RESEARCH COMMUNICATION

Prevalence and Pathogenesis of Barrett’s Esophagus in Luoyang, China

Ru-Gang Zhang¹,²&, Chang-Song Wang³&, Cun-Fang Gao²

Abstract

Background: Prevalence of Barrett’s esophagus (BE) in Luoyang, China, has not been reported, and its pathogenesis is controversial. The aim of this study was therefore to investigate the prevalence of BE and its underlying factors in the city of Luoyang. Method: This was a prospective study in one center. Many patients were analyzed using endoscopy who showed upper gastrointestinal symptoms between August 2006 and June 2007. In addition, the effect of apoptosis-related proteins and heat shock proteins upon BE’s pathogenesis were also investigated by an immunohistochemical protocol. Results: Prevalence of BE was at 4.55% and the mean age of those affected was about 10 years older than for esophagitis. Typical reflux symptoms were significantly lower than with esophagitis, whereas signs of caspase-3 and HSP105 elevation were significantly higher. Expression of TERT, HSP70 and HSP90α in BE cases was significantly lower than in esophagitis. However, there was no statistical difference between the two groups in expression of HSP27. Conclusions: The prevalence of BE is high in Luoyang, which could result from esophagitis despite typical reflux symptoms being relatively uncommon. Initiation and development of BE might be the result of accelerated proliferation, apoptosis and differentiation of original cells to intestinal epithelium.

Keywords: Barrett’s esophagus - prevalence – pathogenesis - Luoyang, China

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Introduction

Barrett’s esophagus (BE) is a change in the distal esophageal epithelium of any length that can be recognized as columnar type mucosa at endoscope and is confirmed to have intestinal metaplasia (IM) by conducting a biopsy of the tubular esophagus (Wang et al., 2008). BE is a recognized precursor to lesions of esophageal adenocarcinoma (EAC), which is arisen ultimately after progression through a sequence of increasing degrees of dysplasia (Fouad et al., 2009).

The prevalence of BE in patients with gastroesophageal reflux disease (GERD) has been reported to be about 10%-20% in western countries (Modiano et al., 2007), about 0.5-2% in Asia (Kim et al., 2007; Sollano et al., 2007) and 7.3% in Africa (Fouad et al., 2009). The prevalence of BE in patients who have undergone upper endoscopic procedures for any reason was found to be 2.1% in Netherlands (van Kerkhoven et al., 2007) and 2.21%-2.75% in China (Zhang et al., 2001; Wang et al., 2006). Published data on the natural history of BE has been variable, with the prevalence of EAC in BE patients in the range of 5% (Aldulaimi et al., 2005). The prevalence of BE patients with upper gastrointestinal symptoms is not currently known. The aim of this study was to evaluate the rate of BE in patients with upper gastrointestinal symptoms.

Current studies in molecular biology mainly focus on the aberrant change at the chromosomal and molecular level from a normal esophagus to one with EAC. The former includes aneuploidy/tetraploidy and 17p loss of heterozygosity (LOH); the latter includes amplifications of certain proteins such as cyclin D1 and c-erbB2, Mutations in p53 and K-ras, overproduction of enzymes such as COX-2 and Bcl-2, deletion or hypermethylation such as in p16 and RUNX3, low counts of cadherin, abnormal telomere length and telomerase subunit expressions, and aberrant miRNA expressions such as miR-21, miR-194, miR-143, miR-145 and miR-215 have been reported (Gertler et al., 2008; Wang et al., 2008; Burnat et al., 2010; Ciriza-de-los-Rios et al., 2010; Smith et al., 2010; Souza et al., 2010). However, there are limited reports emphasizing on molecular level changes of apoptosis and proliferation during the transition from esophagitis to BE.

