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INVESTIGATION OF ESOPHAGEAL CANCER SUBTYPES, EPIDEMIOLOGICAL TRENDS, AND ASSOCIATED RISK FACTORS: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Esophageal cancers represent a significant public health and health problem in many parts of the world. Esophageal cancer development is a multifactorial process associated with various risk factors. Many studies have been identified that have examined various etiologic factors, including genetics, diet, infections, oral health, and underlying diseases.*

This brief review aims to provide a comprehensive survey of cancer epidemiology and a thorough assessment of established and suspected risk factors associated with esophageal cancer by distinct histologic subtypes.

The purpose was to study *the relationship between risk factors and genetic susceptibility in the development of esophageal cancer, with particular emphasis on two distinct histopathological subtypes.*

Methods: *The literature review included a search for scientific publications in the following databases: PubMed, Medline, and Cochrane Lab, using the scientific search engine Google Scholar. The search depth was 10 years.*

The literature review included epidemiology studies and assessing the strength of the relationship between risk factors for esophageal cancer. The review included all studies only among adults, publications in English, as well as publications with clearly formulated conclusions;

The exclusion criteria were case series, case reports, editorials, and conference abstracts. Out of 462 sources found, 45 were included in the analysis.

Results: *Studies show that several factors increase susceptibility to esophageal cancer, including tobacco use, excessive alcohol consumption, opioid abuse, hot food and beverage consumption, gastroesophageal reflux disease, obesity, gastric atrophy, poor oral hygiene, changes in esophageal microbiota, suboptimal diets, viral and bacterial infections, and others. In addition, mutational profiles of esophageal cancer cells have revealed frequent mutations in specific genes, including TP53, NFE2L2, MLL2, ZNF750, and NOTCH.*

Conclusion: *The pathogenesis of squamous cell carcinoma cancer exhibits multifactorial properties, with multiple recognized risk factors contributing to its occurrence. In contrast, the etiology of adenocarcinoma esophageal cancer remains relatively unknown, requiring ongoing research efforts to elucidate its fundamental causal mechanisms.*

Keywords: *squamous cell carcinoma, esophageal adenocarcinoma, epidemiology, risk factors, genetics of esophageal cancer.*

Introduction: In 2020, Esophageal cancer ranked 7th in the structure of oncological morbidity (604,000 new cases) and 6th in mortality (544,000 deaths) [1]. Comparing GLOBOCAN 2020 and GLOBOCAN 2022 data, we found an increase in esophageal cancer incidence and mortality (data for 2022 are presented below).

This disease has two main histological types: squamous cell carcinoma and adenocarcinoma. In Western countries, adenocarcinoma predominates [2], while squamous cell carcinoma predominates in Asia, Eastern Europe, and Africa, accounting for 90% of esophageal carcinoma cases [3].

Esophageal cancer is a significant public health and public health problem in many parts of the world. Esophageal cancer development is a multifactorial process associated with various risk factors. Numerous studies have been identified that have examined various etiologic factors, including genetics, diet, infections, oral health, and underlying medical conditions.

This article briefly reviews the epidemiology of esophageal cancer and provides an overview of confirmed and potential risk factors for esophageal cancer by distinct histopathological subtypes.

The purpose was to study the relationship risk factors and genetic susceptibility in the development of esophageal cancer, with particular emphasis on two distinct histopathological subtypes.

Materials and Methods: A search for scientific publications was conducted in the following databases: PubMed, Medline, and Cochrane Lab, using the scientific search engine Google Scholar. The review included studies devoted to the epidemiology and study of the relationship between risk factors for esophageal cancer. The analysis included publications in English with clearly formulated conclusions, except for case reports and case series, editorials, and conference abstracts. The search depth was 10 years. Out of 462 sources found, 45 scientific publications were included in the analysis.

Results: According to Globocan statistics for 2022, esophageal cancer ranks 11th in the world in terms of prevalence, with an estimated 511,054 cases per year,

and also ranks seventh in the world in terms of mortality, with a total of 445,391 deaths registered per year [4]. In 2022, at the country level, the highest age-standardized incidence rates of esophageal cancer were reported in Bangladesh (16.0 per 100,000 people per year) and Uganda (13.2 per 100,000 people per year). The lowest age-standardized rate in the world was in the Republic of Congo (0.43 per 100,000 people per year). By continent, the highest age-standardized incidence rates of esophageal cancer worldwide were reported in Asia (164.4), Africa (132.3), North America (364.7), and Europe (280) [10].

In the Republic of Kazakhstan, in 2022, 36,225 cases of esophageal cancer were verified, including 16,947 in men and 19,278 in women; 20,686 patients died from this disease, including 11,365 men and 9,321 women [5]. There are significant differences in the incidence of esophageal cancer between different population groups [6-9].

