

Gender difference in gastro-esophageal reflux diseases

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Abstract

The incidence of esophageal adenocarcinoma (EAC) has risen sharply in western countries over the past 4 decades. This type of cancer is considered to follow a transitional process that goes from gastro-esophageal reflux disease (GERD) to Barrett's esophagus (BE,

a metaplastic condition of the distal esophagus), a precursor lesion and ultimately adenocarcinoma. This spectrum of GERD is strongly predominant in males due to an unidentified mechanism. Several epidemiologic studies have described that the prevalence of GERD, BE and EAC in women is closely related to reproductive status, which suggests a possible association with the estrogen level. Recently, we revealed in an *in vivo* study that the inactivation of mast cells by the anti-inflammatory function of estrogen may account for the gender difference in the GERD spectrum. Other studies have described the contribution of female steroid hormones to the gender difference in these diseases. Estrogen is reported to modulate the metabolism of fat, and obesity is a main risk factor of GERDs. Moreover, estrogen could confer esophageal epithelial resistance to causative refluxate. These functions of estrogen might explain the approximately 20-year delay in the incidence of BE and the subsequent development of EAC in women compared to men, and this effect may be responsible for the male predominance. However, some observational studies demonstrated that hormone replacement therapy exerts controversial effects in GERD patients. Nevertheless, the estrogen-related endocrine milieu may prevent disease progression toward carcinogenesis in GERD patients. The development of innovative alternatives to conventional acid suppressors may become possible by clarifying the mechanisms of estrogen.

Key words: Gastro-esophageal reflux disease; Barrett's esophagus; Esophageal adenocarcinoma; Estrogen; Male predominance

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Core tip: Gastro-esophageal reflux disease (GERD), Barrett's esophagus and esophageal adenocarcinoma are epidemiologically recognized to be more prevalent in males due to an unknown mechanism. Our recent

animal study revealed that estrogen contributes to the gender difference by inactivating inflammatory cells. Additionally, several studies demonstrated that estrogen confers epithelial resistance against causative refluxate and modifies adipose tissue metabolism in obese people and prevent the onset of GERDs. Consequently, the estrogen-related endocrine milieu in women could retard the progression of chronic inflammation to esophageal carcinogenesis, which is likely responsible for the predominance of GERD in males.

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INTRODUCTION

Esophageal adenocarcinoma (EAC) has been increasing in many countries, especially in Western countries, over the past 4 decades^[1,2]. EAC has been proposed to be the end result of a stepwise disease process that transitions through gastro-esophageal reflux disease (GERD) and Barrett's esophagus (BE), a condition in which the reflux-damaged esophageal squamous epithelium is replaced by metaplastic columnar epithelium^[3]. EAC, erosive reflux esophagitis (ERD) and BE are widely known to be predominant in males. This gender difference in the spectrum of GERD cannot be explained by prevailing risk factors and has previously been associated with sex steroid hormones, although little is known about the mechanism responsible for this disparity in the incidence. Some types of human gastro-intestinal neoplasms are predominant in males, including colorectal cancer, gastric cancer and esophageal cancer^[4-6]. The gender-specific susceptibility to various diseases in the gastro-intestinal tract has frequently been investigated using experimental animal models^[7,8]. Females are less affected by gastric or intestinal inflammation in response to chemical insult or bacterial infection than males are, which leads to differences in the incidence of gender-specific carcinogenesis^[9]. In these studies, the anti-inflammatory activity of estrogen was considered to contribute to the lower incidence of carcinogenesis in females.

Using an animal model of GERD, we recently published the first report showing that the estrogen level could account for the gender difference in disease incidence^[10]. In this review, we describe the crucial role of estrogen, a primary female sex hormone that exerts various physiological activities, including anti-inflammatory functions, in the sex difference of GERD incidence.

EPIDEMIOLOGY IN GERD, BARRETT'S ESOPHAGUS AND ESOPHAGEAL ADENOCARCINOMA

Accumulating epidemiological evidence shows that the generative period of women is related to the prevalence of GERDs. The difference in age-stratified prevalence between the sexes suggests that estrogen significantly impacts each step of GERD-related carcinogenesis and may consequently be responsible for the predominance of this disease in males.

