gastric cancer can be mediated by hyperglycemia, insulin resistance, shared risk factors, medications, comorbidities, high salt intake or higher *H. pylori* infection rate. gastric cancer patients with diabetes mellitus would have more complications and a poorer prognosis than gastric cancer patients without diabetes mellitus. However, glycemic control may improve, and remission of diabetes mellitus can be seen in diabetes patients after gastrectomy, especially in patients who receive surgical procedures that bypass duodenum and the proximal jejunum. Metformin exerts anti-cancer effects in gastric cancer cells, and observational studies do show a lower risk of gastric cancer associated with metformin use in patients with type 2 diabetes mellitus and an improved survival with reduced recurrence in gastric cancer patients who use metformin. Some future perspectives with regards to the pathological subtypes and anatomical sites of gastric cancer associated with type 2 diabetes mellitus or prevented by metformin, the link between type 1 diabetes mellitus and gastric cancer and the role of gastric microbiota in the development of gastric cancer remain to be explored from various regions found a consistent reduction in gastric cancer risk associated with metformin use [112].

Statins and gastric cancer prevention

Statins, primarily known for their lipid-lowering properties, have been increasingly investigated for their potential role in cancer prevention, including gastric cancer. The mechanisms through which statins exert their anti-cancer effects are diverse and involve inhibition of cholesterol synthesis, modulation of inflammatory pathways, and direct effects on cancer cell proliferation and apoptosis. [114].

Statins have general anti-cancer mechanisms like other agents, such as inhibition of cell proliferation and induction of apoptosis and also have unique properties that contribute to their effectiveness in cancer prevention [114].

The primary mechanism by which statins exert their anti-cancer effects is through the inhibition of the mevalonate pathway. Statins inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, the rate-limiting enzyme in cholesterol synthesis. This inhibition leads to decreased production of mevalonate and its downstream products, such as farnesyl pyrophosphate and geranylgeranyl pyrophosphate, which are essential for the post-translational modification of proteins involved in cell signalling and growth, including Ras and Rho [115]. By inhibiting the mevalonate pathway, statins reduce the activation of these proteins, thereby inhibiting cell proliferation and inducing apoptosis in cancer cells. This metabolic regulation is a unique aspect of statins' mechanism that is not commonly observed with other chemopreventive agents. These effects of statins on gastric cancer were studied using a rat model of N-methyl-N-nitrosourea-induced gastric carcinogenesis. The study found that statins treatment significantly reduced the incidence and multiplicity of gastric tumours [116].

Chronic inflammation is a recognized risk factor for cancer development. Statins have demonstrated anti-inflammatory effects by lowering the levels of pro-inflammatory cytokines, including TNF-α and IL-6. These effects are achieved by inhibiting the NF-κB signalling pathway, which is pivotal in managing inflammation and cancer progression. By influencing these inflammatory pathways, statins help establish an environment that is less conducive to cancer development [117].

Statins have been shown to inhibit EMT by downregulating mesenchymal markers and upregulating epithelial markers. This inhibition of EMT limits the invasive potential of cancer cells, thereby preventing metastasis. This anti-EMT effect is a mechanism of statins that contributes to their cancer preventive properties [118]. Atorvastatin treatment led to downregulation of EMT markers such as vimentin and N-cadherin and upregulation of E-cadherin, a marker of epithelial phenotype. Furthermore, atorvastatin inhibiting the transcription of target genes, mainly via the Smad2/3 pathway, which is involved in promoting EMT and tumour progression. The study also highlighted atorvastatin's role in inhibiting the

expression of cell-surface glycoprotein CD146, a member of the immunoglobulin superfamily, and subsequent breaking of CD146/ERK cascade. These findings provide strong evidence for atorvastatin's potential to prevent gastric cancer through inhibition of EMT and modulation of the immune microenvironment [119].

Statins have been observed to induce apoptosis in cancer cells through multiple pathways. Statins can activate the intrinsic apoptotic pathway by increasing the expression of pro-apoptotic proteins such as Bax and Bak and decreasing the expression of anti-apoptotic proteins such as Bcl-2. Additionally, statins can activate the extrinsic apoptotic pathway by enhancing the expression of death receptors such as Fas. This dual activation of apoptotic pathways enhances the ability of statins to eliminate cancer cells and prevent tumour development [120].

Statins have been observed to boost the infiltration and activity of immune cells, including CD8+ T cells and natural killer cells, within the tumour microenvironment. This modulation of the immune system strengthens the body's capacity to identify and destroy cancer cells. Additionally, statins can decrease the population of immunosuppressive cells like Tregs, thereby bolstering the anti-tumour immune response. This immune-boosting effect is another way in which statins contribute to cancer prevention [121].

Statins have been shown to possess anti-angiogenic properties, which contribute to their anti-cancer effects. Statins can inhibit the expression of vascular endothelial growth factor, a key regulator of angiogenesis, thereby reducing the formation of new blood vessels that supply nutrients to tutors. This inhibition of angiogenesis limits tumour growth and metastasis [122].

A comprehensive meta-analysis to evaluate the association between statin use and the risk of gastric cancer was performed. The analysis included 26 studies with a total of over 8.5 million participants. Subgroup analyses demonstrated that the protective effect of statins was consistent across different populations, including those from Asia, Europe, and North America. Additionally, the analysis revealed that both lipophilic and hydrophilic statins were effective in reducing gastric cancer risk, suggesting a class effect of statins in cancer prevention [123].

Another meta-analysis of 20 studies was done to investigate the impact of statin use on the incidence of gastric cancer. The analysis encompassed data from over 11870553 individuals. The protective effect of statins was particularly significant in studies with longer follow-up periods and higher cumulative doses of statins. Furthermore, the analysis showed that the risk reduction was more pronounced in studies that adjusted for potential confounders such as *H. pylori* infection, suggesting an independent protective effect of statins. These findings underscore the potential of statins as chemopreventive agents against gastric cancer [18].

What was the main concern regarding gastric cancer and the use of medicine in the real world population?

CHAPTER 2

MATERIALS AND METHODS

Information on the general incidence of gastric cancer, total number of cases, adenocarcinoma and other morphological forms of gastric cancerwas retrieved from the National Cancer Register of Ukraine spanning from 2014 to 2021 [124].

Morphological diagnoses of gastric cancer were assigned according to ICD-O-3 and data on the following morphological diagnoses were obtained from 2003 till 2020 [125]. Retrieved information included all the cases of gastric cancer where stomach was indicated as primary site of identification of cancer not considering lymphomas. The data on number of cases and incidence rate of each of the morphological diagnoses were requested on 9th January 2023 and obtained on 10th of January 2023 (Tab. 2.1).

Table 2.1

List of the morphological diagnoses and codes according to ICD-O-3.2

Morphological diagnosis	ICD-O-3.2
Adenocarcinoma NOS	8140
Adenocarcinoma scirrhous	8141
Linitis plastica	8142
Superficial spreading adenocarcinoma	8143
Intenstinal type Adenocarcinoma	8144
Diffuse type adenocarcinoma	8145
Islet cell adenocarcinoma	8150
Malignant gastrinoma	8153
Hepatocellular carcinooma	8170
Adenocarcinoma trabecularna	8190
Adenoid cystic carcinoma	8200
Cribriform carcinoma	8201
Adenomatous polyp	8210
Adenocarcinoma tubular	8211
Parietal cell adenocarcinoma	8214

Table continuation 2.1.

Morphological diagnosis	ICD-O-3.2
Solid adenocarcinoma	8230
Neuroendocrine tumour	8240
Argentaffin carcinoid	8241
Mucinous carcinoma	8243
Mixed adeno-neuroendocrine carcinoma	8244
Adenocarcinoid tumor	8245
Neuroendocrine carcinoma	8246
Neuroendocrine tumor, grade 2	8249
Adenocarcinoma with mixed subtypes	8255
Papillary adenocarcinoma	8260
Villous adenocarcinoma	8262
Adenocarcinoma in tubulovillous adenoma	8263
Clear cell adenocarcinoma	8310
Granular cell adenocarcinoma	8320
Mixed cell adenocarcinoma	8323

Calculation derived annual total, annual age-related and annual incidence rates of gastric adenocarcinoma. Mean, standard deviation (SD), and 95% confidence intervals (95% CI) for each age fraction were calculated. A lineal model was employed to analyse trends the total incidence rates of gastric cancer and incidence rate of adenocarcinoma, with R^2 values computed [126]. The data analysis was conducted using MedCalc for Windows, version 20.2.18 (MedCalc Software, Ostend, Belgium).

The drugs for the study were chosen based on the numbers of results appeared when requested in combination of queries "(class of drugs) AND (gastric cancer)" in Pubmed (class of drug = any of the classes mentioned in the previous paragraph) and based on the literature reviews [127].

ATC codes for each individual medication are assigned according to the World Health Organisation collaboration canter for drug statistics methodology [128].

The data on sales of PPIs, combined drugs for *H. pylori* eradication, cysteine derivatives, NSAIDs, metformin and statins, dispensed by pharmacies and hospitals, were obtained from

PharmXplorer, a market research analytical system of Proxima Research Company (Tab. 2.2) [129].

Table 2.2

List of the medications, according to ATC-codes, included in the study

ATC-code	INN
A02BC01	Omeprazol
A02BC02	Pantoprazol
A02BC03	Lansoprazol
A02BC04	Rabeprazol
A02BC05	Esomeprazol
A02BC06	Dexlansoprazol
A02BD04	Pantoprazole, Amoxicillin and Clarithromycin
A02BD05	Omeprazole, Amoxicillin and Clarithromycin
A02BD09	Lansoprazole, Clarithromycin and Tinidazole
A02BD12	Rabeprazole, Ornidazol and Clarithromycin
A10BA02	Metformin
B01AC06	Acetylsalicylic acid
C10AA01	Simvastatin
C10AA02	Lovastatin
C10AA04	Fluvastatin
C10AA05	Atorvastatin
C10AA07	Rosuvastatin
C10AA08	Pitavastatin
M01AB01	Indometacin
M01AB05	Diclofenac
M01AB08	Etodolac
M01AB15	Ketorolac
M01AB16	Aceclofenac
M01AC01	Piroxicam
M01AC02	Tenoxicam
M01AC05	Lornoxicam
M01AC06	Meloxicam
M01AE01	Ibuprofen
M01AE02	Naproxen

Table continuation 2.2

ATC-code	INN

M01AE03	Ketoprofen
M01AE09	Flurbiprofen
M01AE14	Dexibuprofen
M01AE17	Dexketoprofen
M01AH01	Celecoxib
M01AH02	Rofecoxib
M01AH04	Parecoxib
M01AH05	Etoricoxib
M01AX01	Nabumetone
M01AX17	Nimesulid
N02BA01	Acetylsalicylic acid
R05CB01	Acetylcysteine
R05CB03	Carbocysteine
R05CB15	Erdosteine

We calculated the number of DDDs per 100,000 person-years for each pharmaceutical substance and for entire pharmacological groups [130]. A lineal, exponential and polynomial (quadratic) models were employed to analyse trends in the number of DDDs, with R^2 values computed [126].

No consent of participants and no ethical permissions were required for the performed studies.

CHAPTER 3

GASTRIC CANCER EPIDEMIOLOGY

Gastric cancer incidence rate was decreasing in Ukraine from 2003 till 2020. It dropped almost by 31% ($P < 0.0001$) in 2020 comparing to 2003. The lowest incidence rate was noted in 2020, 8,99 per 100000 habitants – year, and the highest one in 2005, 13,56 per 100000 habitants – year (Tab. 3.1-3.6).

Table 3.1

Gastric cancer incidence rate in Ukraine between 2003 and 2008 (for nosological codes 8140 - 8214)

Morphological diagnosis	ICD-O-3.2	2003	2004	2005	2006	2007	2008
Adenocarcinoma NOS	8140	12,44	12,82	13,09	12,88	12,79	12,36
Adenocarcinoma scirrhous	8141	0,19	0,13	0,17	0,16	0,13	0,11
Linitis plastica	8142	0,00	0,00	0,00	0,00	0,00	0,00
Superficial spreading adenocarcinoma	8143	0,00	0,01	0,00	0,00	0,00	0,00
Intenstinal type Adenocarcinoma	8144	0,01	0,00	0,02	0,01	0,02	0,03
Diffuse type adenocarcinoma	8145	0,07	0,07	0,05	0,04	0,03	0,04
Islet cell adenocarcinoma	8150	0,00	0,00	0,00	0,00	0,00	0,00
Malignant gastrinoma	8153	0,00	0,00	0,00	0,00	0,00	0,01
Hepatocellular carcinooma	8170	0,00	0,00	0,00	0,00	0,00	0,00
Adenocarcinoma trabecularna	8190	0,00	0,00	0,00	0,00	0,00	0,00
Adenoid cystic carcinoma	8200	0,00	0,00	0,00	0,00	0,00	0,00

Table continuation 3.1

Cribriform carcinoma	8201	0,00	0,00	0,00	0,00	0,00	0,00
Adenomatous polyp	8210	0,03	0,03	0,03	0,02	0,02	0,02
Adenocarcinoma tubular	8211	0,04	0,07	0,08	0,06	0,04	0,06
Parietal cell adenocarcinoma	8214	0,00	0,00	0,00	0,00	0,00	0,00

From 2003 to 2020, Ukraine identified a total of 30 distinct forms of primary gastric cancer. The tables presented include only those types diagnosed within this timeframe. Eight consistently occurring forms of gastric cancer were identified: adenocarcinoma NOS (8140), adenocarcinoma scirrhous (8141), intestinal type adenocarcinoma (8144), diffuse type adenocarcinoma (8145), adenocarcinoma tubular (8211), solid adenocarcinoma (8230), neuroendocrine tumour (8240), and papillary adenocarcinoma (8260) (Tab. 3.1-3.6). These forms were diagnosed every year from 2003 to 2020 in Ukraine.

Table 3.2

Gastric cancer incidence rate in Ukraine between 2003 and 2008 (for nosological codes 8230 - 8323).

Morphological diagnosis	ICD-O-3.2	2003	2004	2005	2006	2007	2008
Solid adenocarcinoma	8230	0,10	0,07	0,04	0,07	0,06	0,08
Neuroendocrine tumour	8240	0,01	0,03	0,02	0,03	0,03	0,03
Argentaffin carcinoid	8241	0,00	0,00	0,00	0,00	0,00	0,00
Mucinous carcinoma	8243	0,00	0,00	0,00	0,00	0,00	0,00
Mixed adeno-neuroendocrine carcinoma	8244	0,00	0,00	0,00	0,00	0,00	0,00
Adenocarcinoid tumor	8245	0,00	0,00	0,00	0,00	0,00	0,00
Neuroendocrine carcinoma	8246	0,00	0,00	0,00	0,00	0,00	0,00
Neuroendocrine tumor, grade 2	8249	0,00	0,00	0,00	0,00	0,00	0,00
Adenocarcinoma with mixed subtypes	8255	0,00	0,00	0,00	0,00	0,00	0,00

Papillary adenocarcinoma	8260	0,03	0,03	0,03	0,03	0,02	0,03
Villous adenocarcinoma	8262	0,00	0,00	0,00	0,00	0,00	0,00
Adenocarcinoma in tubulovillous adenoma	8263	0,00	0,00	0,00	0,01	0,01	0,01
Clear cell adenocarcinoma	8310	0,01	0,02	0,01	0,01	0,01	0,01
Granular cell adenocarcinoma	8320	0,00	0,00	0,00	0,00	0,00	0,00
Mixed cell adenocarcinoma	8323	0,00	0,00	0,00	0,00	0,00	0,00

Four forms of gastric cancer were not diagnosed every year: adenomatous polyp (8210) (no cases in 2018), neuroendocrine carcinoma (8246) (no cases from 2003 to 2009), adenocarcinoma in tubulovillous adenoma (8263) (no cases in 2014 and 2020), and clear cell adenocarcinoma (8310) (no cases in 2019) (Tab. 3.2, Tab. 3.4 and Tab. 3.6).

The most notable among these four is neuroendocrine carcinoma, which was absent from 2003 to 2009 but had an incidence rate of 0.01 in 2010 (Tab. 3.2). This rate increased more than ninefold by 2019 ($P < 0.0001$). The upward trend over the years is significant ($R^2 = 0.82$; $P < 0.0001$) (Tab. 3.4 and Tab. 3.6).

Table 3.3

Gastric cancer incidence rate in Ukraine between 2009 and 2014 (for nosological codes 8140 till 8214).

