

## CHANGES IN THE INCIDENCE OF ESOPHAGEAL ADENOCARCINOMA AND SQUAMOUS CELL CARCINOMA IN THE 21ST CENTURY

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**Abstract.** *Esophageal cancer remains one of the most aggressive malignancies worldwide, with adenocarcinoma and squamous cell carcinoma representing the two main histological subtypes. In the 21st century, significant epidemiological shifts have been observed.*

*Adenocarcinoma incidence is rapidly increasing in developed countries, largely driven by obesity, gastroesophageal reflux disease, and dietary habits, while squamous cell carcinoma remains prevalent in regions with high tobacco and alcohol consumption. This review examines the risk factors, regional differences, histological features, diagnostic approaches, and prevention strategies for both subtypes. The integration of molecular markers and endoscopic surveillance has improved early detection and personalized treatment. Understanding these trends is critical for optimizing public health policies, implementing effective prevention programs, and reducing the global burden of esophageal cancer.*

**Keywords:** *Esophageal cancer, Adenocarcinoma, Squamous cell carcinoma, Epidemiology, Risk factors, Barrett's esophagus, Early detection, Molecular markers, Prevention, Gastroesophageal reflux.*

### Introduction

In recent years, esophageal cancer has become one of the major global health threats, drawing significant attention from the medical and scientific community. Among its histological subtypes, esophageal adenocarcinoma and squamous cell carcinoma represent the two primary forms, each with distinct clinical characteristics, etiological factors, and preventive approaches.

In the 21st century, lifestyle changes, including dietary habits, gastroesophageal reflux disease, obesity, smoking, and alcohol consumption, have notably increased the risk of adenocarcinoma. Meanwhile, squamous cell carcinoma has traditionally been more prevalent in developing regions, whereas adenocarcinoma incidence is rising rapidly in both developed and developing countries. Epidemiological data indicate significant shifts in the overall frequency of esophageal cancer in the 21st century. Specifically, adenocarcinoma cases are increasing at a higher rate compared to squamous cell carcinoma, posing new challenges for global healthcare systems. From this perspective, analyzing the 21st-century epidemiology of esophageal adenocarcinoma and squamous cell carcinoma, their changing incidence rates, risk factors, and preventive strategies is a pressing scientific concern. This article aims to highlight the epidemiological trends of the two main histological types of esophageal cancer in the 21st century, identify contributing risk factors, and discuss current approaches to diagnosis and prevention.

### Relevance

Esophageal cancer remains a significant cause of cancer-related morbidity and mortality worldwide. In the 21st century, shifts in lifestyle, dietary patterns, obesity prevalence, and other environmental factors have led to noticeable changes in the incidence of its two main histological types: adenocarcinoma and squamous cell carcinoma. Adenocarcinoma, in particular, has demonstrated a rapidly increasing trend in developed countries, while squamous cell carcinoma remains prevalent in specific regions.

Understanding these epidemiological changes is crucial for the development of effective preventive strategies, early detection programs, and healthcare planning. Given the rising global burden of esophageal cancer, studying its incidence, risk factors, and trends in the 21st century is highly relevant for both clinicians and public health specialists.

### **Aim**

The aim of this study is to analyze the changes in the frequency of esophageal adenocarcinoma and squamous cell carcinoma in the 21st century, identify the primary risk factors contributing to these trends, and evaluate current diagnostic and preventive strategies. By providing a comprehensive overview of recent epidemiological data, this research seeks to inform healthcare professionals and policymakers about the evolving patterns of esophageal cancer and support the development of targeted interventions.

### **Main part**

Esophageal cancer is considered one of the most aggressive malignancies with high mortality rates worldwide. According to the World Health Organization, it ranks among the top ten cancers in terms of incidence and death globally. Every year, more than 500,000 new cases are diagnosed, and the disease claims nearly the same number of lives, reflecting its poor prognosis and late detection in many regions. The incidence is not uniform; high rates are observed in East Asia, parts of Africa, and certain European countries, while North America and some regions of Western Europe report lower overall rates. The disparity in incidence is influenced by various environmental, lifestyle, and genetic factors. In high-incidence regions, squamous cell carcinoma predominates, while in low-to-moderate incidence regions, adenocarcinoma has become increasingly common over the last two decades. Mortality rates remain high due to delayed diagnosis and limited access to advanced therapeutic interventions.

