

Over half a century of research on esophageal cancer in Linxian, the highest incidence area in Henan Province, northern China

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In 1957, Mr. Yang Gui, then the Secretary of the Linxian County Party Committee in Henan Province, spoke at the National Mountain Work Conference in Beijing, pointing out that the major hardships faced by the people of Linxian included a lack of access to water, woeful road conditions, and a high prevalence of esophageal cancer. This speech was reviewed as a conference briefing by the esteemed Premier Zhou Enlai, who immediately instructed officials to investigate the situation and develop appropriate countermeasures.

In 1959, the Henan Provincial Committee and the Provincial Government appointed teaching, scientific research and medical personnel from many medical institutions in Henan Province, including Henan Medical College, to form Henan Provincial Medical Team (Henan Esophageal Cancer Prevention and Treatment Research Cooperation Group), which was stationed in Linxian County (now renamed Linzhou City) to carry out field research on the prevention and treatment of esophageal cancer. Over the past 65 years (1959 – 2024), leveraging the high-incidence field research base in Linxian, several generations of esophageal cancer researchers in Henan have carried out interdisciplinary studies from basic science to clinical applications. Their work has focused on the risk factors, pathogenesis, prevention and treatment of esophageal cancer, yielding a series of original research findings and extensive experience in the prevention and treatment of esophageal cancer in the high incidence areas^[1, 2]. This review highlights the research progress made by three generations of Henan scholars, including Shen

Qiong, Qiu Song Liang, Wang Li Dong, Gao She Gan, Zhou Fu You, Li Xue Min, and Qin Yan Ru, who have dedicated 65 years to advancing the prevention, treatment, and molecular mechanism research of esophageal cancer in high-risk areas of esophageal cancer. This article commemorates the 65th anniversary (1959 – 2024) of the establishment of the high-incidence areas research base for the prevention and treatment of esophageal cancer in Linxian, Henan Province.

1 Review on the history of esophageal cancer field-study and molecular mechanisms in Linxian County (now Linzhou City), Henan Province

1.1 Unique incidence pattern of esophageal cancer in Linxian

Henan Province is one of the high-incidence areas of esophageal cancer in China, with the high-incidence areas (incidence rate > 60/100 000) having a population of over 43.71 million, accounting for 41% of the total population of the province, distributed in 11 cities and covering an area of over 90 000 square kilometers, with the high-incidence area accounting for 92.237 square kilometers, which is 55% of the total area of the province^[3, 4]. The Taihang Mountains area where Henan, Hebei and Shanxi three provinces meet, especially Linxian, Anyang and Hui County in Henan Prov-

ince, are the areas with the highest incidence and mortality rates of esophageal cancer in China and the world. With Linxian as the center of highest incidence in Henan Province, the rate of esophageal cancer decreased significantly with increasing distance. For example, in Fanxian, Henan Province, located approximately 200 kilometers from Linxian, the incidence rate drops from 160/100 000 in Linxian to about 25/100 000^[5]. This distinct incidence pattern in the high incidence area of esophageal cancer in Linxian suggests that environmental and genetic factors play an important role in the development of esophageal cancer^[6], drawing attention of national leaders and scholars^[7].

1.2 Medical team in Henan Province

In November 1957, Comrade Yang Gui, the secretary of the Committee of Linxian, reported the problems of “three impassability” in Linxian (water, road and esophagus impassability) at the National Mountain Production Symposium. Yang Gui’s speech was included in the briefing of the meeting, which aroused the great concern of Premier Zhou Enlai, and appointed the comrades of The General Office of the State Council to find out the situation, and instructed “Understand the situation and devise the countermeasures”^[7]. In November 1959, Henan provincial government appointed Henan Medical College (founded in 1928 in Kaifeng, it was independently established in 1952, called Henan Medical College, moved from Kaifeng to Zhengzhou in 1958, it was renamed Henan Medical University in 1984, and merged with Zhengzhou University and Zhengzhou University of Technology in 2000. It was renamed as Medical College of Zhengzhou University in 1984. The teaching, scientific and medical personnel from Henan College of Traditional Chinese Medicine, Henan Provincial People’s Hospital and Anyang District Hospital organized the Esophageal Cancer Research Cooperative Group of Linxian to carry out field research on the prevention and treatment of esophageal cancer^[8–12]. Since then, under the leadership and support of the Communist Party of China and governments at all levels, the comprehensive prevention and treatment of esophageal cancer in Linxian with the participation of the whole society has been vigorously carried out in the whole county. With Liu Fang Yuan,