Morphological diagnosis	ICD-O-3.2	2009	2010	2011	2012	2013	2014
Adenocarcinoma NOS	8140	12,09	12,49	12,34	12,23	12,00	12,36
Adenocarcinoma scirrhous	8141	0,15	0,13	0,06	0,08	0,07	0,08
Linitis plastica	8142	0,00	0,00	0,00	0,00	0,00	0,00
Superficial spreading adenocarcinoma	8143	0,00	0,00	0,00	0,00	0,00	0,00
Intenstinal type Adenocarcinoma	8144	0,02	0,01	0,02	0,02	0,04	0,05

Diffuse type adenocarcinoma	8145	0,03	0,03	0,05	0,11	0,11	0,09
Islet cell adenocarcinoma	8150	0,00	0,00	0,00	0,00	0,00	0,00
Malignant gastrinoma	8153	0,00	0,02	0,02	0,01	0,01	0,01
Hepatocellular carcinooma	8170	0,00	0,00	0,00	0,00	0,00	0,00
Adenocarcinoma trabecularna	8190	0,00	0,00	0,00	0,00	0,00	0,00
Adenoid cystic carcinoma	8200	0,00	0,00	0,00	0,00	0,00	0,00
Cribriform carcinoma	8201	0,00	0,00	0,00	0,00	0,00	0,00
Adenomatous polyp	8210	0,03	0,02	0,01	0,02	0,01	0,01
Adenocarcinoma tubular	8211	0,05	0,05	0,09	0,04	0,03	0,04
Parietal cell adenocarcinoma	8214	0,00	0,00	0,00	0,00	0,00	0,00

The majority of cases were adenocarcinoma NOS which saw a slight decrease from 96.03% of total cases in 2003 to 95.20% in 2020 (Tab. 3.1 and Tab. 3.5). The highest incidence rate was in 2005 and the lowest in 2020, with a 17.85% drop between 2019 and 2020 ($P < 0.0001$) (Tab. 3.1 and Tab. 3.5). This declining trend is significant ($R^2 = 0.66$; $P < 0.0001$) and mirrors the overall decline in gastric cancer incidence in Ukraine from 2003 to 2020 (Tab. 3.1, Tab. 3.3 and Tab. 3.5).

The combined incidence rate of all other types of gastric cancer was relatively stable, ranging from 0.34 in 2017 to 0.55 in 2019 (Tab. 3.1-3.6).

Table 3.4

Gastric cancer incidence rate in Ukraine between 2009 and 2014

(for nosological codes 8230 till 8323)

Morphological diagnosis	ICD-O-3.2	2009	2010	2011	2012	2013	2014
Solid adenocarcinoma	8230	0,07	0,08	0,08	0,06	0,06	0,03
Neuroendocrine tumour	8240	0,03	0,03	0,03	0,03	0,01	0,02
Argentaffin carcinoid	8241	0,00	0,00	0,00	0,00	0,00	0,00
Mucinous carcinoma	8243	0,00	0,00	0,00	0,00	0,00	0,00
Mixed adeno-neuroendocrine carcinoma	8244	0,00	0,00	0,00	0,00	0,00	0,00
Adenocarcinoid tumor	8245	0,00	0,00	0,00	0,00	0,00	0,00
Neuroendocrine carcinoma	8246	0,00	0,01	0,03	0,03	0,03	0,04
Neuroendocrine tumor, grade 2	8249	0,00	0,00	0,00	0,00	0,00	0,01
Adenocarcinoma with mixed subtypes	8255	0,00	0,00	0,00	0,00	0,00	0,00
Papillary adenocarcinoma	8260	0,02	0,02	0,03	0,02	0,02	0,02
Villous adenocarcinoma	8262	0,00	0,00	0,00	0,00	0,00	0,00
Adenocarcinoma in tubulovillous adenoma	8263	0,01	0,02	0,01	0,01	0,00	0,00
Clear cell adenocarcinoma	8310	0,02	0,02	0,02	0,01	0,02	0,02
Granular cell adenocarcinoma	8320	0,00	0,00	0,00	0,00	0,00	0,01
Mixed cell adenocarcinoma	8323	0,00	0,00	0,00	0,00	0,00	0,00

From 2003 to 2014, adenocarcinoma scirrhous was the second most common type of gastric cancer after adenocarcinoma NOS (Tab. 3.1, Tab. 3.3 and Tab. 3.5). However, it fell to the seventh most common type from 2015 to 2020 (Tab. 3.5), decreasing from 1.5% of total cases in 2003 to 0.47% in 2020 ($P < 0.0001$) (Tab. 3.1 and Tab. 3.5) The lowest incidence was

in 2018 at 0.27%, with a 6.33-fold difference between the highest and lowest rates ($P < 0.0001$) (Tab. 3.1 and Tab. 3.5). This decreasing trend is significant ($R^2 = 0.84$; $P < 0.0001$).

Solid adenocarcinoma was the third most common type from 2003 to 2008, followed by diffuse type adenocarcinoma (Tab. 3.2).

Table 3.5

Gastric cancer incidence rate in Ukraine between 2015 and 2020 (for nosological codes 8140 till 8214)

Morphological diagnosis	ICD-O-3.2	2015	2016	2017	2018	2019	2020
Adenocarcinoma NOS	8140	11,64	11,61	11,04	10,83	10,42	8,56
Adenocarcinoma scirrhous	8141	0,05	0,03	0,04	0,03	0,05	0,04
Linitis plastica	8142	0,00	0,00	0,00	0,00	0,00	0,00
Superficial spreading adenocarcinoma	8143	0,00	0,00	0,00	0,00	0,01	0,00
Intenstinal type Adenocarcinoma	8144	0,06	0,05	0,03	0,04	0,05	0,05
Diffuse type adenocarcinoma	8145	0,11	0,09	0,09	0,09	0,07	0,04
Islet cell adenocarcinoma	8150	0,00	0,00	0,00	0,00	0,00	0,01
Malignant gastrinoma	8153	0,01	0,01	0,00	0,02	0,02	0,00
Hepatocellular carcinooma	8170	0,00	0,00	0,00	0,00	0,00	0,00
Adenocarcinoma trabecularna	8190	0,00	0,00	0,00	0,00	0,00	0,00
Adenoid cystic carcinoma	8200	0,00	0,00	0,00	0,00	0,00	0,00
Cribriform carcinoma	8201	0,00	0,00	0,00	0,00	0,00	0,00
Adenomatous polyp	8210	0,01	0,01	0,00	0,00	0,01	0,00
Adenocarcinoma tubular	8211	0,04	0,05	0,02	0,07	0,14	0,09
Parietal cell adenocarcinoma	8214	0,00	0,00	0,00	0,00	0,00	0,00

Solid adenocarcinoma showed stable incidence with minor fluctuations, while from 2009 to 2020, it became the fourth most common form, and diffuse type adenocarcinoma became the third most common, indicating a slight increase in its incidence (Tab. 3.2, Tab. 3.4 and Tab. 3.6).

The incidence of adenocarcinoma tubular also showed a slight increase from 2003 to 2020, peaking in 2019 (Tab. 3.1 and Tab. 3.5).

The proportion of intestinal type adenocarcinoma increased over 18 times by 2020 from its minimum of 0.03% in 2004 ($P < 0.0001$) (Tab. 3.1 and Tab. 3.5).

Neuroendocrine tumour (8240) and papillary adenocarcinoma (8260) showed stable incidence rates from 2003 to 2020 without significant fluctuations (Tab. 3.2 and Tab. 3.6).

Hepatocellular adenocarcinoma (8170) and linitis plastica (8142) were each diagnosed only once during the 2003–2020 period, in 2005 and 2007, respectively (Tab. 3.1).

Table 3.6

Gastric cancer incidence rate in Ukraine between 2015 and 2020 (for nosological codes 8230 till 8323)

Morphological diagnosis	ICD-O-3.2	2015	2016	2017	2018	2019	2020
Solid adenocarcinoma	8230	0,07	0,08	0,04	0,04	0,07	0,04
Neuroendocrine tumour	8240	0,02	0,02	0,03	0,02	0,02	0,06
Argentaffin carcinoid	8241	0,00	0,00	0,00	0,00	0,00	0,00
Mucinous carcinoma	8243	0,00	0,00	0,00	0,00	0,00	0,01
Mixed adeno-neuroendocrine carcinoma	8244	0,00	0,00	0,00	0,00	0,00	0,00
Adenocarcinoid tumor	8245	0,00	0,00	0,00	0,00	0,00	0,00
Neuroendocrine carcinoma	8246	0,04	0,03	0,04	0,07	0,09	0,07
Neuroendocrine tumor, grade 2	8249	0,00	0,00	0,00	0,00	0,00	0,00
Adenocarcinoma with mixed subtypes	8255	0,00	0,00	0,00	0,00	0,00	0,00
Papillary adenocarcinoma	8260	0,02	0,03	0,02	0,00	0,02	0,01

Villous adenocarcinoma	8262	0,00	0,00	0,00	0,00	0,00	0,00
Adenocarcinoma in tubulovillous adenoma	8263	0,00	0,01	0,01	0,01	0,00	0,00
Clear cell adenocarcinoma	8310	0,01	0,02	0,01	0,00	0,00	0,01
Granular cell adenocarcinoma	8320	0,00	0,00	0,00	0,00	0,00	0,00
Mixed cell adenocarcinoma	8323	0,00	0,00	0,00	0,00	0,00	0,00

No shifts were observed in the age-related incidence rate of gastric cancer. The highest incidence rate was found in the following age groups: 60-64, 65–69, 70–74, 75–79, 80–85, and 85+

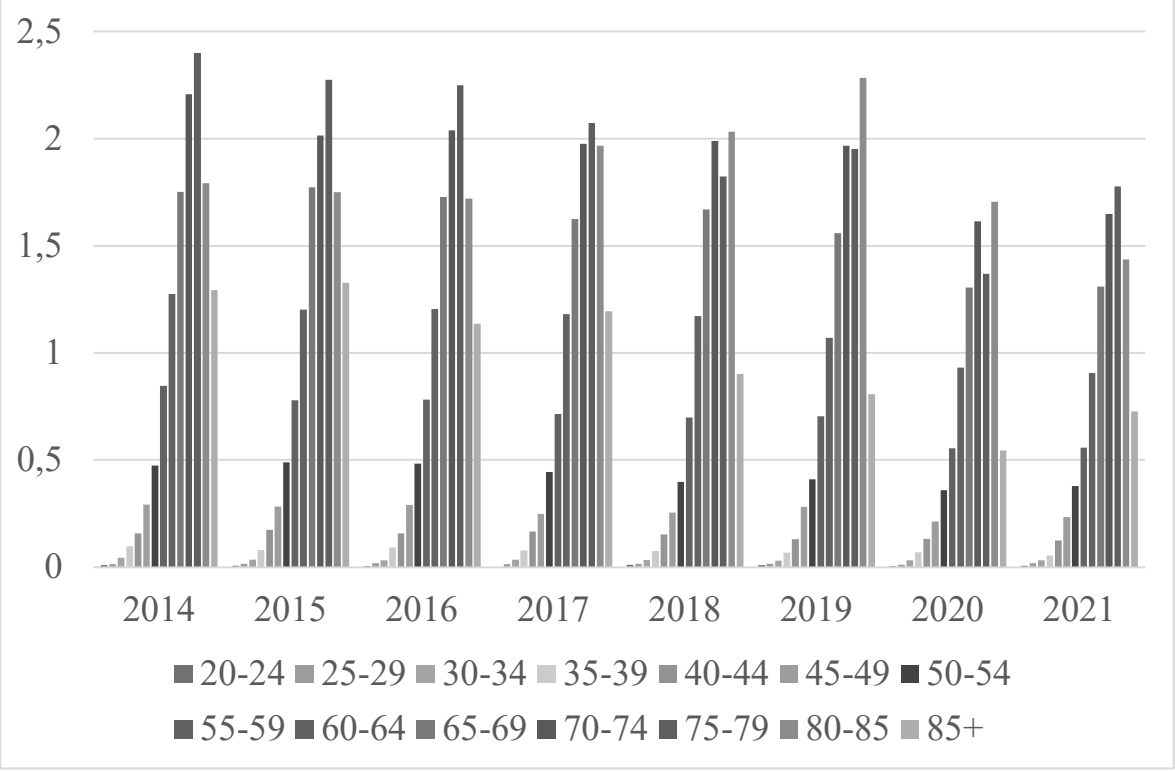

Figure 3.1. Age-related incidence rate of gastric cance.

When it comes to the epidemiology of gastric cancer from 2014 till 2022, the dataset provides interesting insights into the prevalences and rates of cancer cases. In 2014, gastric cancer accounted for approximately 6.2% of the total 135,307 reported cancer cases. By 2016, this prevalence remained stable at around 5.9%, with 8,034 gastric cancer cases out of 135,714 total cases. The proportion of gastric cancer cases continued to decline, reaching 5.4% in 2019 when 7,484 out of 138,509 cancer cases were gastric. In 2020, there was a sharp drop in total cancer cases to 113,368, while gastric cancer cases fell to 6,072, marking a notable decrease in prevalence to 5.4%. The rate of gastric cancer in men was consistently higher than in women, with 5,104 cases in men in 2014, making up about 61% of all gastric cancer cases that year. By 2018, the number of male gastric cancer cases had declined to 4,508, while female cases were 2,984, maintaining a similar gender distribution. In 2021, the overall prevalence of gastric cancer stood at 5.1%, with 6,145 cases out of 120,055 total cancers. The rate of gastric cancer in women dropped from 3,246 cases in 2014 to 2,072 in 2022, indicating a steady decrease over time. In contrast, the prevalence of gastric cancer in men remained higher, though cases declined from 5,104 in 2014 to 3,329 in 2022. The year 2019 recorded the highest total cancer cases, but gastric cancer prevalence was already on a downward trend. The most significant drop in gastric cancer cases occurred between 2019 and 2020, aligning with a broader reduction in total cancer diagnoses. While total cancer cases slightly rebounded in 2021, gastric cancer prevalence remained low. The downward trend in gastric cancer rates suggests improvements in early detection, lifestyle changes, or healthcare interventions. Over the entire period, the proportion of gastric cancer cases within total cancer diagnoses consistently decreased. This trend highlights a shift in cancer epidemiology, with gastric cancer becoming less prevalent over time (Tab. 3.7).

Table 3.7

Epidemiological indexes of gastric cancer in Ukraine, 2014-2022

Year	Gastric cancer rate	Prevalance of people older than 45 years	Prevalence of men	Prevalence of women
2014	1,49%	97,43%	61,13%	38,87%
2015	1,48%	97,37%	61,22%	38,78%
2016	1,49%	97,41%	59,91%	40,09%
2017	1,47%	97,44%	60,59%	39,41%
2018	1,46%	97,42%	60,17%	39,83%
2019	1,46%	97,72%	59,27%	40,73%
2020	1,78%	97,15%	60,62%	39,38%
2021	1,68%	97,38%	61,84%	38,16%
2022	1,90%	94,61%	61,64%	38,36%

Summary of the chapter

General trends shows that the incidence rate of gastric cancer in Ukraine decreased significantly from 2003 to 2020. Eight forms of gastric cancer were diagnosed each year during the study period. The incidence rates for all types of gastric cancer decreased over time.

Adenocarcinoma NOS (Not Otherwise Specified) dominated the case distribution and its incidence rate decreased slightly over the study period. Other types of gastric cancer did not significantly affect the overall epidemiological structure.

Neuroendocrine carcinoma was not diagnosed from 2003 to 2009, but incidence increased significantly from 2010 to 2019.

Adenocarcinoma Scirrhous was the second most common type from 2003 to 2014, then dropped to seventh by 2020.

Solid Adenocarcinoma had stable incidence over time, ranking as the third most common type initially, then fourth after 2009.

Diffuse type adenocarcinoma became the third most common type from 2009 onwards, with a slight increase in incidence.

Incidence rate of intestinal type adenocarcinoma increased significantly from 2004 to higher levels by 2020.

Incidence rates of neuroendocrine tumour and papillary adenocarcinoma remained stable.

Hepatocellular adenocarcinoma and linitis plastica were diagnosed only once each during the study period.

The proportion of gastric cancer cases among total cancer diagnoses steadily stable, without a noticeable change in recent years. The higher prevalence of gastric cancer in men compared to women remained a persistent trend, although both groups experienced a decline in cases. The majority of gastric cancer cases are typically found in individuals over the age of 45.

Main results of this chapter are published in 2 articles and one conference abstracts.

Publications [131, 132, 133]:

1. Chernov, Y. O. (Protas Y.), Haysanovska, V., & Makarenko, O. V. (2024). Gastric cancer in Ukraine: epidemiologic data and its nosological structure between 2003 and 2020. *Przeglad gastroenterologiczny*, *16*(4), 428–433. https://doi.org/10.5114/pg.2024.134840
2. Protas, Y. O, Makarenko, O. V. (2025). Epidemiology of gastric cancer in Ukraine from 2014–2022: rate, sex and age. *Intermedical journal* 1(2025) C. 121-124. https://doi.org/10.32782/2786-7684/2025-1-21
3. Protas Y.O., Makarenko O.V. Gastric cancer epidemiologic data in Ukraine in 2003-2020. Materials of the scientific and practical conference with international participation “Ecologic and hygienic issues of the human life activity”, March 13, 2024. P. 25.