Cysteinyl aspartate–specific protease (Caspase), a family of cysteinyl aspartate–specific proteases, is synthesized aszymogens with a prodomain of variable length followed by a large subunit (p20) and a small subunit (p10). Depending on the structure of the prodomain and their function, Caspases are typically divided into three

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major groups, namely; inflammatory caspase (group I), initiator of apoptosis caspase (group II) and effector of apoptosis caspase (group III). Caspase-3 belongs to the group III and plays a pivotal role in apoptosis after being activated (Lavrik et al., 2006). In previous studies, the expression of Caspase-3 has been found to be increased in non-dysplastic epithelium and dysplastic Barrett’s epithelium compared to normal esophageal squamous epithelium (Parenti et al., 2006).

Telomerase is a DNA polymerase depending on RNA. In human cells and tissues, the presence of telomerase activity correlates well with the level of telomerase reverse transcriptase (TERT) gene transcription. TERT plays a crucial role in cellular proliferation, apoptosis, immortalization and aging (Maser et al., 2002). In BE mucosa from patients who had progressed to ECA, TERT promoters was hypermethylated in 92% of those examined, whereas in BE mucosa from patients who had not progressed to ECA, TERT promoter methylation was found only in 17% of examined patients (Clement et al., 2006).

Heat shock proteins (HSP), also called stress proteins, are induced by specific types of stress, including heat, are well conserved from bacteria to man, they also are biomarkers of stress reaction and endogenous protector protein, and function of molecular chaperone and antiapoptosis, are related to tumorigenesis. HSPs are usually divided into five basic groups according to their approximate molecular mass, namely, HSP100, HSP90, HSP70, HSP60 and small HSP. In all HSPs, the content of HSP70 and HSP90 are the richest (Dzaman et al., 2005). The human HSP70 family consists of at least 12 members. One of the best known members is the heat inducible form HSP70/HSP72, which plays an important role in mediating cytoprotective, antiapoptotic, and immune regulatory effects, and has by far been extensively studied (Didelot et al., 2006). The antiapoptotic mechanism of HSP70 may be protective to mitochondria, and apoptosis independent of caspases can also be inhibited by HSP70 (Cande et al., 2002). In previous studies, the expression of HSP70 has been found to increase in normal esophageal squamous epithelium and decrease in Barrett’s epithelium (Ostrowski et al., 2007).

Usually, the human HSP90 family consists of four members, which are cytoplasmic form, HSP90α and HSP90β, endoplasmic reticulum form, gp96, and HSP75/tumor necrosis factor receptor associated protein that is localized to mitochondrias. Apoptosis-inhibition function is their common characteristic. The release of cytochrome c from mitochondria results in the formation of an Apaf-1–caspase-9 apoptosome and induces the apoptotic protease cascade by activation of procaspase-3 (Pandey et al., 2000). The previous studies have demonstrated that HSP90 could form a cytosolic complex with Apaf-1 and thereby inhibits the formation of the active complex, meanwhile, HSP90 could also inhibit cytochrome c-mediated oligomerization of Apaf-1 and thereby activation of procaspase-9. RNA interference of HSP90α results in the increase of impaired DNA in NIH-3T3 cell and the mechanism-based use of Hsp90 inhibitors, both alone and combination with other drugs, will be effective toward multiple forms of cancer (Chen et al., 2006; Neckers, 2007).

The human HSP105 family has a high molecular mass and consists of HSP105α and HSP105β cytoplasmic forms (Ishihara et al., 2003; Doak et al., 2004). In previous studies, HSP105 could show to suppress apoptosis in macrophage and neuronal cell.

The human HSP27, a small heat-shock protein, consisting of functional phosphorylation and constitutive dephosphorylation form, and has an antiapoptotic and cytoprotective action as inhibiting procaspase activation and increasing the intracellular glutathione content. HSP27 is quite active in a normal squamous epithelium of the esophagus and is directly related to the cell differentiation level, however, there are limited reports at present in Barrett’s epithelium and the HSP27 protein (Soldes et al., 1999; Doak et al., 2004; Ostrowski et al., 2007).