Shen Qiong, Qiu Song Liang, Yang Wen Xian, Wang Rui Lin, Liu Gui Ting, Shao Ling Fang, Miao Jian, Su Ji Hao and other scientists as representatives, the experts of Linxian Esophageal Cancer Research Cooperation Group of Henan Province were stationed in Linxian for a long time, and carried out a multidisciplinary, large-scale, long-term systematic study from basic to clinical research. In the aspects of risk factors, pathogenesis and prevention of esophageal cancer, has made a series of original research results^[13–19]. Among them, Professor Shen Qiong and Qiu Songliang, experts in tumor pathology, were stationed in Linxian in November 1959, and did not return to Henan Medical College until December 1978. They devoted 20 years to the high-incidence site and pathological research of esophageal cancer in Linxian^[20–22]. In 1960, Professor Shen Qiong invented the “esophageal cell sampler” (referred to as “Balloon”), established the diagnostic criteria of esophageal exfoliative cytology, and significantly improved the detection rate of early esophageal cancer^[17–19, 23]. In 1971, Professor Liu Gui Ting was the first in the world to prove that the existence of mycotoxins (*Alternaria alternans*) and nitrosamines may be an important risk factor for the occurrence of esophageal cancer in the high incidence area of esophageal cancer^[9, 10]. In 1989, Professor Qiu Song Liang’s important research results of esophageal endoscopy and mucosal biopsy of asymptomatic population in high-risk areas were published in the *Lancet*, a top international journal^[20]. These studies focused on the epidemiological distribution characteristics of esophageal cancer population in this area, the cellular and histomeric changes in the early stage of esophageal cancer, proposed the concept of early esophageal cancer and precancerous lesions, established the identification criteria of risk factors for esophageal cancer, and used esophageal balloon to conduct early cancer screening, early detection and prevention in a large range of asymptomatic population^[16, 22, 24]. Experience in prevention and control of esophageal cancer has been accumulated, such as anti-mold, deamination, molybdenum fertilizer, treatment of hyperplasia, and change of bad dietary habits^[1, 25, 26]. The scientific spirit of patriotism, dedication, truth-seeking, innovation, cooperation and

dedication of these scientists has inspired several generations of scholars in Henan to devote themselves to the prevention and treatment of esophageal cancer. The esophageal cancer prevention and treatment work of Linxian Esophageal Cancer Research Cooperation Group is welcomed by the people of Linxian, and they are affectionate called “Henan Medical Team”.

1.3 Medical Team in Beijing

According the instructions of Premier Zhou En Lai, in August 1958, Li Bing, then vice president of Ritan Hospital of Chinese Academy of Medical Sciences (now the Cancer Hospital), accompanied by Yang Gui, then secretary of the Committee of Linxian, went to Linxian to learn about the situation of esophageal cancer and delivered the important instructions of Premier Zhou to “Understand the situation and devise the countermeasures” for esophageal cancer and other diseases^[1, 27, 28]. In 1959, Wu Ying Kai, president of Beijing Fuwai Hospital, and Huang Guo Jun, professor of Ritan Hospital, also went to Linxian to investigate the incidence of esophageal cancer under the instructions of Premier Zhou^[7]. In 1964, a medical team composed of Ha Xian Wen, Wang Jian Zhang, Yang Jian, Zhang Da Wei, Wang Guo Qing and Hu Yu Hua from Ritan Hospital of Chinese Academy of Medical Sciences went to Linxian for an epidemiological investigation of esophageal cancer. In 1969, the central medical team (Beijing Medical team and stationed in Linxian), consisting of Ritan Hospital of Chinese Academy of Medical Sciences (now the Cancer Hospital), Institute of Biophysics, Institute of Geophysics and other units, was assigned by the state to carry out a joint research on the prevention and treatment of esophageal cancer in Linxian with the Henan medical team based in Yaocun Commune (now Yaocun Town)^[29].

In 1972, after listening to the report on the work of prevention and treatment of esophageal cancer in Linxian, Premier Zhou instructed that “the prevention and treatment points of esophageal cancer in Linxian should be carried out well, and more points like Linxian should be set up nationwide”^[7]. Subsequently, the research results of esophageal cancer in Linxian were used as the experience and model of Linxian in the field prevention and treatment of other high-incidence

tumors (gastric cancer, nasopharyngeal cancer, cervical cancer, liver cancer and lung cancer, etc.) in China, and remarkable results were obtained.