CHAPTER 4

CONSUMPTION OF FREQUENTLY USED PHARMACEUTICALS IN UKRAINE BETWEEN 2014 AND 2020 ITS EFFECT ON THE GASTRIC CANCER INCIDENCE RATE

From 2014 to 2020, the consumption of PPIs in Ukraine increased steadily. The DDD's rate in 2020 was 98.61% higher ($P < 0.0001$) compared to 2014. Throughout this period, there were no declines or notable deviations. There were two most prominent leap during the period in 2017 and 2019 comparing to the previous years. The trend of increased consumption was reliable and showed stable tendency to increase that can be described by linear regression model (Fig. 4.1).

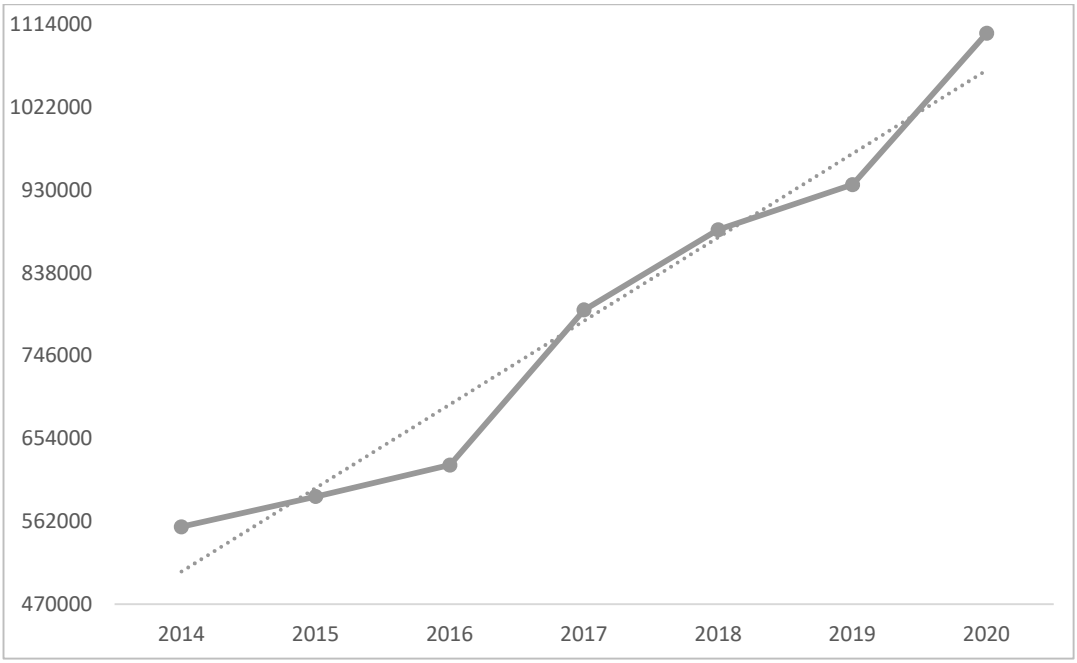

Figure 4.1. Dynamics of the use of PPIs in Ukraine from 2014 till 2020 (in DDDs per 100000 inhabitants, Y-axis). Note: the dotted green line is lineal regression line (equation for the line: $y = 92867x + 413492$, $R^2 = 0{,}9595$).

The trend DDDs for combined drugs used in *H. pylori* eradication showed instability between 2014 and 2020. There were three notable decreases: the first was a 19.18% drop ($P < 0.0001$) in 2015 compared to 2014, followed by a 47.89% decrease ($P < 0.0001$) in 2016 compared to 2015. This second decrease was succeeded by a substantial increase in 2017, which was nearly 2.5 times higher ($P < 0.0001$) than in 2016. The third decrease occurred in 2020, with an 8.02% reduction ($P < 0.0001$) compared to 2019. Because of the instable pattern of the consumption of this group of drugs the trend in the consumption can be plotted by mean of polynomial regression line but the level of reliability is hardly covering half of the results (Fig. 4.2).

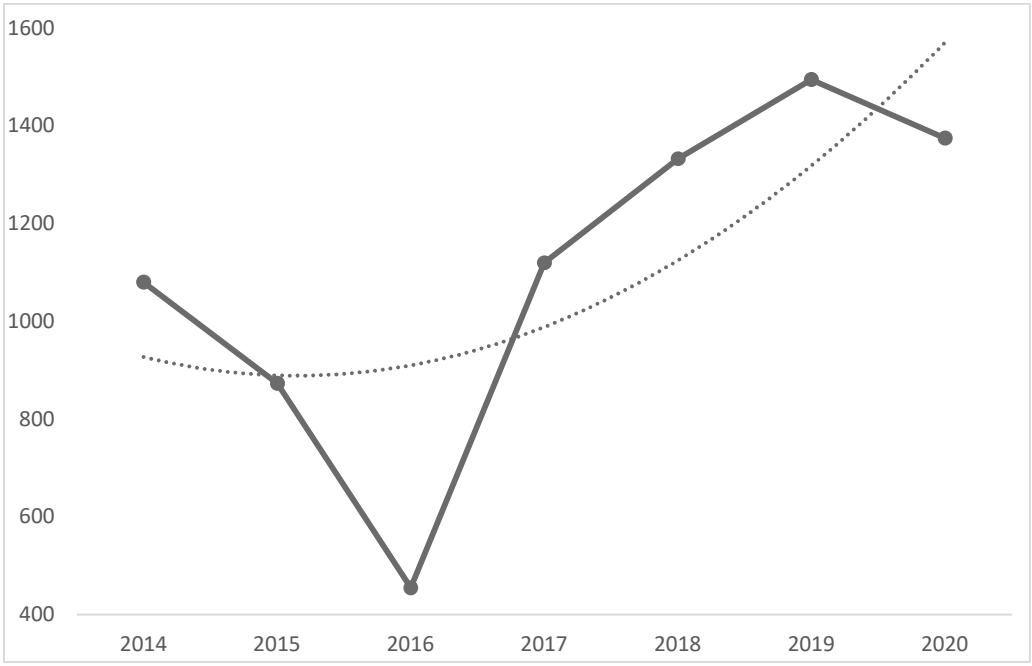

Figure 4.2. Dynamics of the use of combined drugs for *H. pylori* eradication in Ukraine from 2014–2020 (in DDDs per 100000 inhabitants per year, Y-axis). Note: the dotted blue line is the polynomial regression line (equation for the line: $y = 28{,}948x^2 - 124{,}2x + 1022{,}6$, $R^2 = 0{,}5212$).

The patterns of cysteine derivative consumption experienced a notable upward trend in Ukraine during the period from 2014 to 2020. Throughout this period, there were two significant drops in the DDD rate: a substantial decline of 15.02% ($P < 0.0001$) in 2015 compared to 2014 and a smaller decrease of 2.44% ($P < 0.0001$) in 2019 compared to 2018. Additionally, there was a remarkable surge of 36.57% ($P < 0.0001$) in 2016 compared to 2015. By 2020, the DDD rate had grown by 42.06% ($P < 0.0001$) compared to 2014. The trend in consumption of cysteine derivatives is overall stably increasing and can be described reliably by linear regression model (Fig. 4.3).

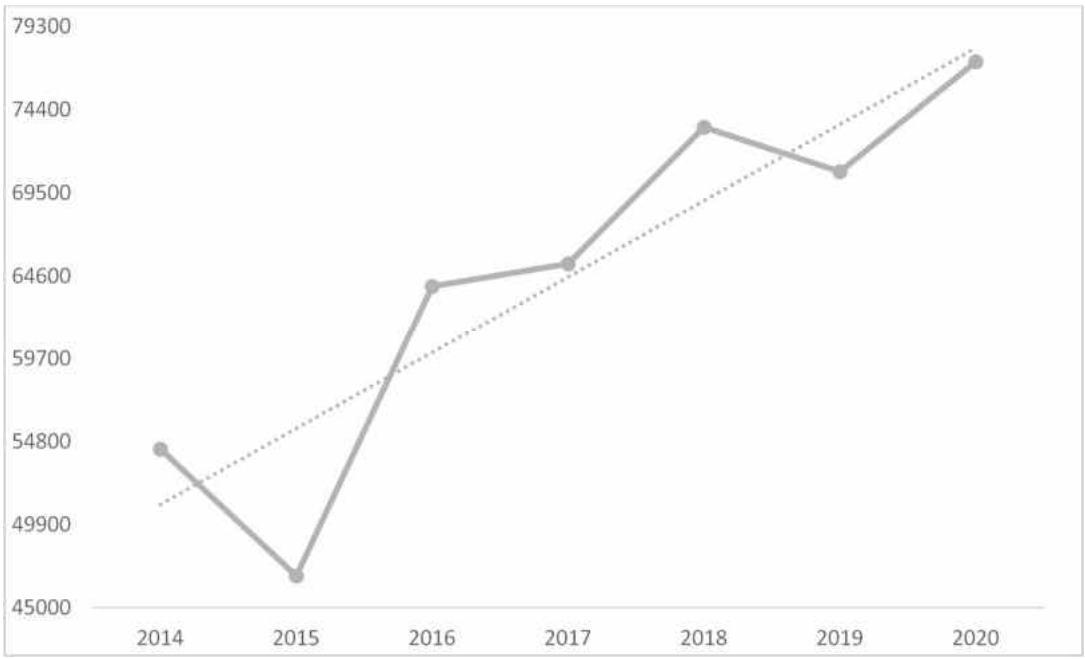

Figure 4.3. Dynamics of the use of cysteine derivatives in Ukraine from 2014 till 2020. (in DDDs per 100000 inhabitants, Y-axis). Note: dotted orange line is linear regression line (equation for the line: $y = 4490{,}4x + 46610$, $R^2 = 0{,}8131$).

The consumption of NSAIDs in Ukraine also experienced growth between 2014 and 2020, marked by two declines and one peak in the DDD rate. The first decline occurred in 2015, with a drop of 9.92% ($P < 0.0001$) compared to 2014, while the second decline was observed in 2020, with a decrease of 3.50% ($P < 0.0001$) compared to 2019. The peak occurred in 2019, showing a significant increase of 26.50% ($P < 0.0001$) compared to 2015. The trend

of the use of NSAIDs is displaying tendency towards increasing. The trend can be plotted with a linear regression model and the trend is reliable (Fig. 4.4).

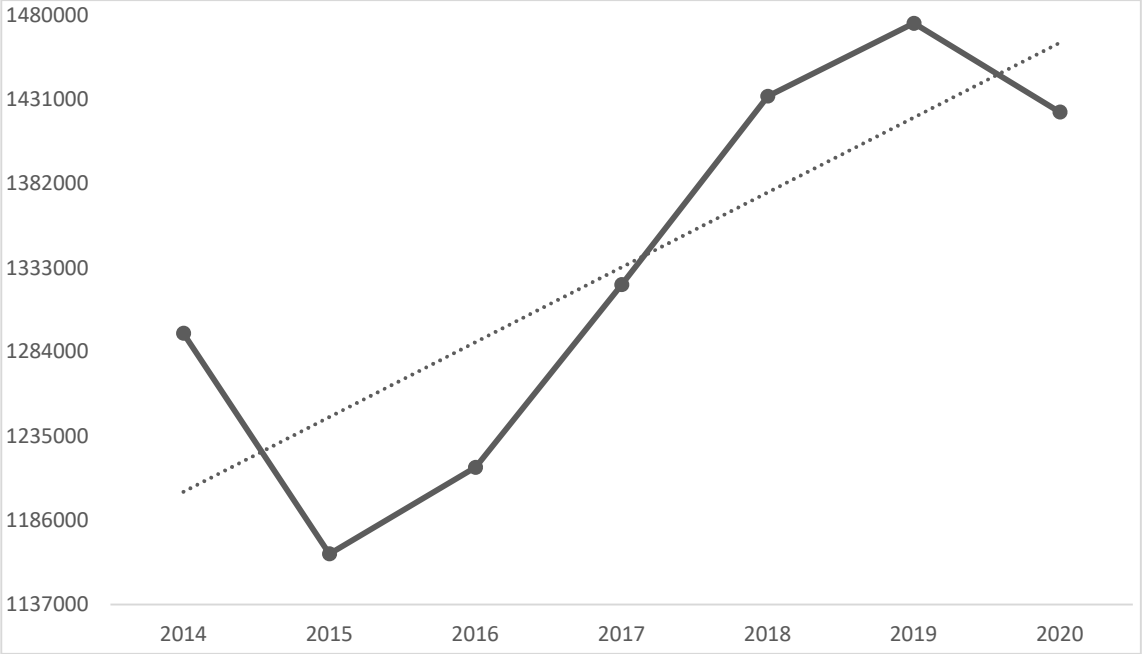

Figure 4.4. Dynamics of the consumption of NSAIDs (in DDDs per 100000 inhabitants, Y-axis) in Ukraine from 2014 till 2020. Note: the dotted violet line is lineal regression line (equation for the line: y = y = 43607x + 1E+06, R^2 = 0,6548).

In terms of low-dose ASA consumption, there was an overall upward trend in Ukraine from 2014 to 2020. This period was characterized by one significant drop, two slight decreases, and two substantial leaps. The notable drop of 8.48% ($P < 0.0001$) was observed in 2015 compared to 2014. The slight decreases occurred in 2018 and 2019, with declines of 0.63% ($P < 0.0001$) and 1.30% ($P < 0.0001$), respectively, compared to the preceding years. The first major leap was in 2017, with a rise of 17.72% ($P < 0.0001$) compared to 2016, followed by another significant leap of 14.97% ($P < 0.0001$) in 2020 compared to 2019. The trend of the use of low doses of ASA is upgoing. The trend id reliable and can be described with a linear regression model (Fig. 4.5).

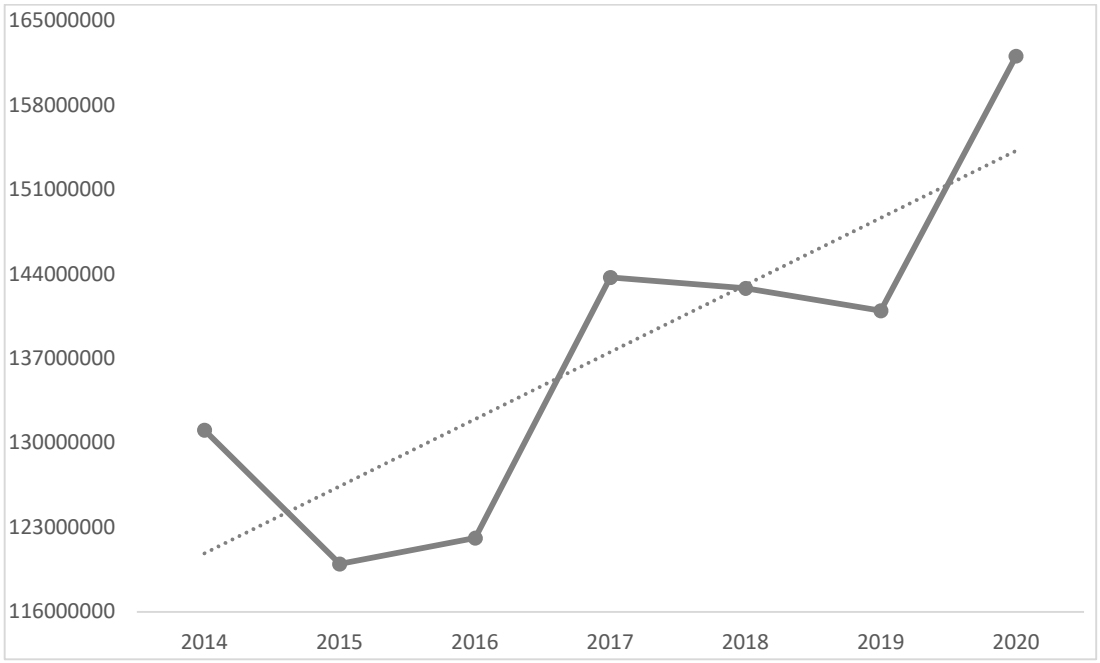

Figure 4.5. Dynamics of the consumption of ASA, low doses (in DDDs per 100000 inhabitants, Y-axis) in Ukraine from 2014 till 2020. Note: the dotted red line is linear regression line (equation for the line: $y = 6E+06x + 1E+08$, $R^2 = 0,6825$).

The consumption rate of metformin displayed a steady increase, with no observed drops or peaks, in Ukraine during the period from 2014 to 2020. By 2020, the DDD rate was 2.41 times ($P < 0.0001$) higher than in 2014. The trend of consumption of metformin is stably growing, reliable and can be described by a linear regression model (Fig. 4.6).