Caspase-3, TERT and HSP all play important roles in the maintenance of the normal esophageal squamous epithelium and the pathogenesis of BE. However, there are few reports on Caspase-3, TERT, HSP70 and HSP27, and no report on HSP90 and HSP105 in patients affected by esophagitis and BE. The aim of this investigation was to prospectively evaluate the expressions of Caspase-3, TERT, HSP27, HSP70, HSP90α and HSP105 in patients with esophagitis and BE.

Materials and Methods

Clinical data and Methods

Patient Population: A cohort of consecutive patients with upper gastrointestinal symptoms from the Luoyang area in China was investigated in a standardized manner using an Olympus CV-70 endoscope (Shinjuku-ku, Tokyo, Japan) between August 2006 and June 2007. Their age, gender, symptoms, endoscopic and pathological results were all respectively registered. The upper gastrointestinal symptoms include typical and atypical reflux symptoms. The former includes sour regurgitation, heartburn and retrosternal pain, and the latter had such symptoms as upper abdominal pain, abdominal distension.

Diagnosis standard of BE and esophagitis: BE is defined by a distal esophageal epithelium is recognized as columnar type mucosa using endoscopy and is confirmed to have IM by biopsy, however, esophagitis is diagnosed when the distal esophageal epithelium is recognized as having columnar type mucosa and is finally confirmed to have metaplasia by the cardiac gland or fundus gland by performing a biopsy (Wang et al., 2008). The presence and extent of Barrett’s epithelium were diagnosed based on the Prague C & M Criteria. The length of Barrett’s epithelium is measured using the circumferential extent (C value) and the maximum extent (M value) above anatomic gastroesophageal junction (GEJ) in centimeters (Sharma et al., 2006). The definition of long-segment BE includes the presence of more than 3 cm of columnar mucosa with intestinal metaplasia extending proximally from GEJ. Segments of columnar epithelium with IM < 3 cm long refers to as short-segment BE. Short-segment Barrett’s esophagus (SSBE) and long-segment Barrett’s esophagus (LSBE) are distinguished solely by the length
of the metaplastic columnar-lined esophagus (Jones et al., 2002).

Biopsy Protocol: During upper endoscopic procedure, anatomic landmarks were carefully defined including the GEJ. The appearance of the squamocolumnar junction (SCJ) was carefully evaluated, noted, and recorded. Biopsies were obtained from columnar mucosa above the GEJ and within the tubular esophagus. All biopsy specimens were obtained using standard biopsy forceps by the turn-and-suction method to maximize the biopsy size. The biopsy protocol included obtaining four-quadrant biopsies every 2 cm from the circumferential range appearing around Barrett’s epithelium in the distal esophagus. Patients with small or irregular tongues of columnar mucosa had two biopsies per tongue and one per patch in the distal esophagus. There were no medical and endoscopic treatments before biopptic samples were taken. Patients signed an informed consent for the study that was reviewed by the Institutional Review Board.

Histopathologic Analysis: All biopsy specimens were fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin (H&E). The diagnosis of BE was confirmed by the presence of goblet cells in the biopsies obtained from the columnar appearing cells of the distal esophagus which were indicative of IM. Two expert pathologists reviewed all biopsy specimens with no prior knowledge of the clinical history of the patients involved.

Experimental Materials and Methods

Immunohistochemical Reagent: Rabbit Anti-Caspase-3 (BA0588), Rabbit Anti-TERT (BA0564), Rabbit Anti-HSP27 (BA0361), Rabbit Anti-HSP70 (BA0928), Rabbit Anti-HSP90α (BA0369) and Rabbit Anti-HSP105 (BA0391) were all rabbit polyclonal antibodies, and purchased from Wuhan Boster Biological Technology, LTD. in China. The Polymer Detection System for Immuno-Histological Staining (PV-6000 kit) was purchased from Beijing zbio Biological Technology, LTD. in China.