1.4 International cooperative research on esophageal cancer prevention and treatment

In 1980, the British Broadcasting Corporation (BBC) visited the Linxian Research Base for the prevention and treatment of esophageal cancer in Linxian, producing a scientific and educational feature film, “Chinese Linxian Cancer Explorers”. This film introduced the experience of the prevention and control of esophageal cancer in Linxian to the world, gaining significant international attention. The International Center for Research on Cancer (IARC) and the National Cancer Institute (NCI) of the United States also visited Linxian successively. Since 1980, it has attracted experts and scholars from leading international cancer research institutions in countries such as the United States, Germany, the United Kingdom, and France to collaborate on esophageal cancer research in Linxian^[19, 20, 30–35].

2 Over half a century of inheritance research on esophageal cancer in Henan Province

The academic degree system, based on meritocracy, was restored in 1981, and in the same year, Henan Medical College applied for a master’s program in pathology, focusing on esophageal cancer. Unexpectedly, the Academic Qualifications Office of The State Council evaluated and approved it as a doctor program instead. Since then, the pathology research team of Henan Medical College has begun three generations of mentorship, and the 65 years (1959 – 2024) of inheritance research has been combined with the prevention and treatment of esophageal cancer in the high-incidence sites of Linxian and Huixian counties in Henan Province. In 1995, led by academic leaders such as Wang Li Dong and others, based on the solid accumulation of esophageal cancer research, the idea of combining clinical, laboratory and high-incidence field research of esophageal cancer was further empha-

sized, and Henan Medical University successfully applied for a doctoral program in gastrointestinal cancer, accelerating the training of high-level professionals in esophageal cancer research in Henan Province. Meanwhile, the inheritance research of esophageal cancer, a unique malignant tumor in Henan province, has been greatly strengthened. In the past 65 years, the third-generation mentoring team of esophageal cancer pathology research in Henan Province has revealed the histological pattern and related molecular mechanism of the multi-stage evolution of esophageal cancer from the perspective of cell, tissue and molecular pathology, and actively carried out level I prevention of esophageal cancer (etiological prevention) and level II prevention of precancerous lesions (pathogenic prevention). In the past 65 years, we have accumulated rich experience and research data of prevention and treatment of esophageal cancer in the field.

2.1 The consecutive three generation pathological research on esophageal cancer

As mentioned above, in 1959, the Henan medical team (the first generation of esophageal cancer research experts in Henan), represented by Shen Qiong, Qiu Song Liang, Yang Wen Xian and Liu Gui Ting, was based in Linxian to carry out research on the prevention and treatment of esophageal cancer in the high-incidence area. From then on, the prelude to the 65-year work of prevention and treatment of esophageal cancer in the high-incidence area by three consecutive generations was started. Professor Shen Qiong and Professor Qiu Songliang were the first group of pathologists in China to conduct field population study in the high incidence area of esophageal cancer in Linxian. They continued to work and live in Linzhou for 20 years, developed the “esophageal balloon” examination method, and established the first international exfoliative cytology diagnostic criteria for esophageal cancer and precancerous lesions^[19]. After the recovery of the postgraduate training system, the older generation of scientists began to cultivate a large number of young talents in esophageal cancer research. Among them, Wang Li Dong (studied under Professor Qiu Song Liang), Dong Zi Ming (studied under Professor Liu Gui Ting) and so on were the representatives of the young scholars, ad-

hering to the selflessness, dedication, innovation and patriotism of the old generation of esophageal cancer experts, and continued to adhere to the field prevention and treatment of esophageal cancer in Linxian and the laboratory research since 1985, forming the second generation of esophageal cancer experts in Henan Province. Since 1995, Gao She Gan, Zhou Fu You, Qin Yan Ru, Wang Qi Ming and Li Xiu Min, the third generation of esophageal cancer experts in Henan Province, who were trained by Professor Wang Li Dong, have been engaged in the prevention and treatment of the high incidence of esophageal cancer in Linxian. During this period, there were also many young scholars of the second and third generation, for example, Dong Zi Gang (under the guidance of Professor Liu Gui Ting), Wang Yao He (under the guidance of Professor Zhang Yun Han) and other young talents who successively took roots in foreign countries and continued to engage in cancer research and made outstanding achievements. Taking the field and experimental research of the high incidence of esophageal cancer in Linxian as an example, this paper briefly reviews and prospects the research progress of the three generations of esophageal cancer and tumor pathology mentors led by Professor Qiu Song Liang.