Public health records indicate that males are disproportionately affected, with incidence roughly three to four times higher than females.

Socioeconomic factors also play a significant role in disease prevalence. Populations with limited access to healthcare, poor nutrition, and high exposure to carcinogens demonstrate elevated risks. Epidemiological surveillance has shown a gradual shift in the dominant histological type from squamous cell carcinoma toward adenocarcinoma in developed countries, indicating a transition linked to modern lifestyle factors such as obesity and gastroesophageal reflux disease. Global strategies for monitoring esophageal cancer emphasize the need for standardized data collection and cancer registries. Such efforts facilitate the identification of trends and regional disparities, enabling policymakers to prioritize resources for prevention, screening, and early treatment. This foundational understanding of global epidemiology forms the basis for analyzing histological trends and changing incidence rates in the 21st century.

Esophageal cancer primarily manifests in two histological forms: adenocarcinoma and squamous cell carcinoma. Adenocarcinoma arises from glandular cells in the lower esophagus, often in areas affected by Barrett's esophagus, which develops as a result of chronic gastroesophageal reflux. Microscopically, adenocarcinoma shows glandular differentiation, mucin production, and varying degrees of cellular atypia. Its progression is frequently associated with metaplasia-to-dysplasia sequences, highlighting the importance of histological surveillance in high-risk patients. In contrast, squamous cell carcinoma originates from the squamous epithelial lining of the esophagus, typically affecting the middle and upper segments.

Histologically, it is characterized by keratinization, intercellular bridges, and nuclear pleomorphism.

Chronic irritation, tobacco and alcohol use, and exposure to dietary carcinogens contribute to cellular mutations, promoting malignant transformation. The aggressive nature of squamous cell carcinoma is reflected in its tendency for early lymphatic spread and regional metastasis. Understanding these histological differences is crucial for both diagnosis and treatment planning. Adenocarcinoma often responds differently to chemoradiotherapy compared to squamous cell carcinoma, and surgical approaches may vary depending on tumor location and histological type. Molecular profiling has further refined classification, revealing distinct genetic alterations in each subtype, including TP53 mutations in squamous cell carcinoma and HER2 overexpression in adenocarcinoma. Histological examination remains the gold standard for definitive diagnosis, guiding clinical decisions and prognosis estimation. By combining endoscopic biopsy, imaging, and molecular analyses, clinicians can accurately identify tumor type, stage, and potential therapeutic targets. Consequently, histological differentiation serves as a critical foundation for understanding epidemiological shifts and implementing effective prevention and management strategies in the 21st century.

In the 21st century, the incidence of esophageal cancer has shown significant global variation, reflecting changes in lifestyle, environmental exposure, and healthcare accessibility.

Epidemiological studies demonstrate a notable increase in adenocarcinoma cases in developed countries, particularly in North America, Western Europe, and parts of Asia. This trend correlates with rising obesity rates, gastroesophageal reflux disease prevalence, and dietary patterns high in processed foods and low in fiber. Conversely, squamous cell carcinoma remains more common in regions with high tobacco and alcohol consumption, such as East Asia and parts of sub-Saharan Africa. While its overall incidence has declined in some Western countries due to public health interventions, regional hotspots continue to report elevated rates. Gender disparities persist, with males consistently exhibiting higher incidence rates for both histological types. Longitudinal data indicate that adenocarcinoma has overtaken squamous cell carcinoma as the dominant subtype in several countries, marking a significant epidemiological transition. Age distribution patterns reveal that adenocarcinoma predominantly affects individuals over 50 years old, whereas squamous cell carcinoma can appear earlier in populations exposed to carcinogenic risk factors. Technological advances in diagnostics, including endoscopic surveillance and imaging, have contributed to more accurate detection and reporting, potentially influencing observed trends. Additionally, improved cancer registries and global collaboration provide comprehensive data for assessing shifts in incidence, mortality, and survival. Understanding these 21st-century trends is essential for tailoring public health strategies, resource allocation, and targeted prevention efforts against esophageal cancer.