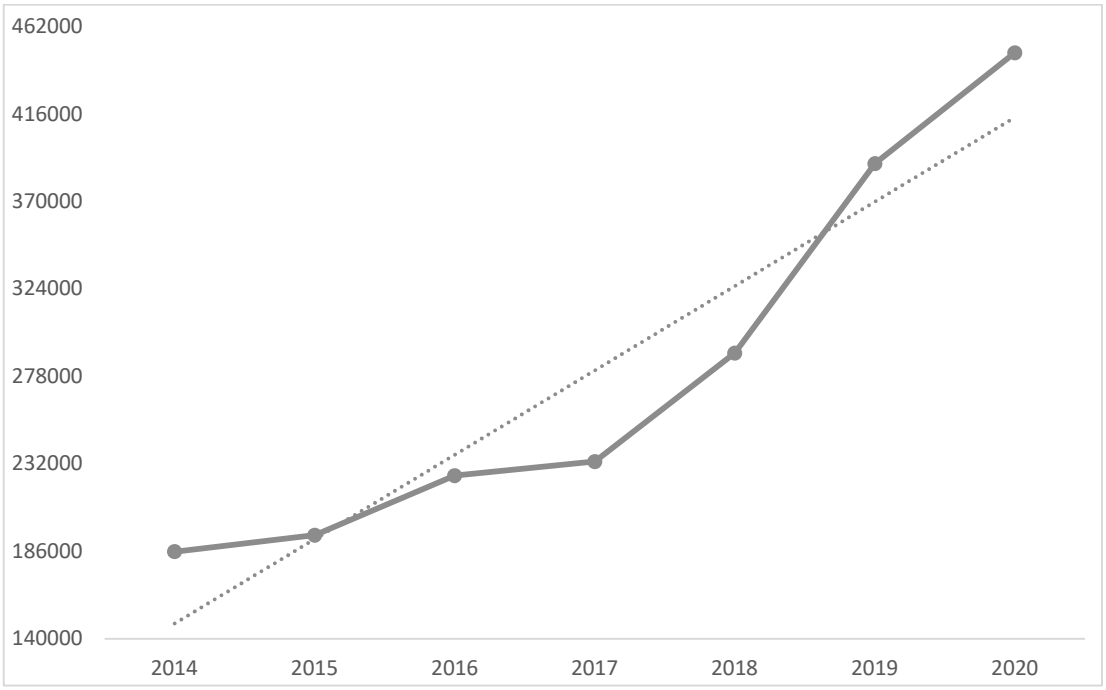

Figure 4.6. Dynamics of the consumption of metformin (in DDDs per 100000 inhabitants, Y-axis) in Ukraine from 2014 till 2020. Note: the pink line is a linear regression line (equation for the line: $y = 44385x + 103588$, $R^2 = 0{,}8924$).

The DDD rate for statins in Ukraine showed a rising trend between 2014 and 2020. There was a notable decrease of 5.94% ($P < 0.0001$) in 2015 compared to 2014. Overall, the consumption increased by 2.99 times ($P < 0.0001$) in 2020 compared to 2014. The trend of consumption of statins is steady upgrowing, reliable and can be plotted by a linear regression model (Fig. 4.7).

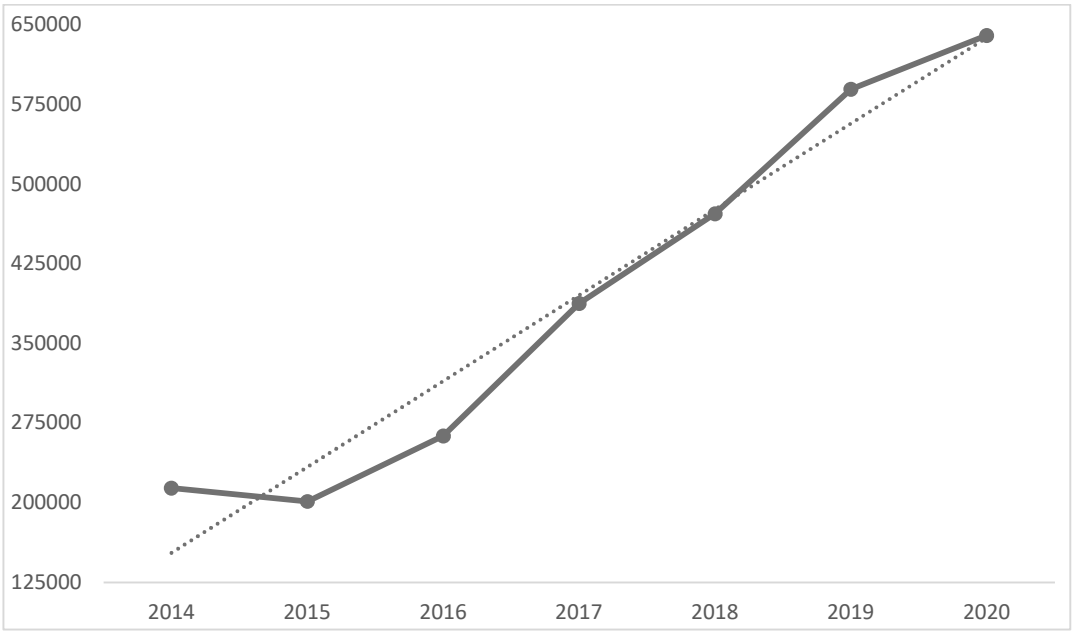

Figure 4.7. Dynamics of the consumption of statins (A) (in DDDs per 100000 inhabitants, Y-axis) in Ukraine from 2014 till 2020. Note: the dotted brown line is linear regression line (equation for the line: $y = 80867x + 71949$, $R^2 = 0{,}9552$).

From 2014 to 2021, the incidence rate of gastric cancer in Ukraine gradually declined, with the most significant drop in 2020, showing a 28.13% decrease compared to 2014 ($P < 0.0001$) (Fig. 4.8).

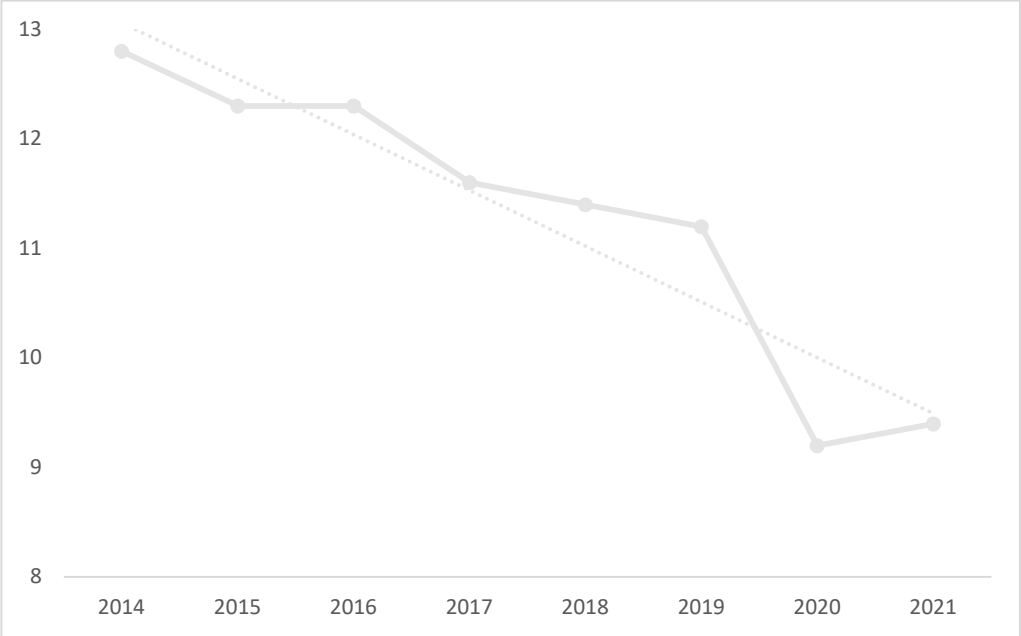

Figure 4.8. Dynamics of the annual incidence of gastric cancer (Y-axis) in Ukraine per 100000 people-year, 2014-2020. Note: The dotted turquoise line is a linear regression line (equation for the turquoise line: $y = -0{,}5095x + 13{,}568$, $R^2 = 0{,}8811$).

Gastric adenocarcinoma emerged as the predominant form of gastric cancer in Ukraine, accounting for 94.56% (95% CI, 93.04–96.56%) of all gastric cancer cases during this period. The incidence rate of gastric adenocarcinoma notably decreased by 30.74% from 2014 to 2020, marking the largest reduction within this timeframe (Fig. 4.9). The trend of gastric cancer and gastric denocarcinoma incidence rate in Ukraine is stably decreasing, reliable and can be plotted by a linear regression model (Fig. 4.8, 4.9).

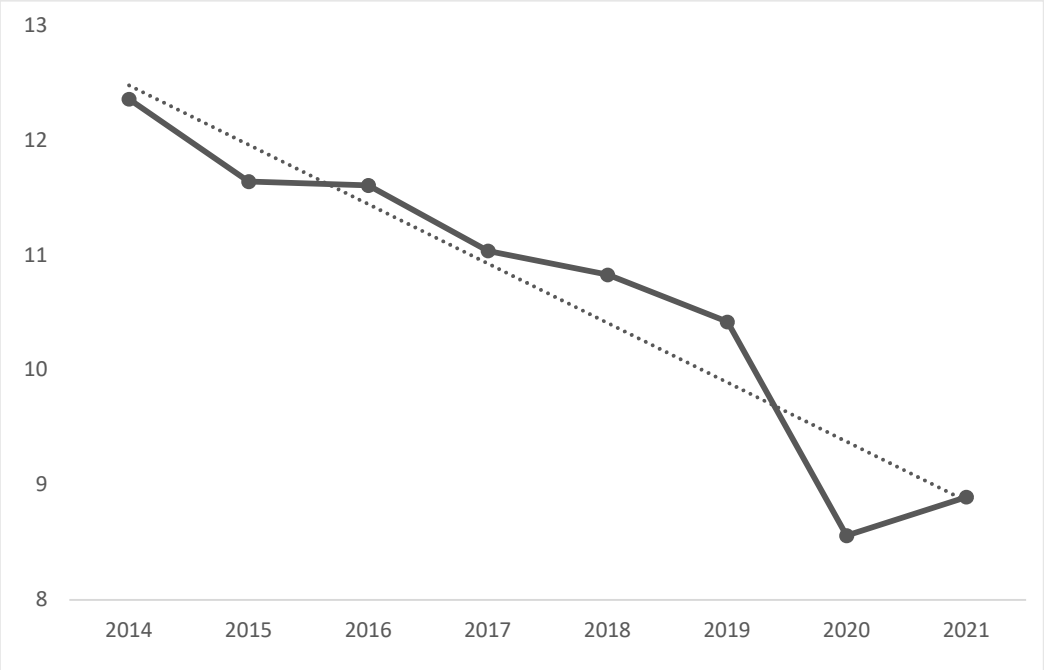

Figure 4.9. Dynamics of the annual incidence of gastric adenocarcinoma (Y-axis) in Ukraine per 100000 people-year, 2014-2020. Note: The dotted purple line is a linear regression line (equation for the line y = -0,5171x + 12,996, R^2 = 0,8978).

Summary of the chapter

From 2014 to 2020, Ukraine observed various trends in medication consumption and the incidence of gastric cancer. Proton pump inhibitors (PPIs) experienced a steady increase over the period, marked by consistent growth, especially notable in certain years. This upward trend was effectively captured using a linear regression model.

In contrast, the consumption of combined drugs for *H. pylori* eradication was unstable. Significant decreases were followed by a sharp increase and another decline towards the end of the period. This erratic pattern was best represented by a polynomial regression model, although its reliability was somewhat limited.

The usage of cysteine derivatives generally increased despite experiencing a couple of declines. After a significant surge in one year, the trend by the end of the period showed a substantial rise from the beginning. This growth pattern was well-modeled using linear regression.

NSAIDs also showed an overall growth trend with a few declines and a notable peak. This pattern was consistently depicted using a linear regression model.

Low-dose ASA consumption increased over the period, characterized by a significant drop early on, minor declines in later years, and substantial rises in the middle and towards the end of the period.

Metformin's usage steadily rose without any significant drops or peaks, while statins also demonstrated a consistent upward trend.

In terms of gastric cancer, the incidence rate in Ukraine declined significantly, with a particularly notable decrease in the last year compared to the beginning of the period.

Adenocarcinoma, the most common form of gastric cancer, saw a substantial reduction, with the declining trends accurately represented by linear regression models.

Main results of this chapter are published in one article and 2 conference abstracts. Publications [134, 135, 136]:

1. Protas, Y. O, Makarenko, O. V. (2025). Use of combined fixed-dose drugs for Helicobacter pylori eradication and gastric cancer incidence indices in Ukraine from 2014 to 2021. *Medicni perspektivi, 30*(1)(2025) C. 202-205. https://doi.org/10.26641/2307-0404.2025.1.325466
2. Protas Y.O., Makarenko O.V. Consumption of proton pump inhibitors in Ukraine from 2014 till 2020. Materials of XI The international scientific and practical distance conference "Management and marketing as parts of modern economy, science, education, practice", March 21, 2024. P. 369.
3. Protas Y.O., Makarenko O.V. Impact of *Helicobacter pylori* eradication and frequently used medications on gastric cancer incidence in Ukraine (2014–2021). Materials of the all-Ukrainian scientific and practical conference "Public health: from analysing the past to understanding the future", October 10, 2024. P. 35-39.

CHAPTER 5

DISCUSSION

5.1. Gastric cancer epidemiology and its nosological structure in Ukraine and worldwide

Gastric cancer declining trend in Ukraine and worldwide and its possible reasons

Recent epidemiological data indicates a declining trend in gastric cancer incidence rates in Ukraine. According to the Ukrainian Cancer Registry, the incidence of gastric cancer has decreased over the past two decades. This decline is consistent with global trends and the factors mostly are the same as worldwide but an influence of some specific regional factors in Ukraine cannot be excluded. Globally, the incidence of gastric cancer has shown a consistent decline over the past few decades [131]. This trend is particularly evident in high-income countries but is also emerging in some middle-income countries. According to data from the Global Cancer Observatory (GLOBOCAN) 2020, the incidence rates of gastric cancer have decreased significantly in regions such as North America, Western Europe, and East Asia [137].

In the United States, Gastric cancer rates declined by 1,23% annually from 1992 to 2019. However, despite the overall decrease, gastric cancer incidence rates rose among individuals under 50 years of age, primarily due to non-cardia gastric cancer, which accounts for 74,3% of all cases. In contrast, cardia gastric cancer, representing 26.7% of all gastric cancer cases, showed declining rates across all age groups except for those aged 80 to 84 years [138].

The analysis reveals a general decline in the age-standardized incidence rate of gastric cancer in both China and Japan from 1990 to 2019, with the decrease occurring at a significantly faster rate in Japan compared to China. Using an age-period-cohort model, the

study confirmed that the cohort effect was the primary driver of the reduction in ASIR for gastric cancer during the study period in both countries [139].

Similar declining trends are observed in European countries, with notable decreases in incidence rates reported in countries like Sweden, the United Kingdom and other developed countries [137].

Several factors can have contributed to the decreasing incidence rates of gastric cancer in Ukraine and worldwide. These include improved management of *H. pylori* infection, dietary changes, higher socioeconomic status, better living conditions, increased awareness and early detection, advancements in medical technology and popularization of healthy lifestyle [3].

H. pylori infection is a major risk factor for gastric cancer. The bacterium causes chronic inflammation of the stomach lining, which can lead to precancerous changes and, eventually, cancer. Efforts to manage and eradicate *H. pylori* infection may have significantly contributed to the decline in gastric cancer incidence in Ukraine and rest of the world [140]. In favour of this also witness the increased sales of combined fixed-dose drugs for *H. pylori* eradication.

A study conducted in Ukraine showed that national efforts to diagnose and treat *H. pylori* infection resulted in a significant reduction in the prevalence of the infection. The study reported that widespread use of antibiotics and PPIs for *H. pylori* eradication led to a decrease in gastric cancer cases [124].

Another research highlighted the impact of *H. pylori* screening in Ukraine. The study found that regions with active screening and treatment aproaches saw a more substantial decline in gastric cancer incidence compared to areas without such programs [141].

Role of the successful eradication of *H. pylori* was shown in many studies. The Taipei global consensus demonstrated that national efforts to screen and treat *H. pylori* infection led to a significant reduction in the incidence of gastric cancer. The consensus reported a significant decrease in spendings on gastric cancer related costs following the implementation of a national *H. pylori* eradication program [142].

Another study highlighted the impact of *H. pylori* eradication on gastric cancer risk in Japan. It showed that individuals who underwent successful *H. pylori* eradication had a significantly lower risk of developing gastric cancer compared to those with persistent infection as well as decrease of spendings on gastric cancer related costs [143].

