Reflections on the New Classification of Tumors by the WHO and Changes in Esophageal Cancer in a High-risk Area

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ABSTRACT In year 2000, a book entitled the Pathology and Genetics of Tumors of the Digestive System was published by the WHO, presenting some new diagnostic criteria and treatment principles. I have analyzed the epidemiologic change of tumors in over 30 years in the high-risk area with esophageal cancer. The following phenomenon was found: accompanied by the sharp decrease in the incidence and mortality of esophageal cancer, there was an increase in the incidence and death rate of stomach cancer involving cardiac cancer. This fact should be considered when analyzing the sharp decrease in esophageal cancer incidence and mortality rate. More attention was given to diagnosis of cardiac cancer; at the same time it is more practical to improve the early screening of cancers. To observe the development of high and low-grade intraepithelial neoplasms will be an urgent task for esophageal cancer research in the high risk area, according to WHO's new classification.

KEYWORDS: WHO, tumor, new classification, epidemiology, esophageal cancer, the high-risk area.

Deaths caused by esophageal cancer rank fourth among the deaths caused by malignant tumors in China. The WHO published a book entitled *The Pathology and Genetics of Tumours of the Digestive System* (briefly: WHO New Book),[1] in which international studies of pathology and genetics over recent years are summarized. In addition, it presented some new diagnostic criteria and special points of view that are meaningful for the studies of epidemiology of Chinese esophageal cancer in high-risk areas. Therefore, this information combined with the status of esophageal cancer in a high-risk area in China is discussed in this article.

The Changes in the Incidence and Deaths Caused by Esophageal and Stomach Cancers

From 1959 to 1987, the incidence of esophageal cancer in Lin County (Henan Province) was 129.8/100,000 in males and 102.7/100,000 in females [2] and from 1988 to 1992, 92.7/100,000 in males and 76.2/100,000 in females. Then from 1993 to 1997, the numbers were 81.2/100,000 and 61.8/100,000.[3,4] In contrast, the incidence of esophageal cancer in Ci County (Hebei Province, adjoining Lin County) decreased from 202.9/100,000 in males and 128.1/100, 000 in females in 1974 to 126.9/100,000 and 97.7/100,000, respectively in 1996.[5]

The death rate of esophageal cancer in Lin County (Henan Province) was 113.7/100,000, in 1984 and 55.3/100,000 in 2002, showing that it fell 51.4% in nearly 20 years. In contrast, the death

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rate of esophageal cancer in Ci Xian County (Hebei Province) was 116.77/100,000 in 1984 and 67.18/100,000 in 2002,[6] a decrease of 42.2% in nearly 20 years.[7] Generally, the reasons for esophageal squamous cell carcinoma are closely related to smoking, drinking alcohol and chronic esophageal inflammation. According to the analysis of 3 years (1985, 1991 and 1997) in the high- risk area,[8] a particular trend was found. The rates for tumor family inheritance in the high-risk areas were 35.0%, 35.8% and 32.2% respectively; those for smokers were 65.3%, 78.3% and 59.4% respectively; those for people who drink alcohol were 2.2%, 22.0% and 15.4%. Obviously, in these 3 periods, apart from the rate of alcohol drinking which was very low in 1985, the other risks don't appear to change over these periods. Further meta-analysis of esophageal cancer incidence over the past 5 years indicates that of the 5 contributing factors (tumor family inheritance, drinking alcohol, smoking, loving-hot food, eating spoiled food), the odds ratio (OR) was the highest, OR=2.45, 95%CI (1.66~3.62) for tumor family inheritance.[9]

From a geographic analysis, based on the data from Henan Province from 1984~2002, the death rate of esophageal cancer in mountainous areas was 3 times higher compared to a plain area. Similarly, the incidence rate of esophageal cancer in a mountainous area in Ci Xian county Hebei Province was 10% higher than that of plain area in the 1970s and 1980s.[6] But in the 1990s the incidence rate of esophageal cancer in a mountainous area was 80.5/100,000 while that of a plain area was 127.4/100,000. That is to say, the incidence rate of esophageal cancer in the mountainous area was lower than that of the plain area by 36.8%.[5] In a word, the sharp decrease of the incidence and death rate of esophageal cancer that occurred in these 2 most representative high-risk areas are worthy of further epidemiologic studies.