GERD

GERD consist of manifestations of esophageal damage due to the reflux of gastric or intestinal contents to the esophagus as well as other symptoms, especially heartburn^[11]. The incidence of GERD has been reported to be almost equal in males and females^[12]. However, GERD is grossly divided into 2 pathological conditions by endoscopy, erosive reflux esophagitis (ERD) and non-erosive reflux esophagitis (NERD), and epidemiologic studies have indicated that ERD is predominant in males (Table 1)^[13-21]. A recent meta-analysis described that the male/female ratio in the prevalence of ERD was 1.57/1 (95%CI: 1.40-1.76)^[22], and the mean age of men with ERD was reported to be lower than that of women. A retrospective, large-scale endoscopic analysis in the UK showed that the mean age of men/women with ERD was 59.7 ± 16.1/64.4 ± 15.1^[18]. Thus, the incidence of ERD positively correlated with age, but female patients tended to be older than male patients^[18,19,23]. Moreover, ERD tended to be more severe in older women than in men, and the increase in the incidence of severe ERD tended to be higher in postmenopausal women than in men^[18,19]. Conversely, NERD is more common in women (Table 1)^[12,16,24,25]. Interestingly, a quantitative esophageal symptom analysis revealed that symptom frequency and severity were significantly higher in women than in men, whereas the endoscopic esophagitis grade or duration of the time at pH below 4 during ambulatory 24-h esophageal pH monitoring did not significantly differ between men and women^[14,26].

BE

The prevalence of BE is not known, in part because this disease is symptomatically silent, which complicates endoscopic studies. Furthermore, the definitions of BE often differ by study. United States gastroenterology societies require esophageal biopsies showing intestinal metaplasia (IM) and goblet cells for a definitive diagnosis of BE because IM is considered a well-established risk factor for adenocarcinoma^[27,28]. Conversely, the British Society of Gastroenterology guidelines noted that the presence of IM in the columnar epithelium of the esophagus is not a prerequisite for the diagnosis of BE due to the difficulty

Table 1 The male/female ratio in the prevalence of erosive esophagitis and non-erosive esophagitis

	Ref.	Country	Number		Study period	Male/female ratio
			Men	Women		
Erosive reflux esophagitis						
United States	El-Serag <i>et al</i> ^[13] , 2002	United States	4092	2617	NA	1.6
	Lin <i>et al</i> ^[14] , 2004	United States	131	63	NA	1.6
Europe	Nilsson <i>et al</i> ^[15] , 2002	Sweden	108	71	1996-1997	1.6
	Jaspersen <i>et al</i> ^[16] , 2003	German/ Austria /Switzerland	1966	1279	2000-2001	1.6
Asia	Ford <i>et al</i> ^[17] , 2005	United Kingdom	1695	1301	2001-2003	1.4
	Menon <i>et al</i> ^[18] , 2011	United Kingdom	13148	11092	1997-2009	1.2
	Furukawa <i>et al</i> ^[19] , 1999	Japan	533	444	1996-1998	1.3
	Koike <i>et al</i> ^[20] , 1999	Japan	98	78	1995-1998	1.3
	Ho <i>et al</i> ^[21] , 2005	Singapore	649	479	1992-2001	1.4
Non-erosive reflux esophagitis						
United States	Richter <i>et al</i> ^[24] , 2000	United States	375	523	NA	0.8
Europe	Damiano <i>et al</i> ^[25] , 2003	United States	73	150	NA	0.5
	Jaspersen <i>et al</i> ^[16] , 2003	German/ Austria /Switzerland	1337	1633	2000-2001	0.9
	Ronkainen <i>et al</i> ^[12] , 2005	Sweden	340	431	NA	0.8

NA: Non-applicable (data not available).