Esophageal adenocarcinoma is primarily associated with chronic gastroesophageal reflux disease (GERD), which often leads to the development of Barrett's esophagus. Barrett's esophagus is characterized by the replacement of normal squamous epithelium in the lower esophagus with glandular epithelium, serving as a predisposing factor for adenocarcinoma. Chronic acid reflux induces genetic and epigenetic changes in epithelial cells, increasing the risk of malignant transformation. Obesity is another significant risk factor. Excess abdominal fat contributes to increased intra-abdominal pressure, enhancing acid reflux and promoting the production of inflammatory mediators. Dietary habits, such as low fiber intake, high consumption of processed foods, and sugary drinks, further elevate adenocarcinoma risk.

Tobacco use and alcohol consumption also play a role, especially when combined, as they exacerbate mucosal damage and contribute to carcinogenesis.

Genetic factors, including mutations in TP53, CDKN2A, and HER2, impair cell cycle regulation and DNA repair mechanisms, facilitating cancer development.

Gender and age are important determinants. Men are more frequently affected, and adenocarcinoma is most commonly diagnosed in individuals over 50 years old. Epidemiological studies show that adenocarcinoma incidence has increased sharply in developed countries over recent decades, reflecting modern lifestyle, dietary, and socioeconomic influences. Stress and physical inactivity are additional contributors, as they exacerbate chronic reflux and promote systemic inflammation. Identifying high-risk individuals and implementing regular surveillance is crucial for early diagnosis and effective prevention of esophageal adenocarcinoma.

Squamous cell carcinoma predominantly affects the middle and upper esophagus. Key risk factors include chronic mucosal irritation, tobacco and alcohol use, and dietary carcinogens such as nitrites and aflatoxins. These factors induce DNA mutations in epithelial cells, leading to malignant transformation. Regional and climatic factors significantly influence the prevalence of squamous cell carcinoma. High rates are observed in East Asia, South America, and sub-Saharan Africa. The elevated incidence in these areas is largely due to high levels of tobacco and alcohol consumption and exposure to dietary carcinogens. Gender disparities persist, with men being more frequently affected than women. Age distribution indicates that the disease primarily affects individuals over 50, although in some regions, cases appear earlier due to combined environmental and lifestyle exposures.

Genetic and molecular factors also play a role. TP53 mutations and alterations in NOTCH and SOX2 genes disrupt cell cycle control, contributing to tumor development. Local dietary habits, including the consumption of very hot beverages and contaminated foods, further increase risk. Understanding squamous cell carcinoma risk factors and regional patterns is essential for designing effective public health interventions, early detection programs, and educational campaigns in high-risk areas.

Early diagnosis of esophageal cancer significantly improves patient outcomes. Effective diagnostic approaches include endoscopy, biopsy, imaging techniques, and molecular markers. Endoscopy provides high-resolution visualization of the esophagus and allows for targeted biopsy of suspicious areas. Histological examination remains the gold standard for tumor classification. Identifying adenocarcinoma versus squamous cell carcinoma is critical for treatment planning. Biopsy results guide clinicians in selecting surgical, chemotherapeutic, or radiotherapeutic strategies. Imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) enable accurate assessment of tumor spread, lymph node involvement, and metastases. Molecular markers, including HER2, TP53, and Ki-67, provide prognostic information and support personalized treatment planning.

High-risk patients, especially those with Barrett's esophagus, chronic reflux, advanced age, or a family history of esophageal cancer, benefit from regular endoscopic surveillance. This approach allows for early detection of adenocarcinoma and timely intervention. Advances in diagnostic technologies enhance detection rates, reduce mortality, and optimize healthcare resource allocation. International collaboration and standardized surveillance protocols further improve the quality and accuracy of esophageal cancer diagnosis.

Preventive strategies focus on reducing exposure to established risk factors. Smoking cessation, limiting alcohol intake, maintaining a healthy diet rich in fiber, and managing obesity are key measures to prevent esophageal cancer. Management of chronic gastroesophageal reflux and monitoring of Barrett's esophagus are also essential.

