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The clinicopathologic significance of estrogen receptors in human gastric carcinoma



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ABSTRACT

In most populations, gastric cancer (GC) is approximately two times more prevalent in men than in women, which may suggest the protective role of sex steroid hormones in gastric carcinogenesis. Steroid hormones such as androgens and estrogens can be synthesized not only in the gonads but also in peripheral tissues. Many researchers have conducted studies examining the expression profile of enzymes involved in steroid synthesis, the occurrence of estrogen receptors (ERs) and the influence of ERs in the development, proliferation and progression of gastric cancer. Some studies have also evaluated the relationship between the presence of ERs and survival prognosis. However, the results of these studies are often controversial and divergent. In a recent study, it was indicated that sex steroid hormones and estrogen receptors are partly involved in gastric cancer but their clinicopathological significance still needs further investigation.

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1. Introduction

Gastric cancer (GC) is one of the most common malignancies worldwide and there are approximately 5000 new cases reported annually [1]. Nevertheless, in most countries the mortality rate has decreased significantly and the incidence of gastric cancer has declined by nearly 75% in the past 50 years [1]. Gastric cancer is a malignant neoplasm of the epithelium of the gastric mucosa, with 90% of all gastric tumors being malignant. Approximately 90–95% of gastric cancer are categorized as adenocarcinomas, which makes

them the most common type of gastric cancer. Gastric adenocarcinoma develops from glandular epithelium of the gastric mucosa [2,3], while other types of gastric cancer such as lymphomas develop from immune system tissues. Less commonly known types of gastric cancer consist of sarcomas arising from connective tissues including hard tissues, soft tissues and liquid tissues, as well as carcinoid tumors that begin in neuroendocrine cells of the gastrointestinal tract and lastly gastrointestinal stromal tumors [3,4]. All mentioned types of gastric cancers were presented in Table 1.

According to Lauren classification, gastric adenocarcinoma consists of two pathological variants—intestinal and diffuse. Intestinal type is a result of an inflammatory process, usually accompanied by chronic gastritis or atrophic gastritis with

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Table 1
Basic characteristics of different types of gastric cancers.

Type of GC	Occurrence [%] of all gastric cancers	Origin	Gender	Age	Survival prognosis
Adenocarcinomas	90–95%	Glandular epithelium of gastric mucosa			
a) Intestinal		Inflammatory process with chronic and atrophic gastritis and intestinal metaplasia and dysplasia	Male	Over the age of 50	Favorable
b) Diffuse		Unchanged mucosa	Female	Under the age of 50	Unfavorable
Lymphomas	4%	Immune system tissues	Male	Over the age of 50	Favorable
Sarcomas	1–3%	Connective tissues (hard, soft and liquid tissues)	Female and male	Under the age of 50	Unfavorable
Carcinoid tumors	2%	Neuroendocrine cells of the gastrointestinal tract	Female	Over the age of 50	Favorable
Gastrointestinal stromal tumors	1%	Interstitial cells of Cajal–ICC	Female and male	Between 55–65 years old	Favorable survival prognosis

intestinal metaplasia and dysplasia. This type of gastric adenocarcinoma has a better prognosis and is more commonly diagnosed among elderly men. In contrast, the diffuse type is associated with unfavorable prognosis due to the late diagnosis when the disease is already in an advanced stage. Diffuse type of gastric adenocarcinoma is more widespread among women and people under the age of 50 [2,4,5]. Clinicopathological data suggests that the development of the intestinal type of GC depends on environmental factors while the diffuse type is more dependent on genetic factors. The intestinal type of gastric adenocarcinoma is more often associated with metastasis via the blood vessels and liver metastasis in comparison to the diffuse type [7].

2. Epidemiology and risk factors of gastric cancer

The incidence of gastric cancer varies among different geographic regions and various ethnic groups. The majority of gastric cancers are most commonly observed in developing countries [6] and the highest incidence rates can be seen in Eastern Asia, South America and Middle America [2,3]. The incidence of gastric cancer increases gradually with age and patients between the ages of 50 and 70 years are the most susceptible to developing this disease. Although the incidence of gastric cancer and its mortality rate has declined over the past 70 years [1,7], it is still one of the most common cancers among men and remains fourth leading cause of cancer death in men worldwide [2]. Researchers report that increased risk of gastric cancer may also be related to low socioeconomic status [2].

GC is a complex and multifactorial disease and its direct cause is still unknown [7]. Among the most common predisposing factors associated with an increased risk of gastric cancer are diet, genetic factors, tobacco use, obesity and infection with *Helicobacter pylori*, which seems to be the principal cause of this disease [2,3]. The presence of *Helicobacter pylori* in gastric mucosa induces inflammatory processes and infections, usually occurring in childhood via the oral route and maintained for a long period of time without any clinical symptoms.

Prevalence of GC is also related to low socioeconomic status which can be explained with poor nutrition and hygiene, such as no toilets and clean running water. Researchers have found that there is a much higher incidence of infections among the populations in underdeveloped countries compared to developed ones [2,7].

Another significant risk factor for developing GC is an inadequate diet. Studies have shown that patients on high salt, smoked or pickled food diets or diets rich in nitrates and nitrites had an increased risk of developing GC, whereas patients on diets containing large amounts of fresh fruits and vegetables had a lower risk of developing this disease [2,3]. The protective effect is related to the presence of vitamin C, vitamin A, vitamin E and beta carotene in these products [7]. The incidence of gastric cancer is also associated with genetic factors. The risk of developing GC is two times higher in the case of family occurrence of this cancer [2,5], however it only represents 5–10% of all cases [7].

Other risk factors of gastric cancer include chronic atrophic gastritis, gastric polyps, obesity, patients with blood type A and

Table 2
Risk factors for developing gastric cancer.

Risk factor	Highest risk of developing gastric cancer	Lowest risk of developing gastric cancer
Gender	Male	Female
Age	50–70 years' old	<50 years old
Geographic region	Eastern Asia, South America, Middle America	Europe
Socioeconomic status	Low, underdeveloped country	High, developed country
<i>Helicobacter pylori</i> infection	+++	
Tobacco use	++	
Diet	Salt, smoked, pickled foods Diet rich in nitrates and nitrites	Large amounts of fresh fruits and vegetables
Genetic factors	Family occurrence of GC	No family occurrence of GC
Obesity	++	
Reflux	+	

+ occurrence of weak positive association with gastric cancer.

++ occurrence of moderately strong association with gastric cancer.

+++ occurrence of strong association with gastric cancer.

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