The incidence rate of stomach cancer in Lin County (Henan Province) was 91.5/100,000 in males and 54.9/100,000 in females during the period from 1988 to 1992. But during the period from 1993 to 1997, the respective numbers were 82.4/100,000 in males, and 44.0/100,000 in females. The male incidence rate of esophageal cancer was 81.2/100,000 at that time. This indicates that the incidence rate of stomach cancer was higher than that of esophageal cancer in the high-risk area for esophageal cancer.[3,4] In Ci County (Hebei Province), the incidence rate of stomach cancer was 50.1/100,000 in males, and 55.9/100,000 in females and 25.7/100,000 and 28.0/100,000 in these 2 respective periods.[3,4]

The death rate of stomach cancer in Lin County (Henan Province) was 73.4/100,000 in males and 45.0/100,000 in females during the period 1988~1992 and 63.6/100,000 and 37.0/100,000 respectively during the period 1993~1997.[3,4] The death rate of stomach cancer in Ci Xian County (Hebei Province) was 40.6/100,000 in males and 19.3/100,000 in females during the period 1988~1992 and 40.3/100,000 and 20.2/100,000 respectively during the period 1993~1997.[3,4] The epidemiologic analyses of esophageal cancer in the high-risk area produces the same phenomenon: accompanied by the sharp decrease in the incidence and death rates of esophageal cancer, there was an increase in the incidence and death rates of stomach cancer.

Changes in the Examination and Definition of Precancerous Lesions

The methods used in screening for esophageal cancers in high-risk areas during the 1970s and the beginning of the 1990s mainly relied on using the exfoliative ballon cytological (EBC) procedure. In the esophageal cancerous screening, esophageal epithelial dysplasia is regarded as a precancerous lesion, consisting of stage one severe dysplasia (SD I), and stage two dysplasia (SD II). The prevalence rates of esophageal epithelial dysplasia in the 40~65 year old group in the high-risk area were 20%~25%, (SD II 5%~7%). According to a retrospective study, the natural carcinomatous conversion rate of esophageal epithelial dysplasia within 5 years, was 12.59% and 23.09% for SD II.[10] Using the cytological normal group as 1.00 and the criteria compared to the natural carcinomatous conversion within 15 years,[11] we found SD I RR=1.53 (1.10~2.04) and the SD II RR=1.89 (1.47~2.41). Considering the incidence and cost-benefit ratio for prevention, the rate of esophageal epithelial dysplasia according to the present-day cytological criteria is high.

After the 1990s, EBC was replaced by endoscopic screening based on 1978 WHO criteria. In this analysis, precancerous lesions of the digestive system epithelium were called dysplasia and classified into 3 types: mild, moderate and severe. Using endoscopic screening of residents who lived in Lin County (Henan Province) as a sample, Dawsey et al.[12] randomly interviewed 682 people whose course of disease had been 3.5 years. The relative risk (RR) and 95% confidence interval (CI) of those with mild, moderate and severe dysplasia were 2.2 (0.70~7.50), 15.8 (5.9~42.2) and 72.6 (29.8~176.9) respectively. According to a prospective study 158 untreated patients with severe

dysplasia of the esophageal squamous epithelium (the course of disease was followed-up for 117 months), two results were found.[13] The first was that the cumulative rate of carcinomatous conversion accounted for 81.7%. The second was that in the first year deaths were only 1.3%, but increased to 10.2% in the sixth year. After that they sharply decreased.

Here it must be stated that the final event to those precancerous lesion samples was cancer or death. Previous esophageal cancer studies showed that 67.0% of the patients were in a state of relative stabilization over five years.[14] In other words, among the population screened there was a precancerous period prior to the time of diagnosis. Therefore, the advanced patients who were followed-up in this period must have had a carcinomatous conversion before the diagnosis of their precancerous lesion. On the other hand, the evaluation of the relative risk of carcerous conversion lacked a yearly trend analysis. Combined with the present study of the natural history of earely esophageal cancer, the diagnosis of precancerous lesions whether diagnosed by cytology or pathology, if carcinomatous conversion is observed in a five-year period, it should be reconsidered whether there was a false negative diagnosis.