Table 2 The male/female ratio in the prevalence of Barrett's esophagus

	Ref.	Country	Number		Study period	Male/female ratio
			Men	Women		
Columnar lined epithelium with intestinal metaplasia						
United States	Rudolph <i>et al</i> ^[30] , 2000	United States	226	83	1993-1998	2.8
	Conio <i>et al</i> ^[31] , 2001	United States	108	46	1969-1998	2.4
	Kubo <i>et al</i> ^[32] , 2013	United States/ Ireland /Australia	786	316	1997-2003	2.5
Europe	Bani-Hani <i>et al</i> ^[33] , 2000	United Kingdom	179	128	1984-1995	1.4
	van Blankenstein <i>et al</i> ^[34] , 2005	United Kingdom	248	127	1982-1996	1.4
	Anderson <i>et al</i> ^[35] , 2003	Northern Ireland	819	473	1993-1999	1.8
	Kulig <i>et al</i> ^[36] , 2003	Germany/ Austria /Switzerland	456	246	2000-2001	1.9
	Pohl <i>et al</i> ^[37] , 2013	Germany	NA	NA	2005-2009	2.6
	Conio <i>et al</i> ^[38] , 2003	Italy	135	31	1987-1997	4.4
	van Soest <i>et al</i> ^[39] , 2005	Netherlands	158	102	1996-2003	1.6
	de Jonge <i>et al</i> ^[40] , 2010	Netherlands	NA	NA	1996-2006	1.7
Asia/Oceania	Ronkainen <i>et al</i> ^[41] , 2005	Sweden	9	7	1998	1.3
	Hvid-Jensen <i>et al</i> ^[42] , 2011	Denmark	7366	3662	1992-2009	2.1
	Hillman <i>et al</i> ^[43] , 2003	Australia	NA	NA	1981-2001	2.5
Columnar lined epithelium irrespective of intestinal metaplasia						
Europe	Coleman <i>et al</i> ^[45] , 2011	Northern Ireland	5482	3897	1993-2005	1.4
	Masclée <i>et al</i> ^[46] , 2014	United Kingdom	7811	4501	2000-2011	1.8
Asia	Dong <i>et al</i> ^[47] , 2013	Netherlands	856	527	2000-2012	1.7
		China	2452	1377	2001-2011	1.8

NA: Non-applicable (data not available).

in excluding sampling errors of the biopsies and the carcinogenic potential in non-IM^[29]. In women, the prevalence of BE, defined as columnar lined epithelium (CLE) with IM, has been reported to be approximately twice as high as in men (Table 2)^[30-43]. Specifically, a meta-analysis demonstrated that the male/female sex ratio of BE with IM was 2.13/1 (95%CI: 1.87-2.46)^[22]. A large cohort study in the Netherlands revealed that the mean age of women with BE was significantly higher than that of men with BE (men/women; 59.3 ± 13.8/65.5 ± 15.0, $P < 0.01$)^[39]. Other studies revealed that the prevalence of BE in women began to

increase after 60 years of age and that the increase in the prevalence of BE in women in the postmenopausal period surpassed that of men^[17,34]. Age-specific increases in BE occurred in parallel with a 20-year age shift between men and women^[34]. Moreover, BE tended to be longer in men than in women, and the incidence of BE with IM was higher in men than in women^[34,44]. Conversely, epidemiologic studies of the prevalence of BE, irrespective of the presence of IM, demonstrated a significant male predominance, but the male/female ratio of this condition was somewhat lower than that of BE (Table 2)^[45-47]. The meta-analysis revealed that the

Table 3 The male/female ratio in the prevalence of esophageal adenocarcinoma

	Ref.	Ethnicity/country	Per million		Study period	Male/female ratio		
			Men	Women				
United States	Dubecz <i>et al</i> ^[48] , 2013	White	40	11	1980	3.7		
		Non-white	23	10		2.3		
		White	65	15	1990	4.4		
		Non-white	30	19		1.6		
		White	90	20		4.5		
Europe	van Soest <i>et al</i> ^[39] , 2005	Non-white	27	18	1996-2003	1.5		
		Netherlands	39	12		3.3		
		England and Wales	Lepage <i>et al</i> ^[49] , 2008	NA	NA	1971-2001	5.0	
			Hvid-Jensen <i>et al</i> ^[42] , 2011	Denmark	56	10	1992-2009	5.6
			Pohl <i>et al</i> ^[37] , 2013	Germany	87	23	2005-2009	3.8
Asia/Oceania	Hillman <i>et al</i> ^[43] , 2003	Australia	11	2	1981-2001	5.5		
		Ozawa <i>et al</i> ^[50] , 2010	Japan	3661		574	2002	6.4
		Chang <i>et al</i> ^[51] , 2002	Taiwan	93%	7%	1981-1995	13.3	
		Fernandes <i>et al</i> ^[52] , 2006	Singapore	96	30	1968-2002	3.2	

NA: Non-applicable (data not available).

male/female ratio of BE was 1.71/1 (95%CI: 1.42-2.04), irrespective of the presence of IM^[22].