2.2 The relationship and difference between the old and the young generation on esophageal cancer

Over the past 30 years, Professor Wang Li Dong (the second generation), under the guidance of Professor Qiu Song Liang (the first generation), has led and trained a group of the third generation of esophageal cancer research experts in Henan Province. There were 61 doctors, including Feng Xiao Shan, Zhou Fu You, Gao She Gan, Qin Yan Ru, Ren Jing Li, Wang Qi Ming, Yuan Ling, Ku Jian Wei, Zhou Jian Wei, Zhou Ying Fa, Wang Dao Cun, Li Jian, Yue Wen Bin, Liu Hong Uan, Ding Guang Cheng, Song Xin, Zhang Dong Yun, and Zhao Xue Ke, etc. Inheriting the dedication and professionalism of the older generation of scientists, new breakthroughs and progress have been made in the molecular mechanism of esophageal cancer, molecular typing and early detection of high-risk populations, and have had a great impact in the

field of esophageal cancer research at home and abroad. The research ideas and contents are continuation and in-depth based on the research of the older generation of scholars (Fig. 1). The progress of re-

search technology and means has provided broader and deeper research space for the new generation of scholars.

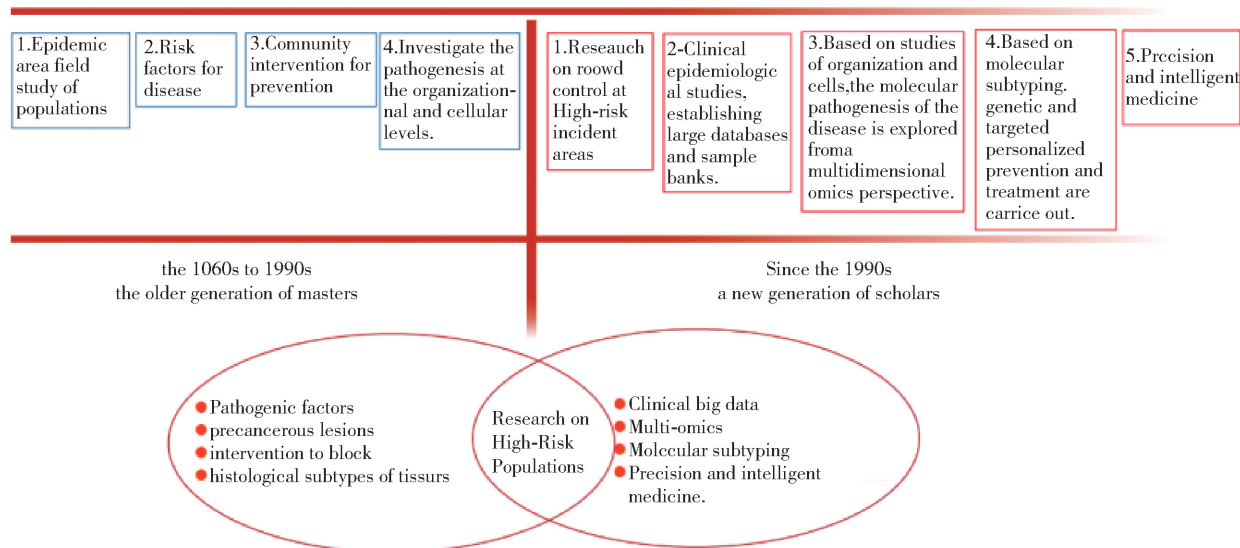


Fig. 1 The connection and difference between the new generation of scholars and the older generation of masters in their research

The understanding of three generations of mentors who have been persisting in the high incidence site and experimental research of esophageal cancer for 65 years: early detection is the key to reducing the mortality rate of esophageal cancer; The bidirectional unstable development of esophageal precancerous lesions (developing in the direction of cancer, or remaining unchanged for many years, or even returning to normal) is a difficulty in accurately identifying asymptomatic high-risk groups for early warning screening and individualized prevention and treatment. The bidirectional unstable development characteristics of esophageal precancerous lesions cannot be explained by morphological changes alone. The use of multidimensional omics combined with clinical phenotypic big data correlation analysis to elucidate the molecular mechanism of esophageal cancer will help to reveal the molecular characteristics of the malignant development of esophageal precancerous lesions and establish an objective evaluation system for molecular classification of high-risk population, which will further achieve the goal of accurate prediction of the progress of precancerous lesions. It is an important guarantee to improve the de-

tection rate of early esophageal cancer and reduce the incidence. The third-generation mentoring team of esophageal cancer research led by Professor Qiu Songliang has carried out systematic research in this field and made important progress, which is briefly described as follows.