Changes in dietary habits and lifestyle factors could have also played a crucial role in the reduction of gastric cancer incidence in Ukraine. The adoption of healthier eating patterns and a decrease in the consumption of risk-associated foods have contributed to this positive trend in many countries worldwide [144].

Researchers analysed dietary trends in Ukraine over the past decade. They found a significant increase in the consumption of fruits and vegetables and a decrease in the intake of smoked, salted, and pickled foods. These dietary changes were associated with a lower risk of gastric cancer [145].

A study on lifestyle factors indicated a decline in smoking rates and alcohol consumption among Ukrainians. The study linked these lifestyle changes to a reduced incidence of gastric cancer, as smoking and excessive alcohol consumption are known risk factors for the disease [146].

Crucial role of changes in dietary habits and lifestyle factors in the declining incidence of gastric cancer have also been shown in other countries, such as Japan and South Korea. The adoption of healthier dietary patterns, including increased consumption of fruits and vegetables and reduced intake of salted and smoked foods, has contributed to lower gastric cancer rates [147].

The Japanese study found a correlation between dietary improvements and reduced gastric cancer risk. Increased intake of fresh fruits and vegetables, along with a decrease in consumption of salty and preserved foods, was associated with a significant reduction in gastric cancer incidence [148].

The South Korean study highlighted the role of reduced smoking rates and alcohol consumption in decreasing gastric cancer risk. The study reported that public health campaigns

targeting smoking cessation and alcohol moderation led to a decline in gastric cancer cases [149].

Advancements in medical technology and the implementation of early detection programs have significantly contributed to the declining incidence of gastric cancer in many countries that might be also the same for Ukraine [150].

Advances in screening and detection of gastric cancer were studied extensively. A study outlines the incidence rates of gastric cancer with high prevalence in Asia and Eastern Europe, including Ukraine, highlighting the critical role of improved diagnostic methods and screening programs in reducing incidence [151, 152].

Biomarkers for gastric cancer screening and early diagnosis are also of high importance. Research into non-invasive biomarkers through liquid biopsy is advancing in worldwide. These biomarkers are derived from various bodily fluids, enhancing early-stage gastric cancer diagnosis and screening accuracy [153]. Implementation of those screening programs in Ukraine could be also beneficial.

Endoscopic screening and surveillance for gastric cancer gives also many opportunities despite challenges. A study discusses how endoscopic screening and surveillance are integral to early detection of pre-symptomatic gastric neoplasia in high-incidence countries, despite the high resource demands [154].

Chronological trend of opportunistic endoscopic screening for gastric cancer and atrophic gastritis is investigated. Researchers show a decrease in gastric cancer detection and atrophic gastritis prevalence in Ukraine, reflecting the effectiveness of the opportunistic endoscopic screening programs implemented [155].

Cell-free DNA methylation profiles enable early detection of colorectal and gastric cancer. Advancements in detecting gastric cancer via cell-free DNA methylation profiles demonstrate high sensitivity and specificity, marking a significant step forward in non-invasive diagnostic methods worldwide as well as in Ukraine [156].

Improved socioeconomic conditions and environmental factors have also contributed to the declining incidence of gastric cancer in Ukraine. Better living standards, improved sanitation, and increased access to healthcare have all played a role in reducing the risk of gastric cancer. A study indicated that economic development and improved living conditions in Ukraine have been associated with a lower risk of gastric cancer. Regions experiencing significant economic growth saw more substantial declines in gastric cancer incidence. Reduction in environmental risk factors, such as exposure to harmful chemicals and pollutants, has also contributed to lower gastric cancer rates. Efforts to improve water quality and food safety standards have been instrumental in this regard [146].

A study indicated that higher socioeconomic status and improved living conditions were associated with a lower risk of gastric cancer. Regions with significant economic development saw more substantial declines in gastric cancer incidence [157].

Access to healthcare is a critical determinant of health outcomes, including cancer incidence and mortality. Higher socioeconomic status typically correlates with better access to healthcare services, which plays a pivotal role in the early detection and treatment of gastric cancer. Improved access to healthcare facilitates several important factors. Individuals with higher socioeconomic status are more likely to participate in regular health screenings, including endoscopic examinations, which are crucial for the early detection of gastric cancer. Early detection is vital for improving the prognosis and reducing mortality rates associated with gastric cancer. Studies have shown that regular endoscopic screening can significantly reduce the incidence of advanced gastric cancer by identifying and treating precancerous lesions and early-stage cancers [158].

Higher socioeconomic status is associated with access to better-quality medical services and healthcare facilities. This includes access to specialized care, advanced diagnostic tools, and experienced healthcare professionals. The quality of medical services can directly impact the outcomes of gastric cancer treatment, with better-equipped facilities and skilled professionals leading to improved survival rates [159].

Access to healthcare also ensures that individuals receive timely treatment for gastric cancer. Delays in treatment can lead to the progression of the disease, making it more difficult to treat and decreasing the chances of survival. Higher socioeconomic status groups are less likely to experience such delays, contributing to better outcomes [159].

Education and awareness about gastric cancer and its risk factors play a crucial role in its prevention and early detection. Higher socioeconomic status is often linked to better education, which in turn affects an individual's health behaviours and attitudes. Educated individuals are more likely to be aware of the risk factors associated with gastric cancer, such as *H. pylori* infection, dietary habits, smoking, and alcohol consumption. This awareness can lead to proactive measures to reduce these risks, such as improved diet and lifestyle choices. Education increases the likelihood of participating in preventive measures, such as vaccination and regular health screenings. Studies have shown that individuals with higher education levels are more likely to undergo regular screenings for various cancers, including gastric cancer, which helps in early detection and reduces mortality rates. Educated individuals are more likely to understand and adhere to treatment plans, including medication adherence, follow-up visits, and lifestyle modifications. This adherence is crucial for the successful management of gastric cancer and reducing recurrence rates [160].

Housing and sanitation are essential components of living conditions that directly impact health outcomes. Improvements in these areas have been associated with a decline in the incidence of various infectious diseases and cancers, including gastric cancer. *H. pylori* infection is a major risk factor for gastric cancer. Improved housing conditions, such as less crowded living spaces and better sanitation facilities, reduce the risk of *H. pylori* transmission and infection. Studies have shown that the prevalence of *H. pylori* is significantly lower in populations with improved housing and sanitation. Poor housing conditions can lead to exposure to various carcinogens, such as radon, asbestos, and mould. Improved housing standards reduce this exposure, thereby lowering the risk of gastric cancer and other respiratory and gastrointestinal cancers [161].

Better housing and sanitation facilities contribute to improved nutrition and food safety. Access to clean cooking facilities and proper food storage reduces the risk of consuming contaminated or spoiled food, which is linked to gastric cancer risk [162].

Access to clean water is a fundamental aspect of public health and plays a significant role in preventing gastric cancer. Contaminated water is a known vector for *H. pylori* transmission. Access to clean drinking water reduces the risk of *H. pylori* infection, thereby lowering the risk of gastric cancer. Studies have documented a correlation between improved water quality and a decline in the prevalence of *H. pylori* infection. Clean water reduces exposure to harmful chemicals, such as nitrates and heavy metals, which are associated with an increased risk of gastric cancer. Ensuring safe water supply is crucial for reducing these exposures. Access to clean water also contributes to overall health and well-being, reducing the incidence of gastrointestinal diseases and promoting better nutrition, both of which are protective factors against gastric cancer [161, 162].

Gastric cancer has consistently shown a higher prevalence in men compared to women, a trend observed across various populations and regions. One major factor contributing to this disparity is the protective effect of estrogen in women. Estrogen is believed to reduce inflammation and inhibit the development of gastric cancer by modulating immune responses and preventing the progression of *H. pylori* infections, a primary risk factor for the disease [163]. This hormonal advantage in women diminishes after menopause, leading to a relative increase in gastric cancer incidence among older women [2, 164].

Additionally, differences in lifestyle and dietary habits contribute to the gender disparity. Men are more likely to consume high-salt and processed foods, excessive alcohol, and tobacco, all of which have been linked to an increased risk of gastric cancer [20]. Smoking, in particular, has been shown to significantly elevate the risk of gastric cancer, with men having higher smoking rates than women in many countries. Moreover, occupational exposure to harmful chemicals, heavy metals, and asbestos is more common in male-dominated industries, further increasing the risk for men [2, 3].

Genetic predisposition also plays a role, as studies suggest that men may be more likely to carry specific genetic mutations associated with gastric cancer susceptibility. Research has shown that genetic variations affecting immune response and inflammation pathways may be more prominent in men, increasing their overall risk for developing the disease [3, 164].

Another factor is healthcare-seeking behavior, where men are generally less likely to undergo routine medical check-ups and screenings compared to women. This delay in seeking medical attention can lead to later-stage diagnoses, which may further contribute to the higher mortality rates observed in men with gastric cancer.

Overall, the persistent trend of higher gastric cancer prevalence in men is multifactorial, involving hormonal protection in women, lifestyle differences, genetic susceptibility, occupational exposure, and healthcare behaviors. Addressing these risk factors through targeted public health interventions, early screening programs, and lifestyle modifications could help mitigate the gender disparity in gastric cancer cases [3, 164]. Environmental factors, including pollution and exposure to carcinogens, are significant contributors to the development of gastric cancer. Improvements in socioeconomic status often led to reduced exposure to these environmental risks. Air pollution is a known risk factor for various cancers, including gastric cancer. Higher socioeconomic status is often associated with living in areas with better air quality and lower levels of industrial and vehicular pollution. Reducing exposure to air pollution can decrease the risk of gastric cancer. Individuals with higher socioeconomic status are less likely to work in occupations with high exposure to carcinogens, such as chemicals, dust, and radiation. Occupational exposure to these substances is a known risk factor for gastric cancer, and reducing this exposure can contribute to a decline in incidence rates. Higher socioeconomic status often correlates with stronger environmental policies and regulations that protect communities from exposure to environmental carcinogens. These policies can include regulations on industrial emissions, waste management, and chemical use, all of which can impact gastric cancer rates [165, 166].

Gastric cancer and its nosological structure based on pathomorphological forms in Ukraine and worldwide

Adenocarcinoma NOS (8140) is the predominant histological type of gastric cancer, accounting for approximately 90-95% of all gastric cancer cases worldwide. According to the World Health Organization, gastric adenocarcinoma NOS constitutes the vast majority of gastric cancer cases globally. Data from GLOBOCAN 2020 indicates that gastric adenocarcinoma NOS remains the leading type of stomach cancer in both developed and developing countries [24].

In Ukraine, similar trends are observed, with adenocarcinoma NOS being the most prevalent form of gastric cancer. The Ukrainian Cancer Registry provides data that aligns with global patterns, highlighting the dominance of this cancer type in the country. The Ukrainian Cancer Registry reports that adenocarcinoma NOS accounts for over 90% of all gastric [131].

Scirrhous adenocarcinoma (8141) is a subtype of gastric cancer characterized by a diffuse thickening of the stomach wall. This form is known for its poor prognosis and aggressive behaviour. While specific incidence rates for adenocarcinoma scirrhous are not commonly reported separately in large-scale epidemiological studies, it is generally considered a rare variant within the spectrum of gastric adenocarcinomas [13].

Intestinal type adenocarcinoma (8144) is one of the most common histological subtypes of gastric cancer. It is often linked to environmental factors such as diet and *H. pylori* infection. A review reported that intestinal type gastric cancer was more common than the diffuse type, indicating a higher incidence rate of the intestinal subtype in certain population. In particular, intestinal-type adenocarcinoma as more prevalent in regions with higher *H. pylori* infection rates and diets rich in salted and smoked foods [3].

The diffuse type of adenocarcinoma (8145), according to the Lauren classification, is characterized by poorly cohesive cells that infiltrate the gastric wall, leading to a thickened and rigid stomach. This subtype has a worse prognosis compared to the intestinal type. The

same review stated that the diffuse type was less common than the intestinal type but still constitutes a significant portion of gastric cancer cases [3].

Tubular adenocarcinoma (8211) is a subtype characterized by the formation of tubular structures within the tumour. The incidence rate of this specific subtype is not commonly reported separately in many studies; however, it is generally included within the broader category of adenocarcinoma NOS [167].

Solid adenocarcinoma (8230) is a less common histological subtype of gastric cancer, known for its dense cellular architecture. Like tubular adenocarcinoma, the incidence of solid adenocarcinoma is often reported as part of the overall incidence of gastric adenocarcinomas [167].

Gastric neuroendocrine tumours (8240) are relatively rare, constituting a small percentage of all gastric neoplasms. The incidence rate of gastric neuroendocrine tumours varies significantly by region and population. A study indicated that gastric neoplasms containing neuroendocrine carcinoma components have a poorer overall survival compared to other forms of gastric adenocarcinoma, highlighting the aggressive nature of this subtype [168].

Papillary adenocarcinoma (8260) is characterized by the presence of papillary structures within the tumour. This subtype is relatively rare, and specific incidence rates are often not separately reported in epidemiological studies. However, papillary adenocarcinoma is included in the broader category of gastric adenocarcinomas [169].

Adenomatous polyps (8210) are benign tumours that can occur in the stomach and have the potential to progress to gastric cancer. A study classified gastrointestinal lesions, noting that adenomatous polyps with depressed parts had higher malignant transformation risks. Lesion size and morphological depression were identified as significant risk factors [170].

Gastric neuroendocrine carcinoma (8246) is a rare and aggressive subtype of gastric cancer. A study based on SEER data found that the prognosis of gastric neuroendocrine carcinoma is better than gastric adenocarcinoma among White patients in the United States.

The incidence rate of gastric neuroendocrine carcinoma remains relatively low compared to other gastric cancer subtypes [171].

Adenocarcinoma arising in a tubulovillous adenoma (8263) is a subtype of gastric cancer that develops from a pre-existing adenomatous polyp. This form is considered part of the adenoma-carcinoma sequence, with adenomatous polyps serving as precursors to invasive carcinoma. Specific incidence rates are not widely reported separately but are included in studies of gastric adenomas and their progression [172].

Clear cell adenocarcinoma (8310) is an extremely rare subtype of gastric cancer, characterized by cells with clear cytoplasm. Due to its rarity, specific incidence rates are not commonly reported in the literature [173].

Hepatocellular adenocarcinoma (8170) is primarily associated with the liver, and its occurrence as a primary tumour in the stomach is exceedingly rare. As such, specific incidence rates for hepatocellular adenocarcinoma in the context of gastric cancer are not typically available [169].

Linitis plastica (8142), also referred to as diffuse infiltrative gastric cancer, is a rare and highly aggressive form of gastric cancer. It is characterized by a thickening of the stomach wall due to diffuse infiltration of cancer cells, leading to a "leather bottle" appearance. The incidence rate of linitis plastica is low but notable for its association with a poor prognosis and the potential for early metastasis [174].

Gastric cancer and its age relate epidemiology

The incidence rate of gastric cancer has remained relatively stable in age-related groups globally, particularly in the older population. Factors contributing to the incidence of gastric cancer among the age groups of 60-64, 65-69, 70-74, 75-79, 80-85, and 85+ are multifaceted and influenced by a combination of genetic, environmental, and lifestyle factors. These factors become more pronounced with aging, leading to higher risks of gastric cancer in older adults, both in Ukraine and worldwide [3, 131].

The global incidence of gastric cancer has shown an increase in certain age groups. A study analysing global, regional, and national trends from 1990 to 2019 demonstrated that gastric cancer incidence among adolescents and young adults has slightly increased, which contrasts with the higher and more stable incidence in older populations. This highlights the age-related susceptibility to gastric cancer, which remains significantly higher in older age groups [111].

Among patients who undergo surgical treatment for gastric cancer, older adults are more likely to present with certain characteristics of the disease. For example, cancer located in the distal third of the stomach, with intestinal-type histology and p53 overexpression, is more common in these age groups. This suggests that biological changes associated with aging may predispose older adults to particular types of gastric cancer [175].

The increasing incidence of gastric cancer in older adults is also influenced by lifestyle factors accumulated over a lifetime. For instance, individuals who initiated smoking at a young age were found to have a higher risk of gastric cancer later in life. A study reviewed the impact of early-life exposures on adult cancer risk, including smoking, emphasizing the significance of age at initiation [176].

Environmental risk factors also play a significant role in the age-related incidence of gastric cancer. Studies have shown that early onset gastric cancer is associated with different environmental exposures compared to older onset cases. Younger patients are more likely to present with metastatic disease, be misdiagnosed, and have a higher mortality rate, emphasizing the importance of early detection and the distinct etiological factors at play across age groups [164].

Cardiac comorbidity is another important factor contributing to the high incidence of gastric cancer in older adults. Older patients with gastrointestinal cancers, particularly those with gastric or oesophageal cancer, have a higher risk of hospitalization due to cardiac issues. This comorbidity complicates the treatment and management of gastric cancer in these patients, further contributing to the disease's burden in older age groups [177].