EAC

The male/female ratio in the prevalence of EAC varies depending on the country or ethnicity (Table 3)^[37,39,42,43,48-52]. Nevertheless, as a whole, EAC is significantly more common in males than in females, irrespective of country or ethnicity. In the United States, United Kingdom, Denmark and Sweden, the incidence of EAC has been increasing in both men and women, whereas the incidence in women has been almost stable or increasing at only a very low rate in Norway and Finland^[1,2,49,53]. In Caucasians in the United States, England and Wales, where the rate of increase of EAC is higher than in other countries, the male/female ratio of 5/1 has not changed over the last 3 decades^[48,49]. However, non-Caucasian men in the US have experienced a slow increase in the incidence of EAC, whereas the incidence in non-Caucasian women has remained almost unchanged over the last 3 decades. Therefore, the male/female ratio of EAC in non-Caucasians in the US ranged from 1.5/1 to 2.0/1 during the study period^[48,49]. The mean age of female BE patients with EAC and high-grade dysplasia was reported to be higher than that of male BE patients (men/women: 64.1 ± 10.7/70.6 ± 7.9), and this trend was the same for other GERDs^[44]. A recent large population-based study demonstrating the annual percentage change in the incidence of EAC revealed that the rate of EAC rapidly increased in men, regardless of age, whereas women aged 50 and older exhibited slowly increasing rates of EAC. However, the rate of increase was higher in women aged 80 years or older than in men, whereas women aged under 50 showed a qualitatively flatter trajectory^[54]. Additionally, this study revealed that the age-adjusted male/female ratio of the incidence steadily declined starting at

age 50, suggesting a disproportionate increase in the incidence of EAC in postmenopausal women. The combined evidence suggests that women lag behind men by 17 years in the development of EAC^[55].

Gender differences in the spectrum of GERD

These epidemiologic studies have demonstrated a profound male predominance in the prevalence of GERD, including ERD, BE and EAC, irrespective of country, ethnicity and decade. The male to female ratio appears to increase as the disease progresses from ERD to BE and subsequent EAC; in other words, the reported male to female ratio in the prevalence of BE was higher than that of GERD, and the reported male to female ratio in the prevalence of EAC was higher than that of BE^[22,37].

Moreover, these 3 reflux-associated disorders share one common feature: the severity and the prevalence of these diseases appear to be closely related to the reproductive hormone status of women. In the postmenopausal period, the prevalence of the GERD spectrum rapidly increased, whereas it was lower than that in men in the reproductive period, which could be responsible for the increased prevalence of GERDs in younger men than women and for dozen-year delay in the development of BE and EAC in women. Additionally, long-segment BE was more common in men than short-segment BE^[34,44]. Sex hormones in women might prevent the development of IM by reducing ERD, which may be responsible for the difference in the prevalence of BE by definition. Considering the anti-inflammatory function of estrogen and the fact that severe reflux and esophageal inflammation are likely to promote the development of BE and subsequent EAC^[56,57], these epidemiologic findings suggest that exposure to estrogen during the reproductive years may protect women from the progression of esophageal metaplasia to carcinogenesis.