1) Construction and application of esophageal cancer and precancerous lesions biobank

Over the past 30 years, the esophageal cancer research team led by Wang Lidong has visited more than 4 000 towns, 120 000 natural villages, and more than 700 hospitals in high-incidence areas nationwide. A cohort of 100 000 asymptomatic patients with esophageal precancerous lesions for 40 years (1985 –) and a cohort of 700 000 patients with esophageal cancer for 50 years (1973 –) were established, and an international standard biobank resource sharing platform was established. Using these big data and biobanking, 15 susceptibility genes and 18 pathogenic genes have been identified for esophageal and gastric cardia cancer. The results of these studies have been reported in *Nat Genet* (2010, 2014), *Gut* (2016), *Nat Commun* (2018, 2015). 2021), *Cancer Discov* (2012) and other in-

ternationally renowned journals^[38-42]. These studies have clarified the interaction between environmental and genetic factors on the occurrence of esophageal cancer, and revealed the molecular basis of esophageal cancer caused by the deficiency of vitamins and trace elements and exposure to nitrosamine discovered by the older generation of scientists, which provides new research ideas and methods for the precise prevention and treatment of esophageal cancer.

2) The latest progress in the etiology of esophageal cancer.

Gao Shengan, as one of the representatives of the third generation of Henan esophageal cancer research team, first found that *Porphyromonas gingivalis* (Pg) infection might be an important risk factor for the occurrence and recurrence of esophageal squamous cell carcinoma^[43]. This finding provides a new research direction and field for the etiology of esophageal cancer, and will have an important impact on the prevention of esophageal cancer.

3) Progress in molecular mechanisms, molecular classification and early detection of esophageal cancer in high-risk population

① Molecular basis of genetic susceptibility to esophageal squamous cell carcinoma and its interaction with environmental carcinogenic factors.

The discovery of esophageal cancer susceptibility genes PLCE1 and C20orf54 in Chinese people has changed the previous understanding of the evaluation and prevention of esophageal cancer by riboflavin, vitamin A and folic acid supplementation in the high-risk population of esophageal cancer, and revealed the impact of the “environmental-genesis-gene interaction” model on early warning screening and individualized prevention and treatment of the high-risk population of esophageal cancer. Wang Li Dong’s research group conducted genome-wide association analysis of 25 000 cases of esophageal squamous cell carcinoma in Chinese Han and control group and found two important susceptibility loci for esophageal squamous cell carcinoma in Chinese population, rs2274223 and rs13042395, which were located in PLCE1 gene of 10q23 and C20orf54 gene of 20p13 (also known as riboflavin transport gene), respectively. RFT2) in Chi-

nese population. Further validation showed that these two SNPs were also significantly associated with the high risk of ESCC in Kazakh and Uygur populations in Xinjiang. These results were published in Nat Genet, which attracted the attention of academic circles at home and abroad^[38]. Subsequently, two other genome-wide association studies of esophageal squamous cell carcinoma from different regions in China published in Nat Genet journal also repeated the validation of PLCE1 susceptibility gene^[44-45]. The PLCE1 gene was verified by the multi-center joint analysis of this project group and two other research groups^[39]. The PLCE1 gene function study found that the 5780G allele variant can lead to the aggravation of esophageal epithelial inflammation by up-regulating PLCE1 mRNA, protein expression and enzyme activity, and further increase the susceptibility of esophageal cancer^[46]. PLCE1 also significantly promoted the proliferation of esophageal cancer cell lines^[47].

② To discover the genetic molecular basis of defective DNA alkylation damage repair caused by the deficiency of riboflavin, vitamin A and folic acid utilization and environmental exposure to nitrosamines, which are the main pathogenic factors in Chinese population, and to provide new insights for individualized prevention.