Immunohistochemical Protocol: All parts of the samples were dewaxed in xylene then rehydrated through a sequence of decreasing the concentration of the alcoholic solutions. After three washes using PBS (pH 7.4), the sections were then microwaved-pretreated in a 10 mmol/L citrate buffer (pH 6.0) for antigen retrieval (three cycles of 5 minutes each at 650 W). Endogenous peroxidase activity was quenched by 0.5 % hydrogen peroxide incubation for 30 min at room temperature. After three washes in PBS (pH 7.4), sections were incubated with primary antibodies according to the same incubation conditions, namely, incubated overnight at 4 °C and 2 h at room temperature, with no dilution. After three washes in PBS (pH 7.4), the sections were then incubated with the Polymer Detection System for Immuno-Histological Staining and then washed two more times in PBS (pH 7.4). The immunoreactivity was revealed using diaminobenzidine (DAB) as the final chromogen. Finally, sections were counterstained with Meyer’s hematoxylin, dehydrated through a sequence of increasing the concentration of the alcohol solutions, cleared (the previous solution was cleared away using xylene and added to with a epoxydic medium (Doak et al., 2004). During each immunohistochemical assay, proof slides were coupled with negative control slides on which the primary antibody was omitted.

Immunohistochemical Analysis: Slides were evaluated by two experienced pathologists, who assessed both the percentages of positive metaplastic cells (< 35%, 35~70% and >70% represent 1, 2 and 3 score respectively) and staining intensity (no, low, medium and high intensity represent 0, 1, 2 and 3 score respectively). Each case was scored according to the formula: IS (index of staining) = i×Pi. Where “i” stands for staining intensity (ranging from 0 to 3 score) and Pi is the percentage of positive cells (ranging from 1 to 3 score). If there is a score of 0 ≤ IS < 2 , the result would be negative (-) and if the outcome is IS ≥ 3, the result is positive (+). Discrepancies in the evaluation were resolved by conjoined re-observation of the cases through a multi-headed microscope.

Data choice

The hiatal hernia and mucosal damage (stenosis and ulceration) were excluded in our clinical analysis. The hiatal hernia, mucosal damage (stenosis and ulceration), Barrett’s dysplasia, and Barrett’s-associated EAC were all excluded in our immunohistochemical analysis.

Data Analysis

For data analysis, the SPSS statistical software package (SPSS Inc.16.0.2, Chicago, Illinois, USA) was used. For descriptive statistics, mean (±SD) was used for normal distributions. T Test was used to compare the IM length or age between the SSBE and LSBE groups. Chi-Square Tests were used to compare chief complaints, and expressions of apoptosis-related proteins and HSP between the two groups. Spearman’s tests were used to compare the correlations of between the apoptosis-related protein and HSP of the two groups. Differences were considered significant when they read as P ≤ 0.05.

Results

Prevalence of BE

A total of 593 consecutive patients (339 men and 254 women) were investigated during a one-year period, and a ratio of male and female was at 1:33. Of the 593 patients, 65 cases were identified with columnar mucosa in the distal esophagus. All of the 27 cases (15 men and 12 women) were diagnosed as contracting BE by using biopsies, and male: female ratios were at 1:25. The mean age was at 59.7±10.8 years. Patients over 60 years of age were 18.18% of the participants in this study. All of the 38 patients (22 men and 16 women) who were diagnosed as having esophagitis by biopsies, the ratio IM length or age between the SSBE and LSBE groups.
Table 1. Chief Complaints of BE and Esophagitis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>BE</th>
<th>esophagitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regurgitation</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Heartburn</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Retrosternal Pain</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Upper Abdominal Pain</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Others</td>
<td>8</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 2. χ²-test of Immunohistochemical Results from Caspase-3 and TERT

<table>
<thead>
<tr>
<th></th>
<th>Caspase-3</th>
<th>TERT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR (%)</td>
<td>NR (%)</td>
<td>PR (%)</td>
</tr>
<tr>
<td>BE</td>
<td>95.45</td>
<td>4.550</td>
</tr>
<tr>
<td>esophagitis</td>
<td>68.42</td>
<td>31.58</td>
</tr>
<tr>
<td>χ²=19.73, P=0.000</td>
<td>χ²=16.46, P=0.000</td>
<td></td>
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</tbody>
</table>