5.2. Consumption of frequently used pharmaceuticals in Ukraine and worldwide and its effect on the gastric cancer incidence rate

PPI's and their role in the development of gastric cancer

The sales of PPIs increase in Ukraine from 2014 till 2020 as well as in the rest of the world.

The main problem is that the epidemiological studies is quite controversial regarding the role of PPIs in the development of gastric cancer. There are epidemiological studies showing association of PPIs with increased risk of gastric cancer as well the studies not supporting the link [14, 178].

To synthesize existing evidence, a systematic review and meta-analysis of observational studies examining the risk of gastric cancer associated with PPI use were conducted. The pooled analysis indicated that PPI use was associated with a significantly increased risk of gastric cancer. The analysis highlighted that the risk remained elevated even after accounting for *H. pylori* eradication, suggesting that PPI use itself may contribute to gastric carcinogenesis. The authors noted significant heterogeneity among the included studies, with variations in study design, population characteristics, and confounding factors [9].

PPIs are frequently used in the treatment and management of *H. pylori* infection, which is a major risk factor for gastric cancer. The consumption of PPIs is integral to the regimen of antibiotics prescribed for *H. pylori* eradication, which subsequently reduces the risk of developing gastric cancer. Studies have shown a decrease in the prevalence of gastric cancer with the successful eradication of *H. pylori*, underscoring the importance of PPIs in these therapeutic strategies [53, 179].

Gastritis, particularly chronic gastritis, is associated with an increased risk of gastric cancer. PPIs are commonly prescribed for the management of gastritis to reduce gastric acidity and alleviate symptoms. This widespread prescription may contribute to the increased consumption of PPIs globally as part of efforts to prevent the progression of gastritis to more severe forms, including cancerous lesions [10, 180].

The implementation of national screening programs for gastric cancer has led to earlier detection and treatment of precancerous conditions, often involving the use of PPIs as part of the treatment protocol. Screening programs have been associated with a 31% decrease in gastric cancer mortality, highlighting the role of PPIs in these preventive measures [181].

Changes in dietary habits and lifestyle, particularly the adoption of a Western diet characterized by high fat and low fibre, have led to an increase in gastric acid-related disorders. PPIs are frequently used to manage symptoms associated with these dietary changes, contributing to their increased consumption. Improved diet and reductions in smoking and *H. pylori* prevalence are linked to decreasing trends in gastric cancer, which in turn influence PPI consumption patterns [181, 182].

The global increase in life expectancy and the resultant aging population have led to a higher prevalence of conditions such as GERD, peptic ulcers, and other gastrointestinal disorders. These conditions often require long-term management with PPIs, thus contributing to the rising consumption of these medications. The age-dependent risk factors for gastric cancer, such as prolonged PPI use, have been identified in various studies, suggesting a potential correlation between age, PPI use, and gastric cancer risk [178, 182].

The availability of PPIs as over-the-counter medications has made them easily accessible to the general public, leading to increased use without medical supervision. This self-medication trend, while providing relief for minor gastric discomforts, may lead to prolonged and inappropriate use of PPIs, increasing the risk of adverse effects, including those related to gastric cancer [183].

Long-term use of PPIs has been associated with an increased risk of gastric atrophy, particularly in individuals with *H. pylori* infection. Gastric atrophy is a known precursor to gastric cancer, and the chronic suppression of gastric acid can exacerbate this condition. The interplay between PPI use, *H. pylori* infection, and the development of gastric cancer remains a critical area of research [9, 10].

The suppression of gastric acid due to PPI use can lead to alterations in the gastric microbiota, promoting the growth of non-*Helicobacter pylori* bacteria. These microbial changes can contribute to an increased risk of gastric cancer, as certain bacterial populations have been linked to carcinogenesis in the gastric environment [184].

PPIs can interact with other medications and affect the absorption of essential nutrients such as vitamin B12, magnesium, and calcium. These interactions can lead to deficiencies that may indirectly influence the risk of gastric cancer by weakening the body's natural defence mechanisms and contributing to an environment conducive to cancer development [185].

The widespread use of PPIs has significant economic implications, not only due to the cost of the medications themselves but also because of the long-term healthcare costs associated with managing the side effects of chronic PPI use. These costs include increased hospitalizations for complications like kidney disease and infections, as well as the treatment of gastric cancer cases potentially linked to PPI use [186].

The increasing consumption of PPIs poses challenges for public health policy and the development of guidelines for their use. There is a need for improved prescription practices that ensure PPIs are used appropriately and only, when necessary, to minimize the risk of gastric cancer and other long-term consequences. Healthcare providers must balance the benefits of PPIs in managing gastric acid-related conditions with the potential risks of long-term use [6, 187].

A cohort study was conducted in Taiwan to explore the potential dose-response relationship between PPI use and gastric cancer risk. The study found a clear dose-response relationship, with higher cumulative doses of PPIs associated with a greater risk of gastric cancer. The risk was particularly pronounced in older adults and those with a longer duration of PPI use, reinforcing the need for cautious long-term prescribing in these populations [188]. [188].

In a prospective cohort study researchers aimed to explore the potential link between PPI use and gastric cancer in a European population. The study found no significant increase

in gastric cancer risk among regular PPI users. The study also examined the impact of the duration of PPI use and found no significant increase in risk with longer durations of use. By controlling for multiple confounders, including lifestyle factors and comorbidities, the study provided robust evidence against a causal relationship between PPI use and gastric cancer [189].

A systematic reviews and meta-analysis to assess the association between PPI use and the risk of gastric cancer were performed. The meta-analysis included studies with diverse populations and methodologies. The meta-analysis noted considerable heterogeneity among included studies but emphasized that higher-quality studies tended to report null or weak associations. The authors highlighted the importance of accounting for bias and confounding factors, such as indication bias (where the underlying condition requiring PPI use might itself be associated with cancer risk) [14, 189].

Consumption of combined fixed-dose drugs for *H. pylori* eradication

In general, trends in consumption of combined fixed-dose drugs for *H. pylori* eradication were not stable from 2014 till 2020 and grown stably only from 2016 till 2020. Worldwide trends show tendencies to stable growing of consumption combined fixed-dose drugs for *H. pylori* eradication. There are several factors that can play driven role for upscaling of consumption of this group of drugs [70].

H. pylori infection is a well-established risk factor for gastric cancer and is highly prevalent globally, particularly in developing countries. The high prevalence of *H. pylori* infection necessitates widespread and effective treatment strategies, which has led to increased consumption of fixed dose combination drugs designed for eradication [190]. In Ukraine and similar regions, the high rates of infection may have made these combination therapies an essential part of medical practice.

The rise in antibiotic-resistant strains of *H. pylori* has complicated treatment regimens, leading to the development and increased use of fixed dose combination drugs. These combinations typically include multiple antibiotics and a proton pump inhibitor (PPI) to

overcome resistance and ensure higher eradication rates. As resistance patterns continue to evolve, the use of such therapies has become more prevalent as they offer a reliable alternative to traditional monotherapies [191].

Fixed dose combination drugs simplify the treatment regimen for patients by combining multiple medications into a single dose. This simplification improves patient compliance and reduces the likelihood of treatment failure [192].

Studies have shown that therapies combining a PPI, antibiotics, and bismuth have achieved high eradication rates, with one study reporting a high eradication rate using a high-dose PPI-bismuth-containing quadruple therapy [193].

Many national and international guidelines now recommend the use of fixed dose combination therapies as the first-line treatment for *H. pylori* eradication. This official endorsement by healthcare authorities has led to their widespread adoption in clinical practice. In Ukraine, as in other countries, adherence to these guidelines can be crucial for reducing the incidence of gastric cancer, given the strong link between *H. pylori* infection and gastric malignancies [70, 190].

Advances in pharmaceutical technology have allowed for the development of more effective and patient-friendly formulations of fixed dose combination drugs. These new formulations can include delayed-release mechanisms and tailored dosage strengths to optimize drug delivery and minimize side effects. Such innovations have enhanced the appeal and effectiveness of these medications, leading to their increased consumption [194].

Successful eradication of *H. pylori* using fixed dose combination drugs significantly reduces the risk of developing gastric cancer. By eliminating the primary causative agent, these therapies help prevent the progression of precancerous lesions to malignant states. This preventive effect is particularly crucial in high-risk populations, such as those with a family history of gastric cancer or those who have undergone curative resection of early gastric cancers [70, 190].

The use of combination therapies can alter the gastric microbiota, which plays a critical role in maintaining gastric health and protecting against pathogens. While the eradication of *H. pylori* is beneficial, the broad-spectrum antibiotics used in these therapies can also disrupt the balance of beneficial bacteria, potentially leading to dysbiosis and increased susceptibility to other infections [7].

The fixed dose combination therapies can cause side effects such as nausea, vomiting, diarrhoea, and abdominal pain, which may affect patient adherence. Additionally, the components of these combinations can interact with other medications, altering their effectiveness or causing adverse reactions. Careful monitoring and management of these side effects are essential to ensure successful treatment outcomes [195].

The widespread use of fixed dose combination drugs has significant economic implications for healthcare systems, particularly in terms of cost and resource allocation. While these therapies are cost-effective in the long term by preventing gastric cancer, the initial costs can be substantial. Ensuring equitable access to these medications and optimizing their use are important considerations for healthcare policymakers [70, 195].

The use of multiple antibiotics in combination therapies raises concerns about the development of antibiotic resistance. Although these therapies are designed to overcome existing resistance, their widespread use could contribute to the emergence of new resistant strains. Continuous surveillance of resistance patterns and the development of new treatment strategies are essential to address this challenge [196].

Fixed dose combination therapies are increasingly being integrated into screening and prevention programs for gastric cancer, particularly in high-risk groups. These programs involve the identification of individuals with *H. pylori* infection and the provision of eradication therapy to prevent the development of cancer. Such comprehensive approaches are likely to further increase the consumption of these medications [197].

Cysteine derivatives consumption and gastric cancer prevention

Consumption of cysteine derivatives shown tendency to upscaling from 2014 till 2020. The use of mucolytic agents such as acetylcysteine, carbocysteine, and erdosteine has been on the rise worldwide, driven by several key factors and associated with various implications for public health [198]. These medications are primarily used in the management of respiratory conditions but also have applications in gastroenterology, particularly in the context of gastric cancer prevention and *H. pylori* eradication [17, 85]. The following discussion outlines the factors contributing to the increased consumption of these mucolytics in Ukraine and explores the possible consequences of their widespread use.

Acetylcysteine, carbocysteine, and erdosteine are primarily used as mucolytic agents to treat respiratory conditions like chronic obstructive pulmonary disease (COPD) and chronic bronchitis. Their use has increased as the prevalence of these conditions rises globally due to factors such as air pollution, smoking, and aging populations [198]. Furthermore, these drugs have been increasingly recognized for their potential benefits in the management of gastric conditions, including their role in disrupting the biofilms and inhibit blood group antigen mediated binding of *H. pylori*, a major risk factor for gastric cancer [17, 85].

The accessibility of mucolytics as over-the-counter drugs in many countries has contributed to their increased consumption. People can easily purchase these medications without a prescription, which promotes their use for self-medication, especially for respiratory discomforts. This widespread availability has led to higher consumption rates across various demographics, for example in Poland [199].

Recent research has explored the use of mucolytics in the prevention and management of gastric cancer, particularly due to their antioxidant properties and ability to reduce inflammation [200]. Acetylcysteine, for instance, has been studied for its potential to prevent the adhesion of *H. pylori* to the gastric mucosa, which is a critical step in the pathogenesis of gastric cancer. This potential therapeutic benefit has led to an increase in the use of mucolytics in both clinical and preventive settings [85].

The eradication of *H. pylori* is a crucial component in reducing the risk of gastric cancer. Acetylcysteine, in particular, has been shown to enhance the effectiveness of antibiotic regimens used to eradicate *H. pylori* by disrupting bacterial biofilms and increasing antibiotic penetration. This has led to a growing interest in incorporating mucolytics into standard *H. pylori* treatment protocols, thus increasing their consumption [201].

The medical community's growing emphasis on evidence-based practice has led to an increased use of mucolytics in various therapeutic protocols. Clinicians are more likely to prescribe these medications as adjuncts in the management of gastric conditions and as part of comprehensive *H. pylori* eradication strategies, supported by clinical guidelines and positive outcomes from recent studies [85, 201].

The antioxidant and anti-inflammatory properties of acetylcysteine, carbocysteine, and erdosteine may confer protective effects against the development of gastric cancer. By reducing oxidative stress and inflammation in the gastric mucosa, these agents could potentially lower the risk of malignant transformation of gastric epithelial cells. Clinical studies have suggested that these effects may be particularly beneficial in patients with chronic gastritis or atrophic gastritis, conditions that predispose individuals to gastric cancer [84, 87].

The use of mucolytics in conjunction with standard antibiotic therapy for *H. pylori* eradication has been associated with improved eradication rates. By enhancing antibiotic penetration and disrupting bacterial biofilms, mucolytics may reduce the likelihood of treatment failure and antibiotic resistance, leading to more successful eradication of *H. pylori* and a consequent reduction in the risk of gastric cancer [85, 201].

Despite their benefits, mucolytics can also cause side effects, particularly when used in high doses or for extended periods. Gastrointestinal disturbances such as nausea, vomiting, and abdominal discomfort are common, and these agents may interact with other medications, potentially affecting their absorption and efficacy. Careful monitoring and appropriate dosing are necessary to minimize these risks, especially in patients with pre-existing gastric conditions [202].

Long-term use of mucolytics could potentially alter the composition of the gastrointestinal microbiota, which plays a crucial role in maintaining gastric health [203]. Changes in the microbiota may influence gastric acid secretion, mucosal defence mechanisms, and the overall integrity of the gastric lining, potentially affecting the risk of gastric cancer. Further research is needed to fully understand the implications of mucolytic-induced changes in the gastric microbiota [204].

The increased use of mucolytics has significant economic implications, both in terms of the direct costs of these medications and the broader healthcare expenses associated with their use. Ensuring the cost-effectiveness of mucolytics, particularly in the context of gastric cancer prevention and treatment, requires ongoing evaluation and the development of guidelines that maximize clinical benefits while minimizing unnecessary costs [205].

NSAIDs consumption and gastric cancer prevention

The increasing consumption of NSAIDs in Ukraine and worldwide has garnered attention not only due to its impact on common health issues but also due to its implications in the context of cancer prevention, particularly gastric cancer. Various factors contribute to this trend, and understanding these factors is crucial in evaluating both the potential benefits and the risks associated with prolonged NSAID use [89, 90].

NSAIDs have been extensively studied for their potential role in cancer prevention. The ability of NSAIDs to inhibit COX enzymes, which are involved in inflammatory processes, suggests a protective role against cancer development. In gastric cancer, chronic inflammation is a well-known precursor to carcinogenesis, making NSAIDs a promising candidate for chemoprevention. Studies have indicated that NSAIDs may reduce the risk of gastric cancer by modulating inflammation and possibly through direct effects on cancer cells [89, 93].

Additionally, dietary interventions have been explored as complementary strategies in cancer prevention. The consumption of antioxidants, such as those found in fruits and certain vitamins, may act as chemopreventive agents, particularly in populations at high risk for gastric

cancer. These dietary factors work synergistically with NSAIDs in reducing oxidative stress and inflammation, further supporting the role of NSAIDs in gastric cancer prevention [206].

Research has also shown that the consumption of polyphenols, a class of antioxidants found in foods such as fruits, vegetables, and tea, may reduce the risk of gastric cancer. This was demonstrated in the Stomach Cancer Pooling Project, which highlighted the potential protective effects of certain polyphenols against gastric cancer. Increased NSAID consumption, when combined with a diet rich in polyphenols, may offer a comprehensive approach to reducing gastric cancer risk [207].

Herbal and alternative therapeutic approaches have also gained traction in recent years. Spices such as turmeric, ginger, and garlic are being explored for their potential in cancer prevention, including gastric cancer. These natural products have anti-inflammatory and antioxidant properties that may complement the effects of NSAIDs, providing a holistic approach to reducing cancer risk. The integration of such dietary interventions into daily routines, particularly in populations with high NSAID consumption, may help mitigate the risks associated with long-term NSAID use [208].

Moreover, the consumption of mushrooms has been associated with a lower risk of gastric cancer. The anti-cancer properties of mushrooms are attributed to their bioactive compounds, which possess antioxidant, anti-inflammatory, and immunomodulatory effects. These properties may work in conjunction with NSAIDs to reduce the incidence of gastric cancer, particularly in populations with high dietary intake of mushrooms [163].

On the other hand, it is essential to recognize the dietary factors that increase the risk of gastric cancer, particularly in regions like Ukraine, where certain food habits may exacerbate the risk. The consumption of salty processed foods has been linked to a higher incidence of gastric cancer, especially in populations with a preference for such diets. This highlights the importance of balancing NSAID use with dietary modifications to reduce gastric cancer risk [206, 209].