Esophageal squamous cell carcinoma and esophageal adenocarcinoma are the two main histological types of esophageal cancer with distinct epidemiological and clinical features. Worldwide, squamous cell carcinoma is the most common subtype of esophageal cancer, accounting for 80% of cases [11]. In contrast, esophageal adenocarcinoma (20%) is the most common subtype in the white population of developed countries and typically occurs in the distal esophagus [11].

Risk factors differ between esophageal squamous cell carcinoma and esophageal adenocarcinoma. Squamous cell carcinoma is a multifactorial disease with a long list of putative risk factors, whereas adenocarcinoma has far fewer established risk factors [12].

A brief description of these risk factors is presented below in Table 1.

Despite the proactive study of the role of genetic factors in the development and prognosis of esophageal cancer, our knowledge in this area remains insufficient. Unlike some other gastrointestinal malignancies, such as colorectal cancer, there is no clear path of tumor ontogenesis for esophageal cancer.

The Cancer Genome Atlas network published the results of a comprehensive genomic analysis of esophageal carcinoma. The analysis of DNA methylation, mRNA expression, and transcriptional profiles unambiguously revealed significant differences between squamous cell carcinoma and esophageal adenocarcinoma, confirming that they belong to two different tumor types. At the gene expression level, adenocarcinoma showed increased E-cadherin signaling and activation of the ARF6 and FOXA pathways through modulation of E-cadherin. Squamous cell carcinoma is characterized by increased activity of the Wnt, syndecan, and p63 pathways, which play a key role in cell differentiation processes. Mutation profiling analysis confirmed frequent mutations of TP53, NFE2L2, MLL2, ZNF750, NOTCH1, and TGFBR2 in esophageal squamous cell carcinoma, while recurrent mutations of TP53, CDKN2A, ARID1A, SMAD4, and ERBB2 were confirmed in esophageal adenocarcinoma [4 3].

Table 2 presents a variety of genetic abnormalities associated with the development of esophageal cancer.

Table 1 – Risk factors for the development of esophageal cancer depending on histological types (adapted from [12])

Factor	Squamous cell carcinoma	Risk Impact Coefficient	Adenocarcinoma	Risk Impact Coefficient	Links
Smoking	Strong relationship	Magnification 3-9 times	Moderate dependence	Increase by 2-3 times	13-14
Alcohol	Strong relationship	5x magnification	There is no connection.	-	15-17
Opium	Moderate connection	Increase by 1.6-2 times	No data	-	18-19
Consumption of beverages at temperatures ≥ 65 °C is classified as "possibly carcinogenic to humans."	Moderate connection	Increase by 2-3 times	There is no connection.	-	20-22
Gastroesophageal reflux disease	Strong relationship	Magnification 5-9 times	There is no connection.	-	23-24
Body mass index	Weak to moderate connection	30% reduction	Light to moderate correlation	Increase by 1.5-2 times	25
Gastric atrophy	Moderately strong connection	Increase by 2 times	There is no connection.		26-27
Deterioration of oral hygiene	• Not brushing one's teeth regularly is associated with a moderately increased risk. • Tooth loss shows a mild to moderate association. • Periodontitis is also associated with an increased risk, but to a lesser extent (40%).	Increase by 2 times Increase by 30-100% 40% increase	Statistically significant correlation between tooth loss and periodontal disease on one hand and an increased risk of developing esophageal adenocarcinoma on the other.	Tooth loss is associated with 1.3-2 times increased risk, and periodontitis – 1.4 times.	28-30
Microbiological properties	The structure of unique bacte-rial populations in the oral cav-ity and esophagus and the de-crease in species richness of microflora in these areas may be associated.	Possible impact	Changes in the composition of gram-negative microflora in the esophagus may contribute to the development of Barrett's esopha-gus, a precursor to adenocarcino-ma.	Possible increase in risk	31-32

Окончание Таблицы 1

Diet	• High-quality diet. • Adherence to vegetarian diets, such as the Mediterranean diet.	Reducing risk Reducing risk	Following dietary guidelines, physical activity, and monitoring BMI can help minimize your risk of develop-ing esophageal cancer.	Reducing risk	33-34
Introducing certain foods	• Excessive consumption of canned vegetables is associated with a moderate increase in risk. • Higher red and processed meat consumption was associated with a weak but statistically significant cor-relation. • Increased consumption of fruits and vegetables greatly reduces the risk. • Higher carbohydrate intake significantly reduces the risk. • Consumption of poultry and fish produces inconsistent results. • Consumption of dietary fats and dairy products.	Increase by 2 times Increase by 30-70% Reduction by 45% Reduction by 40% Connection not established Connection not established	• Increased consumption of fruits and vegetables • Increased consumption of red and processed meat • Increased carbohydrate consumption • Increased consumption of poultry and fish • Increased consumption of dairy products	Reduction by 25% Increase by 30-70% Reduction by 40% Connection not established Unknown	35-40
Viral infection	• There is no reliable association between most subtypes of human papillomavirus (HPV) and the occur-rence of esophageal cancer. Some rare HPV subtypes may be associated with an increased risk. • Data on the association of other viruses with the development of esophageal cancer are contradictory and re-quire further study.	-	No correlation.	-	41
Bacterial infection	*Helicobacter pylori bacteria*	50% reduction	No correlation.	-	42