In the 1960s, it was found that vitamin deficiency, especially riboflavin, retinoic acid and folic acid, which are intermediate metabolites of vitamin A, were the main risk factors for esophageal squamous cell carcinoma in China. Long-term supplementation of these vitamins (such as riboflavin fortified salt) in the population diet has shown significant intervention effects, but there are significant individual differences^[48-53]. Wang Li Dong’s team found that three Chinese esophageal squamous cell carcinoma high-risk susceptibility genes were associated with the riboflavin intracellular and extracellular transport (RFT2) gene^[38], the promoter Region of the normal metabolism of folate in vivo (methylentetrahydrofolate reductase, MTHFR) gene^[54] and the retinoic acid-receptor binding gene (retinoic acid-receptor gene β) gene^[55], respectively. This leads to abnormal gene and protein expression or gene silencing, which further leads to the utilization

disorders of these vitamins, and eventually leads to cell proliferation disorder and carcinogenesis. Population and laboratory studies in high risk areas of esophageal cancer have shown that exposure to nitrosamine may be another important risk factor for esophageal cancer. The project found significant O-alkylguanine⁶ DNA alkyltransferase gene polymorphic alteration (AGT) in the population of Linzhou, Henan Province, which leads to nitrosamine-induced alkyl-repair defects and thus increases the susceptibility to esophageal cancer^[56]. The use of these molecular targets for molecular typing of asymptomatic population can not only objectively define the high-risk population, but also play an important guiding role in individualized prevention.

The above studies have elucidated the molecular genetic basis for the high susceptibility of esophageal squamous cell carcinoma, and revealed the molecular mechanism of the interaction between environmental and genetic factors on the development of esophageal cancer. At the molecular genetic level, these studies have greatly enriched the theories of the relationship between vitamin deficiency, nitrosamine exposure and esophageal cancer discovered by the older generation of Chinese scientists. In addition, the observed individual differences in the intervention of esophageal precancerous lesions by dietary vitamin supplementation were analyzed, based on which new insights on individualized prevention were proposed. These findings provide theoretical basis, molecular targets and new ideas for the screening, early detection and individualized prevention of esophageal squamous cell carcinoma and the development of new drugs.

③ NOTCH1 and p53 gene mutation and p53 – Rb pathway mutation (LOH; Methylation and protein overexpression) are important molecular events leading to the progression of esophageal precancerous lesions. To clarify the molecular mechanism of the bidirectional development of esophageal precancerous lesions.

Wang Li Dong's group and Stephen Melter's group of Johns Hopkins University cooperated with Western esophageal squamous cell carcinoma whole genome exon sequencing results, and found that NOTCH1 gene mutation occurred in esophageal precancerous lesions and was related to the malignant progression of these

precancerous lesions. NOTCH1 gene mutation was found in esophageal squamous cell carcinoma tissues in China and western countries, but not in esophageal adenocarcinoma^[42]. Subsequently, three consecutive sequencing studies on Chinese ESCC published in the famous journals *Nature* and *Nat Genet* repeatedly verified this important finding^[57-59].

④ The mutation of p53 – Rb signaling pathway is the key molecular change in the very early stage of Chinese esophageal squamous cell carcinoma, and it is the main molecular mechanism leading to the continuous development of these early mild lesions into cancer.

By using 7 073 cases of ESCC and paired adjacent normal epithelium, as well as esophageal precancerous lesions and normal biopsies from asymptomatic individuals, we systematically analyzed the mutations, LOH, methylation, phosphorylation, mRNA and protein expression of p53 – Rb signaling pathway genes. The changes of p53, Rb, p14, p15, p16, p21, Cyclin D1, PCNA, Bax, MDM2 and Bcl2 signaling pathway and their relationship with the morphology and progression of precancerous lesions were analyzed^[5, 60-67].

4) screening and predicting the progression of esophageal precancerous lesions (13 autoantibodies, including p16); A panel of molecular markers (PLCE1 and other 28 markers) for molecular subtyping of high-risk populations was established. Using these markers, 46,955 asymptomatic residents in high-risk areas were screened for esophageal cancer, and the early cancer detection rate was 14 times high

Wang Li Dong's group found that the specific protein profiles of esophageal precancerous lesions and cancer tissues identified by proteomic and genomic technologies could be reflected by the detection of autoantibodies in peripheral blood^[68-71]. Further studies have found that serum autoantibodies can identify and predict the progression of esophageal precancerous lesions. When these targets were applied to 46 955 asymptomatic residents in high-incidence areas of esophageal cancer in the Taihang Mountains in the north and Xianzhu in Zhejiang province in the south, the rate of early cancer detection was increased by a factor of 14 as compared with traditional endoscopic screening.