SMOKING AND ALCOHOL

Esophageal malignant neoplasms can be roughly classified into two histological types of cancer, esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EAC), and both types are more common in males than in females^[58]. Tobacco smoking and excessive alcohol consumption are widely recognized as risk factors for ESCC^[59]. Moreover, the male predominance of ESCC is attributed to the higher prevalence of environmental risk factors in men, such as current or past tobacco smoking and the excessive consumption of alcohol^[60]. Similarly, a number of observational studies have identified current or past tobacco smoking as a risk factor for EAC. In patients with BE, current and past smoking history increases the risk for progression to high-grade dysplasia and adenocarcinoma by approximately two-fold^[61]. However, a recent cohort study reported that the male predominance in EAC could not be attributed to differences in smoking histories^[62]. This study demonstrated a similar male predominance of EAC before and after adjusting for smoking (men/women ratio, 95%CI: before 9.9%, 6.5-15.1; after 8.7%, 5.7-13.4). On the other hands, some epidemiological studies showed that the excessive consumption of some types of alcohol, such as liquor, promoted the progression of BE to EAC^[63]. Nevertheless, alcohol consumption has not been associated with the male/female ratio in GERD, BE and EAC.

OBESITY IN THE GERD SPECTRUM

Obesity is an important risk factor for GERD, BE and EAC. Consequently, this condition has garnered increasing attention, particularly because the incidence of these diseases increased in parallel with obesity^[64,65]. To date, no single mechanism that can account for this profound increase has been identified, and the mechanism by which obesity promotes the development of BE and EAC remains unclear. Abdominal obesity has been hypothesized to induce GERD *via* mechanical mechanisms by increasing the abdominal pressure, which subsequently relaxes the lower esophageal sphincter to expose the lower esophagus to gastric acid and increase the risk of GERD and, consequently, BE^[66-68]. Additionally, the contents of the duodenal juice that could reflux into the esophageal lumen may differ in obese individuals. A vagal abnormality associated with obesity may cause a high output of bile and pancreatic enzymes, thus making the refluxate more toxic to the esophageal mucosa^[69].

In general, obesity is often evaluated using a proxy, the body mass index (BMI), and an increased BMI is fairly consistently associated with a higher risk of EAC^[37,70]. However, recent studies have suggested that intra-abdominal or central obesity rather than BMI are more consistently associated with GERD and

BE^[32,71-73]. Another meta-analysis showed a strong relationship between central obesity and EAC after adjusting for BMI^[74]. However, the association between BMI and GERD or BE has been inconsistent between the sexes^[37,64,65]. A case-controlled study conducted in Japan also demonstrated a strong association between BMI and BE in men, whereas these two factors were not associated in women^[75]. Although abdominal obesity has been documented to be a risk for these diseases, independent of BMI, the precise mechanism responsible for the gender difference has yet to be determined. A recent study using the National Health and Nutrition Examination Survey data described that men predominantly display central obesity, which consists of mainly visceral adipose tissue, and this presentation is less common in women^[76]. Abdominal obesity might cause mechanical dysfunction at the gastro-esophageal junction and make the gastro-duodenal reflux contents more harmful, which may partly explain the observed sex disparities in the disease.

Visceral fat is associated with particular metabolic compounds and a different balance of adipose-related hormones, including insulin-like growth factor, tumor necrosis factor α (TNF- α), and interleukin 6 (IL-6), and adipokines, such as leptin, many of which have also been found to be linked to carcinogenesis in other types of cancer^[77,78]. Leptin, an adipokine, is secreted by adipocytes and regulates food intake and energy consumption^[79]. In humans, the serum leptin level closely correlates with body fat mass, and obese people are typically hyperleptinemic, a condition that results from leptin resistance^[79]. In an *in vitro* study, leptin was shown to be mitogenic and angiogenic; it was also shown to induce proliferation in a variety of human cell types, including esophageal cancer cell lines^[80]. A recent case-controlled study revealed that higher concentrations of serum leptin were associated with an increased risk of BE^[81]. In this study, the serum leptin levels positively correlated with the risk of BE in men, but this correlation tended to be negative in women^[81]. Although the general serum leptin level in women is 3- to 4-fold higher than that in men, the incidence of BE is inversely related to the leptin level in women.