Table 2 – Overview of genetic abnormalities associated with esophageal cancer [44]

Genetic abnormality	Squamous cell carcinoma	Adenocarci-noma
Cell cycle	90%	86%
RTK anomaly	59%	76%
Cell differentiation	57%	42%
Chromatin remodeling	36%	22%

Studies of molecular abnormalities in esophageal cancer have revealed similarities with tumors in adjacent anatomical regions. Thus, esophageal adenocarcinoma exhibits similar molecular characteristics to gastric adenocarcinoma, and esophageal squamous cell carcinoma exhibits significant similarities to head and neck squamous cell carcinoma [4 4].

Discussion: This review analyzes the current understanding of the epidemiology, predisposing, and possible risk factors for the development of esophageal cancer, distributed by the main histological subtypes of the disease. The identified risk factors were categorized into genetic predispositions, dietary and eating habits, concomitant diseases, infections, microbiome composition, metabolic disorders, and other factors. It is important to note that the available literature does not contain data on the relationship between these risk factors and the prognosis of the disease. Additional studies are needed to confirm the identified results and clarify their impact on tumor biology.

Recent advances in the molecular analysis of esophageal cancer have convincingly demonstrated that adenocarcinoma and squamous cell carcinoma are genetically and biologically distinct oncological diseases. The identified specific genetic abnormalities indicate differences in the physiological mechanisms of development of these tumors, which requires the development of individual therapeutic approaches.

It is important to note that the molecular profile of esophageal adenocarcinoma shows similarities with the chromosomal instability characteristic of gastric cancer. However, esophageal squamous cell carcinoma shows genetic similarities with other categories of malignancies.

The studies demonstrate the need for personalized treatment of each histological subtype of esophageal cancer and their separate consideration in clinical trials. This is especially important when studying the effectiveness of neoadjuvant, adjuvant, and systemic chemotherapy.

Conclusion: The pathogenesis of squamous cell carcinoma is multifactorial, with well-established risk factors contributing to its development. In contrast, the etiology of esophageal adenocarcinoma remains poorly understood and requires continued research to identify the underlying causal mechanisms.

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АҢДАТПА

ӨҢЕШ ҚАТЕРЛІ ІСІГІНІҢ ГИСТОЛОГИЯЛЫҚ ТИПТЕРІН ЭПИДЕМИОЛОГИЯЛЫҚ ТЕНДЕНЦИЯЛАРЫН ЖӘНЕ ОНЫМЕН БАЙЛАНЫСТЫ ҚАУІП ФАКТОРЛАРЫН ЗЕРТТЕУ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі. *Өңеш қатерлі ісігі – әлемнің көптеген бөліктерінде денсаулық сақтаудың күрделі мәселесі болып табылады. Өңеш қатерлі ісігінің дамуы әртүрлі қауіп факторларымен байланысты көп факторлы процесс болып табылады. Әртүрлі этиологиялық факторларды, соның ішінде генетикалық, диеталық, инфекциялық, ауыз қуысының денсаулығын және онымен байланысты ауруларды талқылайтын көптеген зерттеулер жүргізілді.*

Бұл қысқаша шолу қатерлі ісік эпидемиологиясына жан-жақты шолу жасайды және өңеш қатерлі ісігінің анықталған және күдікті қауіп факторларын нақты гистологиялық типтер бойынша бағалайды.

Зерттеудің мақсаты *– бұл зерттеудің мақсаты өңеш қатерлі ісігінің дамуындағы қауіп факторлары мен генетикалық бейімділік арасындағы қарым-қатынасқа баса назар аудара отырып, екі түрлі гистологиялық субтиптерге ерекше назар аудара отырып, кешенді эпидемиологиялық зерттеу жүргізу болып табылады.*

Әдістері: *Әдебиеттерді шолу келесі мәліметтер базасындағы ғылыми жарияланымдарды іздеуді қамтыды: PubMed, Medline, Cochrane Lab, Google Scholar ғылыми іздеу жүйесін қолдану арқылы. Іздеу тереңдігі – 10 жыл.*

Әдебиеттерге шолу мыналарды қамтиды: эпидемиология, өңеш қатерлі ісігінің қауіп факторларының байланысының күшін сипаттайтын және бағалайтын зерттеулер. Шолу тек ересектерге арналған барлық зерттеулерді, ағылшын тілдеріндегі жарияланымдарды, сондай-ақ нақты тұжырымдары бар басылымдарды қамтиды;

Шығарылу критерийлеріне жағдайлар сериясы, жағдай туралы есептер, редакциялық мақалалар және конференция тезистері кірді. Барлығы 462 дереккөз табылып, талдауға 45 ғылыми жарияланым енгізілді.