Pharmacological therapy, such as proton pump inhibitors, reduces acid exposure and decreases the risk of adenocarcinoma progression. Endoscopic surveillance of high-risk patients ensures early diagnosis. Regional prevention programs, educational campaigns, and promotion of healthy lifestyles reduce overall disease risk. Efforts include dietary interventions, anti-smoking and alcohol reduction campaigns, and encouraging regular physical activity. Genetic and molecular profiling allows for identification of high-risk individuals and development of tailored preventive strategies. Minimally invasive surgical techniques, such as endoscopic mucosal resection, are effective for early-stage tumors and support modern preventive approaches. Comprehensive prevention strategies enhance resource utilization in healthcare systems, lower disease incidence, and improve survival rates. Global collaboration and continuous epidemiological monitoring are essential to update and refine preventive measures.

### **Discussion and Results**

The analysis of epidemiological data on esophageal adenocarcinoma and squamous cell carcinoma in the 21st century reveals several notable trends and regional disparities.

Adenocarcinoma has shown a marked increase in incidence, particularly in developed countries such as North America, Western Europe, and parts of Asia. This trend correlates strongly with lifestyle changes, including rising obesity rates, increased prevalence of gastroesophageal reflux disease, and consumption of processed foods with low fiber content. The results suggest that these modifiable risk factors significantly contribute to the observed rise in adenocarcinoma cases.

Conversely, squamous cell carcinoma incidence has generally declined in some developed regions but remains high in East Asia, sub-Saharan Africa, and certain parts of South America. The prevalence in these areas is associated with persistent exposure to tobacco, alcohol, dietary carcinogens, and environmental factors. Gender differences remain pronounced, with males disproportionately affected in both histological types, consistent with global epidemiological patterns. Histological analysis confirms distinct biological behaviors of the two subtypes. Adenocarcinoma typically arises in the lower esophagus, often associated with Barrett's esophagus, and shows glandular differentiation with mucin production. Squamous cell carcinoma originates in the middle and upper esophagus, exhibiting keratinization and intercellular bridges. These differences explain variations in clinical presentation, progression patterns, and response to treatment modalities, emphasizing the need for tailored management strategies. Risk factor assessment further supports the role of both environmental and genetic contributors. Mutations in TP53, HER2 overexpression in adenocarcinoma, and alterations in NOTCH and SOX2 in squamous cell carcinoma highlight the molecular heterogeneity of esophageal cancer. These findings underscore the importance of integrating molecular diagnostics into clinical practice for risk stratification and personalized therapy.

The results of this study also highlight the effectiveness of preventive strategies. Lifestyle modification, management of gastroesophageal reflux, endoscopic surveillance in high-risk populations, and public health interventions targeting smoking and alcohol consumption contribute to the reduction of disease incidence and improve early detection rates. Additionally, minimally invasive surgical techniques and pharmacological therapy have improved clinical outcomes for early-stage tumors. The 21st-century trends in esophageal cancer incidence demonstrate a clear epidemiological transition. Adenocarcinoma is increasing rapidly in developed regions, while squamous cell carcinoma remains regionally prevalent in areas with high-risk exposures.

The integration of epidemiological, histological, and molecular data provides a comprehensive understanding of the disease and supports the development of effective prevention, early detection, and management strategies. These findings can guide policymakers, clinicians, and public health authorities in optimizing healthcare resources and reducing the global burden of esophageal cancer.

### Conclusion

In conclusion, the epidemiology of esophageal adenocarcinoma and squamous cell carcinoma has undergone significant changes in the 21st century. Adenocarcinoma incidence is rising rapidly in developed countries, driven largely by lifestyle factors such as obesity, gastroesophageal reflux, and dietary habits, whereas squamous cell carcinoma remains prevalent in regions with high tobacco and alcohol consumption. Histological and molecular differences between the two subtypes emphasize the importance of precise diagnosis and individualized treatment strategies. Risk factor identification, early detection through endoscopic surveillance, and implementation of preventive measures significantly contribute to reducing disease burden and improving patient outcomes.

Overall, understanding the dynamic trends, risk profiles, and regional variations of esophageal cancer is essential for developing effective public health policies, optimizing healthcare resources, and implementing targeted prevention and treatment programs. These efforts are crucial to mitigate the global impact of esophageal cancer and enhance survival rates in affected populations.

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