CONTRIBUTION OF ESTROGEN TO THE GENDER DIFFERENCE IN THE INCIDENCE OF GERD SPECTRUM

Obesity

Estrogen is reported to be involved in the regulation of metabolism in adipose tissue^[82]. An animal study using mice demonstrated that obesity was induced by reducing the ability to synthesize estrogen and by knocking out the estrogen receptor- α (ER- α)^[83,84]. Additionally, estrogen increases the leptin mRNA levels in adipose tissue, and this deficiency impairs central

leptin sensitivity^[85,86]. Moreover, estrogen was found to influence leptin receptor expression and hypothalamic sensitivity to leptin, thus driving subcutaneous body fat accrual over visceral fat in a rat animal model to result in the inverse relationship between visceral fat and the estrogen level. Eventually, visceral fat accumulation becomes evident when the circulation estrogen levels are sufficiently low in postmenopausal women^[87,88]. Differences in the distribution of body fat between men and women, *i.e.*, the accumulation of visceral fat in men and subcutaneous fat in women, might account for the increased prevalence of some types of GERD-related disorders in men.

The relationship between leptin level and the difference in the prevalence of BE between the sexes is controversial. Although leptin induced the proliferation of ER- α -overexpressing mammary gland cells *in vitro* via signal transducer and activator of transcription 3 (STAT-3), which regulates inflammatory and apoptotic processes, it did not promote the proliferation of ER- α -overexpressing cells. Instead, leptin slightly decreased the proliferation of these cells^[89]. Human esophageal epithelium predominantly expresses ER- α ; thus, the higher concentration of estrogen in women prior to menopause than men might prevent the leptin-induced development of BE and, subsequently, EAC in women although further studies is needed to clarify the precise mechanism^[90].

Immune response

Sex steroid hormones are well known to modulate the immune system in many organs^[91]. Estrogen, a sex steroid hormone, has been reported to exhibit anti-inflammatory activity, such as reducing the migration, adhesion and production or secretion of chemical mediators. In our study, which utilized a rat model of surgically induced reflux esophagitis, we demonstrated that estrogen attenuates reflux esophagitis *via* the inactivation of mast cells, which express estrogen receptors and are ubiquitous in the esophageal epithelium^[100]. This study revealed that female rats were significantly less damaged by reflux esophagitis than male rats, and ovariectomy in female rats diminished the attenuation of esophageal damage. Furthermore, the administration of estrogen to both ovariectomized rats and male rats suppressed reflux esophagitis-induced mucosal injury. We also revealed that estrogen inhibited TNF- α expression by mast cells in the context of reflux esophagitis, which alleviated esophageal damage. The direct impact of estrogen on mast cells is evidenced by the inhibition of cytokine production and the fact that mast cells are primarily involved in the initiation of tissue damage induced by reflux esophagitis^[92,93]. Esophageal mast cells are an integral component of the estrogen-mediated response, which could result in the predominance of GERDs in males. Although this report is the first *in vivo* study to demonstrate the involvement of a sex

hormone in the gender difference *via* the inactivation of inflammatory cells in GERD, other candidate mechanisms implicate sex steroid hormones in the prevention of the stepwise progression from GERD to EAC. Some studies demonstrated that estrogen repressed the monocyte/macrophage system in some pathological conditions involved in the development of postmenopausal disorders^[94-96]. Our study, as described above, also revealed the involvement of tissue macrophage inhibitory factor (MIF) expression in a GERD animal model^[100]. MIF is expressed by various cell types, including esophageal squamous cells, and regulates inflammation and the innate immune response involved in macrophage infiltration and TNF- α production^[97]. We revealed that estrogen significantly suppressed the esophageal MIF level. Because estrogen has been shown to target MIF to enhance cutaneous wound healing *via* the inactivation of macrophages, anti-inflammatory functions related to estrogen might contribute to the gender difference in the incidence of reflux esophagitis^[98,99]. Conversely, other *in vivo* studies revealed that estrogen promoted the pro-inflammatory response in macrophages *via* ER- α ^[100,101]. Interestingly, the cooperation of epidermal ER- α counter-regulator of ER- α and the activation of macrophage ER- α appeared to be required for the effective promotion of cutaneous wound healing^[102].

Similar to macrophages and mast cells, neutrophils and lymphocytes are reported to express various sex steroid receptors, including ERs^[103]. Although these inflammatory cells and their related cytokines are considered to be associated with the epithelial damage caused by harmful refluxate and the development of BE^[104], the precise mechanism responsible for the development of BE or subsequent carcinogenesis has yet to be elucidated^[104-108]. Some experimental models demonstrated that estrogen modulated the activation of neutrophils and lymphocytes *via* ER^[103], whereas others that estrogen inactivated these cells^[109]. Further study is needed to elucidate the mechanisms by which sex steroid hormones affect the GERD spectrum by altering the activity of inflammatory cells.