PR, positive rate; NR, negative rate

Type of BE at endoscope

According to the Prague C & M Criteria, BE is divided into two types, namely SSBE and LSBE. The former was found in 81.48% of the participants (22/27) and the average length of the IM epithelium was at 2.861±0.0204 cm; the latter was prevalent in 18.52% (5/27) of the participants and average length of the IM epithelium was at 4.500±1.000cm. The average length of the SSBE was noticeably less than that of the LSBE’s length (t=3.178, P=0.005). There were no statistically significant differences in the ages of those affected between the two groups (t=0.196, P=0.847) because the average age of those with SSBE was reported at 59.94±10.72 years and the average age of those affected with LSBE was at 58.75±12.71 years old (Figure 2).

Chief complaints of BE

Chief complaints of those affected with BE included sour regurgitation, heartburn, retrosternal pain, upper abdominal pain and abdominal distension. Upper abdominal pain, sour regurgitation and heartburn were common symptoms amongst BE patients, however, only 9 cases (33.33%) had shown typical reflux symptoms. Sour regurgitation, heartburn and retrosternal pain were usual symptoms in esophagitis patients, but 31 cases (81.58%) had the typical reflux symptoms (Table 1). The typical reflux symptoms of BE patients were significantly lower than those with esophagitis (χ²= 50.00, P=0.000).

IM, dysplasia and adenocarcinoma of BE

In all of the 27 BE patients studied, 3 cases (11.11%) had low grade dysplasia (LGD), 1 case (3.70%) had high grade dysplasia (HGD) and 1 case (3.70%) had BE adenocarcinoma (Figure 3). The mean age of non-dysplastic BE patients was at 59.24±9.654 years old, and the mean age of patients who had dysplasia and adenocarcinoma was at 61.40±15.31 years old. Although the number of non-dysplastic BE patients were more than dysplasia and adenocarcinoma’s, there were no significant differences in ages amongst the participants (t=-0.386, P=0.703). Our results also showed that 5 patients who had dysplasia and adenocarcinoma were all SSBE. Meanwhile, we also found that IM of BE epithelium was patchy within the columnar epithelium and was always surrounded by cardiac-type mucosa. Moreover, the dysplasia of BE epithelium was usually multicentric.

Immunohistochemical Results of Caspase-3 and TERT

Immunohistochemical staining results of Caspase-3 and TERT in the sampled BE and esophagitis tissues are

![Image of Table 1](image1)

![Image of Table 2](image2)

![Image of Figure 1](image3)

![Image of Figure 2](image4)

![Image of Figure 3](image5)

![Image of Figure 4](image6)
Prevalence and Pathogenesis of Barrett’s Esophagus in Luoyang

Table 3. \( \chi^2 \)-test of Immunohistochemical Results from HSP27, HSP70, HSP90\( \alpha \) and HSP105

<table>
<thead>
<tr>
<th>Protein</th>
<th>PR (%)</th>
<th>NR (%)</th>
<th>PR (%)</th>
<th>NR (%)</th>
<th>PR (%)</th>
<th>NR (%)</th>
<th>PR (%)</th>
<th>NR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSP27</td>
<td>77.27</td>
<td>22.73</td>
<td>31.82</td>
<td>68.12</td>
<td>9.091</td>
<td>90.91</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>HSP70</td>
<td>50.00</td>
<td>50.00</td>
<td>47.37</td>
<td>52.63</td>
<td>42.11</td>
<td>57.89</td>
<td>63.16</td>
<td>36.84</td>
</tr>
<tr>
<td>HSP90( \alpha )</td>
<td>( \chi^2=1.727, P=0.422 )</td>
<td>( \chi^2=13.73, P=0.001 )</td>
<td>( \chi^2=14.73, P=0.000 )</td>
<td>( \chi^2=14.73, P=0.000 )</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HSP105</td>
<td></td>
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Table 4. Spearman’s Test of Immunohistochemical Results from Poptosis-related Protein and HSP