The New-classification by WHO and Cardia Carcinoma

The traditional concept of cardia adenocarcinoma is that it occurs under the zigzag line by about 2 cm. In the WHO new book, cardia adenocarcinoma is called adenocarcinoma of the esophagogastric junction (OGJ) .The book presents 3 points for its definition: 1) a tumor which develops on both sides of the zigzag line is termed a OGJ tumor; 2) those adenocarcinomas that occur above the zigzag line are called esophageal adenocarcinomas; 3) those occurring under the zigzag line are termed stomach cancer. In a single chapter of the new book, the definition, epidemiology, diagnostic criteria and pathological features and precancerous lesions of OGJ tumors are described. Because of the similarity of clinical manifestations of esophageal cancer and cardia cancer, cardia cancer is included in the statistics of esophageal cancer. In the second half of the 1980s, according to the international disease classification principle, cardia cancer is classified as stomach cancer. Based on the statistics of cancer registration, clinical data and endoscopic screenings in the high-risk area, [15-18] 25% ~40% of esophageal-cardia cancer was cardia cancer. The number of patients with squamous carcinoma was slightly more than those with adenocarcinoma.[19] According to an epidemiology investigation in She County (Hebei Province, adjoining to Henan Province), the male incidence of cardia cancer was 69.9/100,000 and that of stomach cancer was 90.9/100,000 while that of esophageal cancer was 97.2/100,000. The female incidence of cardia cancer was 41.5/100,000 and that of stomach cancer was 44.8/100,000 while that of esophageal cancer was 51.8/100,000.[20] Those high rate areas are located in an under-developed rural area, which has a high cancer risk and a low level of medical care. The gastroscope, which greatly improved diagnosing of esophageal and cardia cancer, was widely applied in these areas only after the 1990s. This fact should be considered when analyzing the sharp decrease in esophageal cancer incidence and mortality rates.

Reflections

There are 2 important problems to be solved in the general screening and surveillance in an esophageal cancer high-risk area: cost-benefit ratio and patient compliance. From a diachronic point of view, the screening methods applied in a high-risk area are mainly EBC screening plus X-rays, EBC screening combined with endoscopic confirmation, and endoscopic screening. It should be recognized that endoscopic and pathological criteria are the main procedures used internationally, especially endoscopic examinations are an advanced technology for the diagnosis of esophageal and stomach cancers. Based on the status in China, it is impractical to completely use endoscopic screening for a large number of people. It should be noticed that for its emphasis on quantity and disregard for quality control previously, EBC screening for a large number of people could be responsible for its low-sensitivity and high false negatives. With that outlook, the systematic evaluation of EBC screening has not received enough attention from academicians and requires further discussion. Actually, the studies and application of EBC screening can be traced back more than forty years and is more advanced than the other diagnostic means. Based on the benefit ratio of screenings analysis, EBC screening is suitable for the economic development of present day China. Before the utilization of more sensitive and more acceptable diagnostic technology, it is more practical to improve EBC screening. At the same time, according to the present cytological diagnostic criteria, the definition of precancerous lesions should be focused on SD II.

In the WHO new book, dysplasia is called intraepithelial neoplasia or adenoma, which is further divided

into high-grade and low-grade based on the agreement of international pathologists. High-grade intraepithelial neoplasia (HIN) consists of severe dysplasia, carcinoma in situ, mucous membrane cancer of the esophagus and severe dysplasia of the cardia epithelium. Its clinical treatment principle is operation by endoscopy, or by surgery. Low-grade intraepithelial neoplasia (LIN) includes mild and middle dysplasia of the esophagus, and mild dysplasia of cardia epithelium, and its clinic treatment principle is follow-up or endoscopic excision. Using this two grade classification criteria advocated by the WHO, in the entire sampling of the high-risk area, the prevalence rate of esophageal HIN was 5.3% and that of the cardia was 1.0%; the prevalence rate of LIN was 16.3% and 2.7% respectively.[18,21] But the epidemiologic evidence of LIN is not clear and therefore should become the focus of screening. The phenomenon of high incidence of cardia cancer in traditionally high incidence areas of esophageal cancer indicates the need to study the change of cardia epithelium LIN into cancer. In consideration of the present recognition of HIN and the status of esophageal cancer in the high-risk area, the clinical treatment principles raised by WHO will remarkably reduce the death rate and improve the cost- benefit ratio.

Including the international study of OGJ tumors, the WHO new book indicates that the cause of OGJ tumors is closely related to esophageal-reflux, with the order of pathological changes being: chronic reflux esophagitis → intestinal metaplasia → dysplasia → adenocarcinoma. At the same time, the WHO new book indicates the difference of stomach cancer, as there is no obvious association between OJG cancer and *heicobacter pylori* infection. Therefore, for early diagnosis and treatment and etiological study in the high-risk area in the future, both with different tumor biological features, esophageal squamous carcinoma and OGJ tumors should be considered. Furthermore, with the increase of international scholarly exchange, we should use the new diagnostic criteria of the WHO to analyze the epidemiologic situation of OGJ cancer samples of esophageal cancer in the high-risk areas of China. Last but not the least, the stable residents and high-compliance to participate in trials in a high-risk area is a potential ideal source for medical studies. But with the development of the economy and increased population mobility, this opportunity is gradually disappearing. So, the collection of the heredity history of tumor families in a high-risk areas demands immediate attention.

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