Epithelial barrier functions

A series of epidemiologic studies demonstrating a male predominance in the incidence of ERD and the subsequent metaplasia-carcinoma sequence have suggested that women are somewhat resistant to esophageal damage. To our knowledge, gender has not been shown to affect esophageal barrier function. In our recent study, estrogen enhanced the esophageal structural resistance to refluxed acid, concomitant with the up-regulated expression in esophageal occludin, a tight junctions protein that plays a crucial role in the esophageal mechanical defense system, which might explain the male predominance of GERDs^[110,111]. A thorough study of the role of estrogen

in enhancing the esophageal resistance and a more detailed understanding of the junctional proteins are needed^[112].

HORMONE REPLACEMENT THERAPY

In this review, we demonstrated that estrogen in females could be responsible for the striking male predominance in the spectrum of GERDs. This potentially protective function might enable us to apply estrogen as a therapeutic agent for GERD patients. A few cohort studies have described that hormone replacement therapy (HRT) use in postmenopausal women was associated with a reduced risk of EAC^[113,114]. Specifically, HRT was reported to reduce the risk of EAC in women by approximately 50%. However, a population-based, retrospective cohort study of men heavily exposed to estrogen revealed that this treatment did not reduce the risk of EAC^[115]. In fact, HRT was associated with an increased risk of GERD. A similar positive association between postmenopausal HRT use and acid reflux symptoms has been reported in population-based studies^[116]. This association between increased GERD risk and taking HRT was erased by examining endoscopic diagnoses for ERD^[113]. These results suggest that HRT is likely to be associated with symptoms of GERD but not with esophageal tissue damage induced by gastric reflux.

In patients with GERD, reflux may result in the direct activation of pain receptors^[117]. Several types of nociceptors have been identified in the esophagus and reported to be involved in the perception of reflux^[118]. One of these pain receptors, the transient receptor potential cation channel subfamily V member 1 (TRPV1), has received particular attention in human GERD patients and is considered a primary receptor in the perception of acid reflux because it is activated by protons and responsive to pH values below 6^[119]. Several studies have found that patients with GERD express higher levels of TRPV1 in their esophageal mucosa than patients without GERD, and distal esophageal TRPV1 expression has been shown to be higher in patients with NERD than in patients with ERD^[120,121]. Despite the lack of evidence concerning the relationship between esophageal TRPV1 expression and sex steroid hormones, estrogen was reported to increase TRPV1 expression and contribute to pain transmission in a recent human study of endometriosis^[122]. Thus, estrogen might contribute to enhance esophageal nociception female GERD patients. These findings might be related to several studies reporting that the incidence of NERD, *i.e.*, symptomatic GERD, is higher in women than in men, whereas the overall prevalence of GERD does not differ between men and women. Therefore, the modulation of the estrogen-related signal pathway may reduce the esophageal inflammation induced by gastric reflux and prevent the development of BE and EAC, but it

may also enhance pain sensitivity to gastric reflux, which might be responsible for the higher incidence of symptomatic GERD in women than in men. Therefore, the simple administration of female sex hormones will not likely be an effective therapy for GERD patients.

CONCLUSION

Taken together, GERDs are significantly more common in men than in women. The dynamics in the prevalence of ERD, BE and EAC closely correlate with the reproductive status of women, which reflects the level of the sex hormone estrogen. This potential effect of estrogen could delay the development of BE and subsequent EAC *via* its anti-inflammatory function and acquisition of epithelial resistance in the esophagus against causative refluxate, which is likely responsible for the sex difference in the GERD spectrum. The identification of the crucial role of the estrogen-related endocrine milieu in GERD could contribute to establishing risk stratification for EAC and an endoscopy-based surveillance program for BE patients, the utility of which has yet to be validated^[123]. Moreover, the elucidation of this mechanism could lead to new therapeutic strategies that might supersede conventional acid-suppressive medications, which have failed to completely prevent the esophageal carcinogenesis caused by GERD.

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