<table>
<thead>
<tr>
<th>Protein</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspase-3</td>
<td>-1</td>
<td>0.000</td>
</tr>
<tr>
<td>TERT</td>
<td>+1</td>
<td>0.000</td>
</tr>
<tr>
<td>HSP70</td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>HSP90( \alpha )</td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>HSP70</td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>HSP105</td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>HSP90( \alpha )</td>
<td></td>
<td>0.000</td>
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<tr>
<td>HSP105</td>
<td></td>
<td>0.000</td>
</tr>
</tbody>
</table>

Correlative Analysis of Caspase-3, TERT, HSP70, HSP90\( \alpha \) and HSP105

In conducting a Correlative analysis of (the proteins) Caspase-3, TERT, HSP70, HSP90\( \alpha \) and HSP105 the rates results are shown in Table 4. In patients with BE, the expression of HSP70 was strongly positively correlated with that of HSP90\( \alpha \) (r=+1, P=0.000), and the rates of Caspase-3 and TERT, HSP70 and HSP105, HSP90\( \alpha \) and HSP105 were all strongly inversely correlated with each other (r=-1, P=0.000).

Discussion

In Luoyang, the prevalence of BE amongst the population was 4.553% in all patients checked who had shown upper gastrointestinal symptoms. The numbers were higher than the prevalence of BE in other areas in China (2.21%-2.75%) (Zhang et al., 2001; Wang et al., 2006), however the numbers are lower than Western countries (10%-20%) (Modiano et al., 2007). The difference passably relates to increased awareness and recognition of BE, or a sharp increase due to improvement of living standard. In addition, the difference of dietary habits, geographical factors and race should also be considered when making a conclusion about the causes of BE. Because the incidence of BE was 41.54% in the patients checked with upper gastrointestinal symptoms and with columnar mucosa in the distal esophagus during our investigation, it should be considered to make a biopsy in the columnar mucosa of the distal esophagus.

Partial esophagitis could transform into BE because the average age of BE patient’s were older than esophagitis patients of about 10 years. Though the number of non-dysplastic BE patients were more than the dysplasia and adenocarcinoma’s, their average age did not show any significant differences. These data suggest that the progenitor cells from the basal...
layer of esophageal epithelium (Sawhney et al., 1996) may directly differentiate typical intestinal epithelium or intestinal epithelium accompanied by dysplasia according to the genetic background of an original cell and microenvironment of the cellular differentiation. Our view is not different from the current view which says BE dysplasia may result from the intestinal epithelium of BE (Casson et al., 2005; AI 2009). Thus, it will be more important to find dysplasia in a patient than trying to a goblet cell in a BE epithelium.

Although the mean length of an IM epithelium in a SSBE sample was markedly less than LSBE', the number of SSBE patients were more than LSBE in our data; moreover, all BE patients who had complications with dysplasia and adenocarcinoma were found to have SSBE. It suggests that SSBE has a higher risk factor and more attention needs to be given to this phenomenon which was shown in our clinical work.

Our investigations show that the number of BE patients who had typical reflux symptoms were markedly less than those who had esophagitis. The data does not coincide with the major data at present (AI 2009), and the difference is not clear yet. It suggests that other factors should be also considered besides reflux esophagitis in the beginning stages and development of BE. It will be worth studying further.

Our clinical investigation showed that the prevalence of BE was high, and it might be of some concern to pay attention to the patients' morbid diet and race. BE could result from esophagitis, however, its typical reflux symptom was seldom seen in patients. BE accompanied with dysplasia might be related to the genetic background of an original cell and the microenvironment of cellular differentiation. We should pay more attention to SSBE in our clinic work.