3 Annals of esophageal cancer research in Henan

Table 1 Annals of esophageal cancer research in Henan

No.	Year	Memorabilia
1	1957	Comrade Yang Gui, secretary of the Party Committee of Linxian, mentioned the problem of “three impasses” (water, road and esophagus) in Linxian at the national mountain production symposium, and Yang Gui’s speech was included in the briefing of the meeting, which aroused the great attention of Premier Zhou Enlai and made an important instruction: “Find out the situation and work out countermeasures.” ^[7]
2	1959	The Henan Provincial Party Committee and the provincial government appointed the teaching, scientific research and medical personnel from Henan Medical College, Henan College of Traditional Chinese Medicine, Henan Provincial People’s Hospital, Anyang District Hospital and other units to form the Linxian Esophageal Cancer Research Collaboration Group of Henan Province, with Professor Liu Fang Yuan as the leader and Shen Qiong, Qiu Song Liang and Yang Wen Xue as the main members, to carry out on-site research on the prevention and treatment of esophageal cancer. ^[8-12]
3	1960	Professor Shen Qiong and Qiu Song Liang invented the “esophageal cell extractor” (referred to as balloon) and established the diagnostic criteria for esophageal excision cytology. ^[17]
4	1963	The first review on the cytology of esophageal carcinoma exfoliation
5	1964	A medical team composed of Ha Xian Wen, Wang Jian Zhang, Yang Jian, Zhang Dawei, Wang Guo Qing and Hu Yu Hua from Ritan Hospital of the Chinese Academy of Medical Sciences went to Linxian to conduct an epidemiological investigation of esophageal cancer
6	1969	The state assigned the Central Medical team (Beijing Medical Team, Linxian Medical Team) composed of Ritan Hospital of the Chinese Academy of Medical Sciences (now Cancer Hospital Chinese Academy of Medical Sciences), Institute of Biophysics of the Chinese Academy of Medical Sciences, Institute of Geophysics and other units to be stationed in Linxian, based in Yaocun Commune, to conduct joint research on the prevention and treatment of esophageal cancer in Linxian together with the Henan Medical team ^[29]
7	1971	Professor Liu Gui Ting was the first in the world to prove that the presence of mycotoxins (<i>Streptomyces alternatus</i>) and nitrosamines in Linxian, Henan Province, an area with a high incidence of esophageal cancer, is an important risk factor for esophageal cancer ^[9-10]
8	1973	After listening to the research report on the prevention and control of esophageal cancer in Linxian, Premier Zhou En Lai instructed: “Linxian esophageal cancer prevention and control points should persist in doing well, and more points like Linxian should be done throughout the country.” ^[7]
9	1978	Shen Qiong and Qiu Song Liang represented by the experts of the Esophageal Cancer Research Collaboration Group in Linxian, Henan Province, returned to Henan Medical College after 20 years of field research
10	1978	The “Investigation of the incidence and epidemic factors of esophageal cancer (including Chicken pharyngoesophageal cancer)” completed by Henan Provincial Cancer Prevention and Control Research Office and other units won the National award of the first National Scientific Conference and the National Medical and Health Science Conference
11	1978	The “Study on the etiology of esophageal cancer” completed by the Tumor Prevention and Control Research team of Henan Province won the National award of the first National Scientific Conference and the National Medical and Health Science Conference
12	1978	The “Early diagnosis of esophageal cancer” completed by the Tumor Prevention and Control research team of Henan Province won the national award of the first National Scientific Conference and the National Medical and Health Science Conference
13	1978	The “Research on the relationship between esophageal epithelial hyperplasia and carcinogenesis” completed by Henan Provincial Cancer Prevention and Control Research Team and other units won the ministerial award of the first National Scientific Conference and the National Medical and Health Science Conference
14	1978	The “Histochemistry research of Esophageal Cancer and cardiac Cancer” completed by the Department of Histology and Embryology of Henan Medical College won the provincial award of the first National Scientific Conference and the National Medical and Health Science Conference
15	1978	The “Surgical Improvement of esophageal Cancer” completed by Henan Cancer Prevention and Control Research Team and other units won the provincial award of the first National Scientific Conference and the National Medical and Health Science Conference