Нәтижелері: *Зерттеулер өңештің қатерлі ісігіне сезімталдықты бірнеше факторлардың жоғарылататынын көрсетеді, соның ішінде темекі тұтыну, алкогольді шамадан тыс тұтыну, опиоидтерді теріс пайдалану, ыстық тамақ пен сусындарды тұтыну, гастроэзофагеальды рефлюкс ауруы, семіздік, асқазанның атрофиясы, ауыз қуысының гигиенасы нашар болуы, өңеш микробиотасының өзгеруі, субоптималды емес диеталар, вирустық және бактериялық инфекциялар және т.б. Сонымен қатар, өңештің қатерлі ісік жасушаларының мутациялық профильдері TP53, NFE2L2, MLL2, ZNF750, NOTCH қоса алғанда, арнайы гендерде жиі мутацияларды анықтады.*

Қорытынды: *Жалпақ жасушалық карцинома қатерлі ісігінің патогенезі оның пайда болуына ықпал ететін көптеген мойындалған қауіп факторларымен бірге көп факторлы қасиеттерді көрсетеді. Керісінше, өңеш қатерлі ісігінің аденокарциномасының этиологиясы салыстырмалы түрде белгісіз болып қала береді, бұл оның негізгі қоздырғыш механизмдерін анықтау үшін үздіксіз зерттеулерді қажет етеді.*

Түйінді сөздер: *жалпақ жасушалы карцинома, өңеш аденокарциномасы, эпидемиология, қауіп факторлары, өңеш обырының генетикасы.*

АННОТАЦИЯ

ИССЛЕДОВАНИЕ ПОДТИПОВ РАКА ПИЩЕВОДА, ЭПИДЕМИОЛОГИЧЕСКИХ ТЕНДЕНЦИЙ И СВЯЗАННЫХ ФАКТОРОВ РИСКА: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Рак пищевода представляют собой значительную проблему в области здравоохранения во многих странах мира. Развитие рака пищевода – это многофакторный процесс, связанный с различными факторами риска. Было выявлено множество исследований, в которых изучались различные этиологические факторы, включая генетические, диетические, инфекции, здоровье полости рта, фоновые заболевания.*

Данный литературный обзор описывает эпидемиологию рака пищевода и оценки установленных и возможных факторов риска по раздельным гистологическим подтипам, такими как плоскоклеточный рак и аденокарцинома.

Цель исследования *– проведение всестороннего эпидемиологического обследования, сосредоточенного на взаимосвязи между факторами риска и генетической чувствительности при развитии рака пищевода, с особым акцентом на отдельные гистопатологические подтипы.*

Методы: *Проведен поиск научных публикаций в следующих базах данных: PubMed, Medline, Cochrane Lab при помощи научной поисковой системы Google Scholar. В обзор были включены исследования, посвящённые эпидемиологии и изучения связи между факторами риска рака пищевода. В анализ вошли публикации на английском языке с четко сформулированными выводами, за исключением отчётов о случаях и сериях случаев, редакционных статей и тезисов конференций. Глубина поиска – 10 лет. Всего было найдено 462 источника, включено в анализ 45 научных публикаций.*

Результаты: *Исследования показывают, что некоторые факторы повышают чувствительность к раку пищевода, в том числе курение, алкоголь, потребление наркотических веществ, потребление горячих пищевых продуктов и напитков, гастроэзофагеальная рефлюксная болезнь, ожирение, атрофия желудка, плохая оральная гигиена, изменения в микробиоте пищевода, субоптимальные диеты, вирусные и бактериальные инфекции и другие. Кроме того, мутационные профили раковых клеток пищевода обнаружили частые мутации, такие как TP53, NFE2L2, MLL2, ZNF750, NOTCH.*

Заключение: *Патогенез рака плоскоклеточной карциномы проявляет многофакторные свойства, с множеством признанных факторов риска, способствующих его возникновению. Напротив, этиология аденокарциномы рака пищевода остается относительно изученной, требуя постоянных исследовательских усилий по выявлению ее фундаментальных причинных механизмов.*

Ключевые слова: *эпидемиология, факторы риска, генетика рака пищевода, плоскоклеточная карцинома, аденокарцинома пищевода.*

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