NSAIDs are also being considered for repurposing in cancer treatment and prevention, particularly in gastrointestinal malignancies like gastric and colorectal cancer. The repurposing of NSAIDs offers an opportunity to capitalize on their anti-inflammatory properties while minimizing the risks associated with their use. Ongoing research is focused on identifying the most effective NSAID regimens for cancer prevention, as well as exploring their potential in combination with other therapeutic approaches [210].

Additionally, lifestyle modifications, including the eradication of *H. pylori* infection and changes in dietary habits, have been recognized as critical components of gastric cancer prevention strategies. Increased NSAID consumption may complement these preventive measures by reducing inflammation and potentially lowering the risk of gastric cancer development in high-risk populations [6, 211].

Despite the potential benefits of NSAIDs in cancer prevention, there are concerns regarding their long-term use, particularly in relation to gastrointestinal adverse effects. Chronic NSAID use is associated with adverse effects such as gastric ulcers, bleeding, and perforation [90]. These risks are exacerbated in individuals with existing gastrointestinal conditions, such as *H. pylori* infection. Therefore, careful consideration of the risks and benefits of NSAID use is necessary when developing cancer prevention strategies [212].

Emerging research has also highlighted the importance of genetic factors in determining an individual's risk for gastric cancer. For example, a study conducted in Korea found that dietary potassium intake, influenced by genetic variations such as TNF-α rs1800629, was associated with a reduced risk of gastric cancer. This suggests that personalized dietary recommendations, in combination with NSAID use, may be an effective approach to cancer prevention [213, 214].

It is also crucial to address the impact of dietary patterns on gastric cancer risk. The consumption of preserved vegetables, a common dietary practice in some regions, has been identified as a risk factor for gastric cancer. In contrast, dietary modifications that reduce the

intake of preserved foods while increasing the consumption of protective foods, such as those rich in antioxidants, may help mitigate the risks associated with NSAID use [215].

Consumption of the low doses of ASA and gastric cancer prevention

The increased consumption of low-dose ASA has garnered attention worldwide, including in Ukraine, particularly due to its potential role in the prevention of gastric cancer. Several factors contribute to this trend, including the widespread use of low-dose ASA for cardiovascular protection and emerging evidence supporting its role in cancer prevention. However, the implications of this increased use, especially with regard to gastrointestinal adverse effects, require careful consideration [32, 103, 104].

Low-dose ASA has been associated with a reduced risk of gastric cancer in individuals without atherosclerotic cardiovascular disease, according to a population-based cohort study. This protective effect may be linked to ASA's ability to inhibit COX enzymes, which play a role in inflammation and tumorigenesis. Additionally, evidence suggests that the preventive effects of ASA on gastric cancer may differ between men and women, although the exact mechanisms underlying this gender disparity remain unclear. This indicates the need for further research to understand how gender influences the efficacy of ASA in cancer prevention [96, 103, 104].

ASA may contribute to the prevention of gastric cancer by reducing risk factors and improving the early detection of lesions. This aligns with the broader strategy of enhancing prevention, diagnosis, and treatment of early gastric cancer. Incorporating low-dose ASA into prevention programs may offer a promising approach to reducing gastric cancer incidence, especially when combined with other preventive measures such as lifestyle modifications and regular screeningi [103, 104, 211]

Although much of the focus on ASA has been on its cardiovascular benefits, its role in cancer prevention is becoming increasingly recognized. In particular, ASA's anti-inflammatory properties may help reduce the chronic inflammation that is often a precursor to gastric cancer. This has led to the exploration of ASA as a potential chemopreventive agent,

with ongoing studies evaluating its efficacy in reducing cancer risk across various populations [62, 98, 99, 104].

While the benefits of ASA in cancer prevention are promising, it is essential to balance these benefits with the potential risks, particularly in relation to gastrointestinal health. Long-term ASA use is associated with an increased risk of gastrointestinal bleeding and ulcers, which can negate its preventive effects in certain individuals. Therefore, careful assessment of individual risk factors is crucial when considering the use of low-dose ASA for cancer prevention [32, 98, 212].

The safety and effectiveness of ASA in gastric cancer prevention may also depend on its interaction with other medications and treatment regimens. For example, low-dose ASA has been studied in combination with other drugs, such as chemotherapy agents, to assess its impact on treatment outcomes in advanced gastric cancer. These studies have shown that combining ASA with chemotherapy may improve progression-free survival and overall survival in patients with advanced disease without increasing the risk of adverse reactioni [97, 100, 101].

Metformin consumption and gastric prevention

The increasing consumption of metformin worldwide, including in Ukraine, has been driven by its primary use in managing type 2 diabetes. However, a growing body of evidence has highlighted metformin's potential role in cancer prevention, particularly in the context of gastric cancer. This shift towards exploring the broader applications of metformin is supported by both preclinical and clinical studies that emphasize its anti-tumour effects [16, 105, 108, 109, 113, 186, 216].

Metformin has shown protective effects against gastric cancer by reducing the risk and improving survival rates among patients. This has positioned metformin as a potential chemopreventive agent against gastric cancer. The mechanisms underlying these protective effects are linked to metformin's ability to influence cellular pathways involved in cancer

progression, including the inhibition of mTOR signalling and the reduction of IGF signalling, both of which are crucial in gastric cancer development [107, 109].

Furthermore, studies have shown that metformin can reduce gastric cancer risk by exerting anti-tumour effects. The drug's mechanism of action involves inhibiting tumour cell proliferation, inducing apoptosis, and reducing inflammation, which are critical factors in gastric cancer prevention. The reduction of gastric cancer incidence through metformin use has been supported by evidence from population-based studies that have identified a dose-response relationship between metformin consumption and decreased gastric cancer risk [112, 217].

One large-scale nationwide cohort study demonstrated that metformin use was associated with a reduction in gastric cancer mortality among diabetic patients. Moreover, the study found that the protective effects of metformin extended beyond diabetic populations, showing a dose-response reduction in gastric cancer risk among the general population. This has further strengthened the case for metformin as a viable option for gastric cancer prevention [22, 27, 113, 216].

The anti-cancer potential of metformin has been a subject of intense research, with studies consistently highlighting its ability to prevent and treat various types of cancer, including gastric cancer. The drug's impact on cancer prevention is not limited to its effects on metabolic pathways but also involves modulating the tumour microenvironment, reducing angiogenesis, and improving immune responses against tumours [16, 107, 108].

Risk stratification, combined with endoscopic screening, is another important strategy in gastric cancer prevention, especially in countries with a high incidence of the disease. Metformin, when integrated into such preventive strategies, could play a crucial role in reducing gastric cancer mortality. The inclusion of metformin in cancer prevention protocols could complement existing screening methods and help identify high-risk individuals who would benefit the most from preventive treatments [2, 26]. In addition to metformin, other compounds such as berberine have shown potential for gastric cancer prevention by acting on

multiple steps of the Correa's cascade, including suppressing *H. pylori* infection and controlling mucosal inflammation. These findings suggest that a combination of metformin with other preventive agents could offer a synergistic approach to reducing gastric cancer risk in high-risk populations [93].

It is also important to note that lifestyle modifications, such as maintaining a healthy weight and eradicating *H. pylori* infection, remain key components of gastric cancer prevention strategies. Metformin's potential benefits in cancer prevention should be viewed within the broader context of these lifestyle changes, which can further reduce gastric cancer risk [93, 211].

The long-term use of metformin for cancer prevention should be carefully considered, particularly in populations with a high prevalence of stomach pathologies associated with increased cancer risk. Studies have shown that treatment aimed at eradicating *H. pylori* infection, a known risk factor for gastric cancer, could be significantly enhanced by the concurrent use of metformin, which could help reduce cancer risk in these high-risk groups [93, 216, 218].

Statins consumption and gastric prevention

The increasing consumption of statins worldwide, including in Ukraine, is largely driven by their primary role in managing hyperlipidaemia and preventing cardiovascular events. However, recent research has uncovered their potential role in cancer prevention, particularly in the context of gastric cancer. Statins, originally developed to lower cholesterol, have been shown to possess anti-cancer properties that make them a promising candidate for gastric cancer prevention [114, 117, 118].

Several studies have demonstrated a significant association between statin use and reduced incidence of gastric cancer. For instance, a meta-analysis found that statins were associated with reduced gastric cancer incidence and improved survival rates. The analysis included data from both Eastern and Western populations, underscoring the global relevance of statins in gastric cancer prevention [18, 123].

In patients who have eradicated *H. pylori* infection, statins have been shown to further reduce the risk of gastric cancer. This protective effect was observed in a duration- and dose-response manner, suggesting that long-term and consistent use of statins may be particularly beneficial in reducing gastric cancer risk in these populations [219].

Moreover, the use of statins has been associated with a reduction in gastric cancer mortality in the general population. This association highlights the potential role of statins in preventing gastric cancer-related deaths, particularly when used alongside other preventive medications such as ASA and metformin [220].

The mechanisms by which statins exert their protective effects against gastric cancer include their ability to regulate *H. pylori* virulence factors and reduce ROS production. By modulating these factors, statins can inhibit the development of gastric cancer, making them a valuable tool in cancer prevention strategies [114, 115].

Preventive strategies for gastric cancer also include screening, prevention and treatment, which have been successful in reducing gastric cancer mortality in Asian amd Western populations. Integrating statin use into these programs could enhance their effectiveness by targeting high-risk individuals who would benefit the most from preventive interventions [18, 123; 115].

The chemopreventive effects of statins in gastric cancer are being explored alongside other strategies, such as dietary modifications, proton pump inhibitor use, and *H. pylori* eradication. The combination of these approaches may offer a comprehensive strategy for reducing gastric cancer risk in both high-risk populations and the general population [18, 123, 219].

Limitations of the results on increased use of frequently used drugs

The increase in DDDs of PPIs, combined drugs for *H. pylori* eradication, cysteine derivatives, NSAIDs, low-dose ASA, metformin, and statins has implications for the incidence of gastric cancer, particularly adenocarcinoma NOS (8140), the predominant histological subtype of gastric cancer [6, 85]. However, there are significant limitations associated with the

rising use of these drug classes, which could affect their long-term efficacy in preventing gastric cancer and may inadvertently contribute to an increase in incidence under certain conditions [6, 221].

One of the key limitations of increasing PPI use is the potential for prolonged suppression of gastric acid, which can result in hypergastrinemia. Chronic hypergastrinemia is known to promote the growth of enterochromaffin-like cells and lead to gastric mucosal hypertrophy, which can predispose patients to the development of gastric atrophy and, ultimately, adenocarcinoma. This risk is particularly concerning in patients who are prescribed PPIs long-term for GERD or peptic ulcers, and might be in those who use PPIs in combination with antibiotics for *H. pylori* eradication [9, 15, 222].

Furthermore, the alteration of the gastric microbiota due to chronic acid suppression may contribute to an increased risk of gastric cancer. The reduction of gastric acidity creates an environment conducive to bacterial overgrowth, particularly non-*Helicobacter pylori* bacteria, which have been implicated in gastric carcinogenesis. While short-term use of PPIs for *H. pylori* eradication is beneficial, the long-term impact of altered microbiota due to PPI use is not fully understood, and this poses a significant limitation to the use of PPIs in reducing gastric cancer risk [19, 41, 56].

Additionally, studies have shown conflicting results regarding the direct association between PPI use and gastric cancer risk. Some epidemiological studies suggest an increased risk of gastric adenocarcinoma with prolonged PPI use, while others do not find a significant association after adjusting for confounding factors. This inconsistency in the data highlights the need for more robust and controlled studies to better understand the true relationship between PPI use and gastric cancer incidence [9, 14].

While the use of combined fixed-dose drugs for *H. pylori* eradication has been critical in reducing the incidence of gastric cancer, particularly adenocarcinoma NOS, there are limitations to this approach. The increasing prevalence of antibiotic-resistant strains of *H. pylori* complicates eradication efforts and may lead to treatment failures, which can result in

persistent infection and a higher risk of gastric carcinogenesis. As antibiotic resistance continues to rise globally, particularly in low- and middle-income countries like Ukraine, the effectiveness of current eradication regimens may be compromised, limiting their impact on reducing gastric cancer incidence [3, 70, 223].

Another limitation is patient adherence to eradication therapy. Fixed-dose combination therapies can be associated with gastrointestinal side effects, such as nausea, vomiting, and diarrhoea, which may lead to poor adherence and incomplete treatment. Incomplete eradication of *H. pylori* not only increases the risk of gastric cancer but also contributes to the development of antibiotic-resistant strains. Therefore, patient compliance remains a critical factor in the success of these therapies [70, 224].

Moreover, while the eradication of *H. pylori* has been shown to reduce the risk of developing gastric cancer, particularly in high-risk populations, the long-term benefits of eradication are not universal. Individuals who have already developed atrophic gastritis or intestinal metaplasia, two precursors to gastric adenocarcinoma, may still be at risk of cancer development even after successful *H. pylori* eradication. This highlights the limitation of relying solely on eradication strategies and underscores the need for continued surveillance in high-risk populations [143].

The rising use of cysteine derivatives, such as acetylcysteine, carbocysteine, and erdosteine, primarily as mucolytic agents for respiratory conditions, has been explored for their potential benefits in disrupting *H. pylori* biofilms and enhancing antibiotic efficacy in eradication protocols. However, there are several limitations associated with their increased use in the context of gastric cancer prevention. One key limitation is the potential alteration of the gastric microbiota due to the antioxidant and anti-inflammatory properties of these agents. Long-term use of cysteine derivatives could lead to dysbiosis, which may inadvertently create an environment conducive to carcinogenesis [82, 143].

Furthermore, while cysteine derivatives have shown promise in improving eradication rates of *H. pylori*, their role in reducing gastric cancer risk remains uncertain. The disruption

of biofilms, inhibition of blood group antigen mediated biding and enhanced antibiotic penetration are beneficial for eradication, but the long-term impact of these agents on the gastric mucosa and cancer risk is not well established. More research is needed to understand the implications of chronic cysteine derivative use on gastric cancer incidence [114].

The chemopreventive effects of NSAIDs, including low-dose ASA, in reducing the risk of gastric adenocarcinoma are well documented, primarily through their inhibition of COX enzymes and the reduction of inflammation. However, the long-term use of NSAIDs and ASA is associated with significant gastrointestinal toxicity, including the risk of gastric ulcers, bleeding, and perforation. These adverse effects limit the widespread use of NSAIDs and ASA as preventive agents for gastric cancer, particularly in individuals with pre-existing gastrointestinal conditions [73, 96].

Another limitation is the potential for varying effects based on individual patient characteristics, such as genetic predisposition, gender, and concurrent use of other medications. For example, the protective effects of low-dose ASA on gastric cancer risk may differ between men and women, and certain genetic variants may influence the efficacy of NSAIDs in reducing cancer risk. This variability underscores the need for personalized approaches to NSAID and ASA use in cancer prevention [225]. (Wong, 2019; Zobdeh et al., 2022).

Moreover, while NSAIDs and ASA have shown potential in reducing the risk of gastric cancer, their long-term use without appropriate gastrointestinal protection can lead to complications that may outweigh their benefits. The challenge lies in balancing the chemopreventive effects with the risks of gastrointestinal toxicity, particularly in high-risk populations [225].

Metformin, widely used for the management of type 2 diabetes, has garnered attention for its potential role in reducing the risk of various cancers, including gastric adenocarcinoma. However, there are limitations to the use of metformin as a chemopreventive agent for gastric cancer. While studies have shown a protective effect of metformin in diabetic populations, the

impact of metformin on gastric cancer risk in non-diabetic individuals remains unclear [217, 225].

Additionally, the mechanisms through which metformin exerts its anti-cancer effects, such as the inhibition of the mTOR signalling pathway and reduction of IGF signalling, may vary between individuals, leading to inconsistent results in cancer prevention. Furthermore, the long-term use of metformin in non-diabetic populations may carry risks that have not been fully elucidated, such as potential metabolic effects that could influence cancer risk [112, 225].

The use of metformin in combination with other cancer preventive strategies, such as *H. pylori* eradication and lifestyle modifications, may enhance its efficacy in reducing gastric cancer risk. However, the optimal dosage and duration of metformin treatment for cancer prevention, as well as its potential interactions with other medications, require further investigation [112, 225].

Statins, commonly prescribed for hyperlipidaemia and cardiovascular prevention, have also been studied for their potential anti-cancer properties, including their ability to reduce the risk of gastric adenocarcinoma. However, the long-term use of statins is associated with several limitations that may impact their role in gastric cancer prevention. For instance, the potential side effects of statins, such as myopathy, liver dysfunction, and an increased risk of diabetes, must be considered when evaluating their use for cancer prevention [226].

Moreover, while statins have been shown to reduce the risk of gastric cancer in certain populations, particularly those who have eradicated *H. pylori*, the generalizability of these findings to broader populations is uncertain. The duration- and dose-response effects of statins on cancer prevention are still being explored, and more research is needed to determine the optimal use of statins in reducing gastric cancer incidence [212, 218].