The positive rate of Caspase-3 was 95.45% in BE patients in our study. In previous studies the expression of this apoptotic factor was increased in non-dysplastic and dysplastic Barrett’s epithelium compared to normal squamous epithelium, which agreed with the results of our study (Dzaman et al., 2005). Caspase-3 increased rates in our Barrett’s cases compared to esophagitis shows the tendency of apoptotic increase in BE’s mucosa. Our results suggest that intestinal type epithelium of BE owns a feature of spontaneous apoptosis, and also suggest that the original cell of the BE specimen has the tendency of accelerated proliferation and differentiation for the integrality of esophageal epithelium.

Our investigations showed that the Barrett’s cases had lower TERT rates than esophagitis, which was similar to previous data (Clement et al., 2006). It suggests that the reproductive activity of Barrett’s epithelium is lower than the esophagitis, and also shows that it is consistent with higher apoptosis caused by increased rates of Caspase-3 in our studies.

In previous studies, the expression of HSP70 was increased in normal esophageal squamous epithelium and decreased in Barrett’s epithelium (Ostrowski et al., 2007). Our results found that the expressions of HSP70 and HSP90α were all decreased when compared with BE epithelium to esophagitis. It’s worth noting, that it might be the first time that HSP90α expression in BE has been studied. It suggests that Barrett’s epithelium owns a feature of spontaneous apoptosis and tendency of cellular DNA instability (Chen et al., 2006; Neckers 2007). However, the expression of HSP105 was increased when comparing BE epithelium to esophagitis rates in our investigations. It suggests that Barrett’s epithelium has a highly cytoprotective function for the first time. Based on the results of H&E staining in our biopsies and the data published (Paull et al., 1976), differences of HSP70, HSP90α and HSP105 expressions suggests that proliferation and apoptosis of Barrett’s epithelium may be regional and heterogeneous, and the end-result could come from their comprehensive effects.

HSP27 has an abundant expression in normal squamous epithelium of the esophagus and isn’t so proliferate in Barrett’s epithelium (Soldes et al., 1999; Doak et al., 2004; Ostrowski et al., 2007). However, there is no statistical difference between BE epithelium and esophagitis in our study. The deviation may attribute to the different biopsy position of the endoscopy, because BE IM is patchy within columnar epithelium (Jones et al., 2002), or is always the most proximal squamous epithelium (AI 2009). Therefore, the difference needs further investigation.

Our immunohistochemical results showed the high rates of expression of Caspase-3 and HSP105, and low expression rates of TERT, HSP70 and HSP90α. Our presumption is that the BE epithelium might have two tendencies of apoptosis and proliferation, and the tendency of apoptosis might be major for under expression of TERT, HSP70 and HSP90α, and over expression of Caspase-3. The initiation and development of BE might be the result of accelerated proliferation and differentiation of the original cells at the basal layer of esophageal epithelium to intestinal epithelium during excessive apoptosis of normal esophageal epithelium (Glickman et al., 2001; Sarosi et al., 2008). If the original cells accelerated their proliferation and differentiation acquires dysplastic characteristics, esophageal adenocarcinoma might occur during this condition.

Our conclusions were that the prevalence of BE was high in Luoyang, and BE could come from esophagitis, its typical reflux symptom was seldom, BE accompanied dysplasia might be related to the genetic background of the original cells and microenvironment of cellular differentiation, BE epithelium might have the two tendencies of apoptosis and proliferation and the tendency of apoptosis might be major, the initiation and development of BE might be the result of an accelerated proliferation and differentiation of the original cells at the basal layer of esophageal epithelium to intestinal epithelium, and esophageal adenocarcinoma might occur if the original cells accelerated proliferation and differentiation acquire dysplastic characteristics.

Limitations of this study include; the small number of patients with upper gastrointestinal symptoms, which prohibit drawing firm conclusions on prevalence, endoscopic and pathological characterizations in Luoyang. In addition, the small number of patients with BE also prohibit drawing firm conclusions on pathogenesis of
BE. Prospective multicenter trials are required to assess whether our promising results are translatable to a wider and larger patient population, and to pathogenesis of BE.

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**References**