Possibilities of solutions of the limitation and healthcare digitalisation

Digitalization of healthcare offers transformative potential in monitoring the use of drugs such as PPIs, combined drugs for *H. pylori* eradication, cysteine derivatives, NSAIDs, low-dose ASA, metformin, and statins, particularly given the increasing DDDs of these

medications in Ukraine and worldwide. This digital transformation can play a pivotal role in managing and reducing gastric cancer incidence rate, mostly the predominant form of gastric cancer. The digitalization of healthcare has enhanced the monitoring of drug usage and improved the tracking of disease incidence rates [227].

The digitalization of healthcare systems facilitates real-time tracking and integration of patient data, which is critical for monitoring the use of these drug classes. Electronic health records, integrated with national prescription databases, enable healthcare providers to monitor patient adherence, prescription patterns, and long-term drug use. This is particularly important for medications like PPIs, where prolonged use has been associated with an increased risk of gastric cancer, including adenocarcinoma NOS. With digital tools, clinicians can set automated alerts for long-term PPI users, prompting a reassessment of the necessity of continued use or adjustments in therapy to mitigate cancer risk. The digitalization of healthcare is currently of great importance in managing adverse drug effects and facilitating the early identification of high-risk cancer patients [178].

Moreover, digital platforms can enable the aggregation of patient data across different regions, providing a comprehensive overview of drug utilization trends. In Ukraine, where *H. pylori* eradication strategies involve the use of combined fixed-dose drugs, the ability to track the success rates of eradication therapies and patient outcomes can be significantly improved through a centralized digital system. Such systems can flag regions with higher rates of treatment failure, prompting targeted interventions to address antibiotic resistance or adherence issues [75].

Digital health technologies, including artificial intelligence (AI) and machine learning, can play a crucial role in personalizing treatment regimens based on individual risk factors. AI-driven algorithms can analyse large datasets from electronic health records, identifying patients at high risk of developing gastric cancer due to prolonged use of NSAIDs, low-dose ASA, or statins. By analysing factors such as genetic predispositions, lifestyle choices, and

comorbidities, AI can help tailor preventive strategies and optimize drug regimens to minimize cancer risk while maintaining therapeutic efficacy [134].

For instance, metformin has shown promise in reducing gastric cancer risk in diabetic populations, but its impact on non-diabetic individuals remains unclear. AI-driven tools can help identify which patients are most likely to benefit from metformin for cancer prevention, optimizing its use and preventing unnecessary exposure to potential side effects. Similarly, the use of statins for cancer prevention could be better personalized through digital risk assessments, ensuring that only patients with a favourable risk-benefit profile are prescribed these drugs for long-term use [228].

The rise of telemedicine and remote monitoring platforms has become increasingly relevant, particularly in the post-pandemic world. These digital tools allow for continuous monitoring of patient drug use and health outcomes without the need for frequent in-person visits. For drugs like cysteine derivatives, which are used to manage chronic conditions such as COPD and have potential implications for gastric cancer prevention, remote monitoring can ensure adherence while simultaneously tracking any gastrointestinal side effects that may necessitate treatment adjustments [229].

Telemedicine platforms can also be utilized to remotely monitor patients undergoing *H. pylori* eradication therapy. Regular follow-ups via telemedicine can ensure that patients complete their treatment regimens and report any adverse effects early, preventing incomplete eradication that could contribute to gastric cancer risk. Furthermore, telemedicine provides an opportunity for healthcare providers to offer continuous support and education to patients on lifestyle modifications that complement pharmacological interventions, such as dietary changes that reduce cancer risk [230].

The ability to collect and analyse large-scale data on drug usage patterns through digital health systems can inform public health interventions aimed at reducing gastric cancer incidence. Predictive analytics, driven by big data, can help identify population-level trends in drug use and their correlation with gastric cancer outcomes [231]. In Ukraine, where the use

of PPIs and other drugs is on the rise, predictive models could help forecast future cancer incidence rates based on current prescription trends, allowing for timely public health responses.

For instance, if data indicates a growing trend of long-term NSAID use in certain populations, public health agencies could implement targeted educational campaigns on the risks of chronic NSAID use and the importance of gastroprotective measures (Montagnani et al., 2016). Similarly, data-driven interventions could be deployed in regions where *H. pylori* eradication rates are suboptimal, focusing on improving adherence and addressing barriers to successful treatment [231].

The proliferation of mobile health applications can empower patients to take an active role in managing their own healthcare. Apps designed to track medication adherence, report side effects, and provide educational resources can enhance patient engagement and improve outcomes. For example, patients prescribed PPIs could use digital apps to monitor their usage and receive reminders for follow-up appointments, ensuring that long-term use is regularly evaluated by healthcare provider [232].

Similarly, digital health apps could be employed to support patients undergoing *H. pylori* eradication therapy. These apps could provide step-by-step guidance on how to take their medications, report side effects, and connect with healthcare providers for timely interventions. Such tools are particularly valuable in low-resource settings, where access to in-person care may be limited, and they can play a critical role in improving adherence and reducing gastric cancer risk [137].

One of the key challenges in the digitalization of healthcare is ensuring interoperability between different systems and platforms. For digital health interventions to be effective in monitoring drug use and reducing gastric cancer incidence, seamless data sharing between healthcare providers, pharmacies, and public health agencies is essential. This is particularly important in Ukraine, where regional disparities in healthcare access and resources can impact patient outcomes. A national digital health infrastructure that facilitates real-time data sharing

could bridge these gaps and ensure that all patients receive standardized care, regardless of their location [69].

Interoperability also enables the integration of data from various sources, such as pharmacy records, laboratory results, and patient-reported outcomes, providing a comprehensive picture of drug use and its impact on health. This holistic approach is critical for understanding the long-term effects of drug classes like metformin and statins on gastric cancer risk and for identifying any emerging patterns that warrant further investigation [233].

While digitalization offers numerous benefits for monitoring drug use and reducing gastric cancer risk, it also raises important ethical considerations, particularly regarding data privacy and security. The collection and analysis of patient data on a large scale require robust safeguards to protect patient confidentiality and prevent unauthorized access to sensitive information. This is especially relevant in the context of AI-driven predictive models, where data from millions of patients may be used to inform public health interventions [234].

Furthermore, as digital health tools become more widely adopted, there is a risk of exacerbating health disparities if certain populations, such as those in rural or underserved areas, have limited access to these technologies. Ensuring equitable access to digital health tools and addressing the digital divide will be crucial for maximizing the benefits of digitalization in reducing gastric cancer incidence worldwide [235].

The digitalization of healthcare presents a powerful opportunity to monitor and optimize the use of PPIs, combined drugs for *H. pylori* eradication, cysteine derivatives, NSAIDs, low-dose ASA, metformin, and statins, all of which play a critical role in gastric cancer prevention. By leveraging digital tools such as electronic health records, AI-driven algorithms, telemedicine platforms, and apps, healthcare systems can enhance drug utilization monitoring, personalize preventive strategies, and implement data-driven public health interventions. However, the success of these digital initiatives will depend on addressing key challenges related to interoperability, data privacy, and equitable access to healthcare technology [236].

CONCLUSIONS

The study presents a comprehensive analysis of gastric cancer incidence trends, nosological structure, gender disparities, and age-related prevalence in Ukraine from 2003 to 2022, data on the sales of proton pump inhibitors, statins, metformin, nonsteroidal anti-inflammatory drugs, cysteine derivatives were assessed and their trends in DDDs by mean of epidemiological and statistical methods.

This research systematically evaluates the potential risk and protective roles of commonly used pharmaceuticals in gastric cancer development and prevention. The increasing consumption of statins, NSAIDs, and metformin has been quantitatively linked to the decline in gastric cancer incidence, suggesting a possible chemopreventive effect. Additionally, the study explores the effectiveness of fixed-dose combination therapies for *H. pylori* eradication, which have contributed to the observed reduction in gastric cancer cases in Ukraine. A novel aspect of this research is the potential role of cysteine derivatives in inhibiting *H. pylori* adhesion and enhancing eradication success, a previously underexplored avenue in gastric cancer prevention strategies.

By comparing national data with global trends, the study identifies critical gaps in gastric cancer screening, early detection, and pharmacological interventions, proposing strategic improvements in healthcare policies. The integration of epidemiology, pharmacology, and public health perspectives emphasizes a more holistic approach to gastric cancer prevention, advocating for the optimization of pharmacological interventions alongside traditional risk-reduction measures.

As gastric cancer incidence continues to decline, sustaining and building upon this progress requires ongoing public health efforts. The digitalization of healthcare and the incorporation of patient-linked data offer transformative opportunities to enhance cancer prevention and treatment. Advanced technologies, including AI-driven predictive models and personalized medicine, can optimize early detection, treatment efficacy, and healthcare

resource allocation. Ensuring equitable access to medical advancements, promoting healthy lifestyles, and reinforcing preventive strategies will further reduce the burden of gastric cancer. The future of gastric cancer prevention lies in the intersection of data-driven decision-making, personalized care, and innovative public health initiatives.

1. This research investigated the trends in incidence, age distribution, and nosological structure of gastric cancer in Ukraine from 2003 to 2022. The highest incidence rate was recorded in 2005, while the lowest was observed in 2020. Between 2003 and 2020, the incidence rate decreased by 30.63%, with a 33.71% reduction compared to 2005 (95% CI, $P < 0.0001$). The most significant drop occurred between 2019 and 2020, reaching 17.97% (95% CI, $P < 0.0001$). From 2014 to 2021, the incidence rate of gastric cancer in Ukraine decreased by 26.56% ($P < 0.0001$). The research also highlights that men accounted for approximately 61% of cases, with over 94% of patients being above the age of 45 throughout the study period.
2. Key risk factors influencing gastric cancer development were assessed, including *H. pylori* infection, dietary habits, and lifestyle factors. The effective management and eradication of *H. pylori* have significantly contributed to declining incidence rates, supported by national screening programs. However, antibiotic-resistant strains pose a challenge, necessitating ongoing monitoring and treatment updates. Public education campaigns targeting smoking cessation, alcohol moderation, and dietary modifications have also shown success in reducing gastric cancer risk.
3. The role of pharmacological agents in influencing gastric cancer risk and prevention was explored. Proton pump inhibitors (PPIs) saw a 98.61% increase in consumption from 2014 to 2021 ($P < 0.0001$). NSAID use exhibited fluctuations but increased overall, with a peak of 26.50% in 2019 compared to 2015. Low-dose ASA usage rose significantly in 2017 (+17.72%, $P < 0.0001$) and 2020 (+14.97%, $P < 0.0001$), despite minor declines in 2015, 2018, and 2019. Statin consumption nearly tripled by 2020 ($P < 0.0001$), while metformin use steadily increased, reaching a 2.41-fold

rise in 2021 ($P < 0.0001$). Cysteine derivative consumption followed a similar trend with an overall 42.06% increase ($P < 0.0001$) by 2020 compared to 2014.

4. The effectiveness of pharmacological regimens for H. pylori eradication was evaluated. Combined drug use exhibited instability, with declines in 2015 (-19.18%, $P < 0.0001$), 2016 (-47.89%, $P < 0.0001$), and 2020 (-8.02%, $P < 0.0001$), alongside a sharp rebound in 2017, nearly 2.5 times greater than in 2016 ($P < 0.0001$). These findings underscore the need for clear guidelines to optimize eradication protocols and enhance treatment adherence.
5. Comparative analysis of gastric cancer epidemiological trends and treatment strategies in Ukraine and other regions worldwide highlighted areas for improvement. Despite declining incidence rates, disparities in healthcare access remain a challenge. The integration of digital health technologies, AI-driven predictive models, and personalized medicine can enhance cancer prevention and treatment efforts.
6. Based on these findings, evidence-based recommendations are proposed to improve early detection, prevention, and treatment strategies for gastric cancer. The adoption of advanced screening technologies, such as endoscopic surveillance and non-invasive biomarker testing, is essential for early-stage detection. Digital health tools, including mobile apps and remote monitoring, can enhance patient participation in screening programs. Public health initiatives should focus on optimizing pharmacological and screening protocols while leveraging digitalization to improve resource allocation and treatment efficiency.
7. In summary, this research provides critical insights into gastric cancer trends in Ukraine, emphasizing the impact of risk factors, pharmacological interventions, and public health strategies. By integrating data-driven decision-making, personalized care, and innovative healthcare technologies, significant progress can be made in reducing gastric cancer incidence and improving patient outcomes.

PRACTICAL RECOMMENDATIONS

1. Development of electronic patient registries and disease monitoring. Establishing a unified electronic registry for patients with precancerous conditions, *Helicobacter pylori* infection, and gastric cancer will enhance disease trend monitoring, optimize preventive strategies, and improve treatment outcomes through centralized access to medical data.
2. Digital monitoring of drug prescriptions and effectiveness. Implementing a national electronic system to track the use of proton pump inhibitors, statins, NSAIDs, metformin, and other medications will enable assessment of their role in gastric cancer prevention. This will support more evidence-based prescribing and reduce the risk of inappropriate medication use.
3. Expansion of telemedicine and remote patient monitoring. Utilizing telemedicine for gastroenterology consultations, remote monitoring of at-risk patients, and electronic reminders for necessary screenings will promote early detection of pathologies and improve gastric cancer prevention.

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SUPPLEMENT A

PRESSENTATIONS OF THE MATERIALS OF THE DISSERTATION

1. Abstracts: Protas Y.O., Makarenko O.V. Gastric cancer epidemiologic data in Ukraine in 2003-2020. Materials of the scientific and practical conference with international participation “Ecologic and hygienic issues of the human life activity”, March 13, 2024. 33
2. Abstracts and presentation: Protas Y.O., Makarenko O.V. Consumption of proton pump inhibitors in Ukraine from 2014 till 2020. Materials of XI The international scientific and practical distance conference “Management and marketing as parts of modern economy, science, education, practice", March 21, 2024.
3. Abstracts and presentation: Protas Y.O., Makarenko O.V. Impact of Helicobacter pylori eradication and frequently used medications on gastric cancer incidence in Ukraine (2014–2021). Materials of the all-Ukrainian scientific and practical conference “Public health: from analysing the past to understanding the future”, October 10, 2024.
4. Presentation: Protas Y.O. Understanding Helicobacter pylori adhesion to gastric mucosa: insights and preventive approaches. Scientific and practical internet conference with international participation “Topical issues of clinical pharmacology and clinical pharmacy”, October 29, 2024.

SUPPLEMENT B

«Затверджую»
Проректор з наукової роботи ДДМУ
Д.мед.н., професор
Олександр ГУДАР'ЯН

_____ 2025 року

АКТ ВПРОВАДЖЕННЯ

1. **Назва пропозиції для впровадження:** Епідеміологія раку шлунка та моделі споживання лікарських препаратів в Україні: внесок і наслідки.
2. **Автор впровадження:** Протас Євген, аспірант кафедри соціальної медицини, громадського здоров'я та управління охороною здоров'я Дніпровського державного медичного університету, 49044, м. Дніпро, вул. В. Вернадського, 9.
3. **Джерела інформації:**

1. Chernov, Y. O. (Protas Y), Haysanovska, V., & Makarenko, O. V. (2024). Gastric cancer in Ukraine: epidemiologic data and its nosological structure between 2003 and 2020. Przeglad gastroenterologiczny, 16(4), P.428–433. https://doi.org/10.5114/pg.2024.134840
2. Protas, Y. O, Makarenko, O. V. (2025). Use of combined fixed-dose drugs for Helicobacter pylori eradication and gastric cancer incidence indices in Ukraine from 2014 to 2021. Medicni perspektivi, 30(1). P. 202 -205https://doi.org/10.26641/2307-0404.2025.1.325466
3. Protas, Y. O, Makarenko, O. V. (2025). Epidemiology of gastric cancer in Ukraine from 2014–2022: rate, sex and age. Intermedical journal 1(2025). P. 121-124 https://doi.org/10.32782/2786-7684/2025-1-21

4. **Де і коли впроваджено:**
Кафедра соціальної медицини, громадського здоров'я та управління охороною здоров'я
5. **Результат впровадження**: вивчені епідеміологічні тенденції раку шлунка, в тому числі його основних форм, а також можливі моделі споживання лікарських засобів в Україні, які можуть впливати на розвиток раку шлунка.
6. **Ефективність впровадження:** Результати наукових досліджень впроваджені в науково-методичну роботу кафедри соціальної медицини, громадського здоров'я та управління охороною здоров'я в курс фармакоепідеміології. Використання розробки показало, що ефективність впровадження відповідає критеріям, які наведені у джерелах інформації.
7. **Зауваження та пропозиції:** не вносилися.

Відповідальний за впровадження
Завід. кафедри соціальної медицини,
громадського здоров'я та управління охороною здоров'я
д.мед.н., професор Лілія КРЯЧКОВА