- 16 1978 The “Determination of cellular immune function in patients with esophageal cancer” completed by Henan Medical College and other units won the provincial award of the first National Scientific Conference and the National Medical and Health Science Conference
- 17 1978 The “Cytological measurement of early and advanced esophageal squamous cell carcinoma” completed by the pathology teaching and research group of Northern Henan Medical College won the provincial award of the first National Scientific Conference and the National Medical and Health Science Conference
- 18 1980 Zhang Tan Mu’s research team completed the “anti-tumor experimental study of Rabdodendrin” won the second prize of Scientific and Technological Progress in Henan Province
- 19 1980 Li Ding Jiu research team completed the “esophageal cavity microwave heater treatment of esophageal cancer” won the second prize of science and Technology progress in Henan Province
- 20 1980 The British Broadcasting Corporation (BBC) specially went to the Linxian Esophageal Cancer prevention and control research base to shoot a scientific and educational film “China’s Linxian Cancer Explorers” to introduce the experience of esophageal cancer prevention and control in Linxian to the world
- 21 1980 Professor Yang Chung Shu of New Jersey Medical School in Newark, New Jersey, USA, came to Henan to carry out China-US collaborative research on esophageal cancer^[72]
- 22 1982 Scientists from the National Cancer Institute of the United States went to China to carry out China-US collaborative study on esophageal cancer
- 23 1983 The first monograph “Esophageal Cancer” edited by Henan Medical College was published by People’s Medical Publishing House^[3]
- 24 1988 Scientists from the German Cancer Research Center, the University of Heidelberg in Germany, the University of Cambridge in the UK, the International Cancer Research Center, the Italian National Cancer Research Center, Louisiana State University in the US and many other international research institutes and cancer research centers came to Henan to carry out international cooperative research on esophageal cancer^[73, 74]
- 25 1989 Professor Qiu Song Liang has devoted many years to esophageal biopsy histological precancerous lesions and his important research results have been published in the international top journal Lancet^[20]
- 26 1990 Cheng Cun Shuan’s research team completed the “Study of partial pharyngeal wall and total esophagectomy in the treatment of cervical esophageal cancer” won the second prize of Science and Technology Progress of Henan Province
- 27 1992 Liu Gui Ting’s research team completed the “Etiological significance of *Alternaria alternata* in human esophageal cancer” won the second prize of the Ministry of Health
- 28 1993 Wang Li Dong’s Research team reported the relationship between P53 protein changes and esophageal Cancer for the first time in the journal Cancer Research^[60]
- 29 1994 The monograph “Esophageal Cancer” edited by President Du Bai Lian of Henan Medical University was republished by China Science and Technology Press^[4]
- 30 1996 The research on tumor hyperthermia conducted by Henan Cancer Hospital and other units, with the study on microwave hyperthermia in the esophagus as the main focus, has won the Second Prize for Scientific and Technological Progress Award in Henan Province
- 31 1997 The research paper on esophageal cancer p53 gene by Wang Li Dong’s research team was included in the American Journal of Gastroenterology Yearbook^[75]
- 32 1998 The “Study on Enhancing the Therapeutic Effect of Aldehyde Folic Acid/5-Fluorouracil-Cisplatin Therapy for Esophageal Cancer” completed by Wang Rui Lin’s research team won the second prize of Scientific and Technological Progress Award of Henan Province
- 33 1998 Yuan Ke’s research team completed the “research on new technology of extraction and separation of anti-cancer active ingredients of *Rabdosia Rabdosia*” won the second prize of Scientific and Technological Progress Award of Henan Province
- 34 2000 Professor Wang Li Dong was awarded the National Outstanding Young Scientist Award for “Molecular Mechanisms of Multi-stage Evolution of Esophageal Carcinogenesis”
- 35 2001 The “Study on the mechanism of Esophageal Cancer” completed by Wang Li Dong’s research team won the second prize of Scientific and Technological Progress Award of Henan Province
- 36 2003 Zhao Wei Xing’s research team completed the “relationship between the contents of trace elements in esophageal mucosa and hair and oncogene mutation in people with high and low incidence of esophageal cancer” won the second prize of Scientific and Technological Progress Award of Henan Province

- 37 2005 The Department of Education of Henan Province approved the establishment of the key subject open Laboratory of esophageal cancer in colleges and universities of Henan Province, and appointed Professor Wang Li Dong as the director
- 38 2005 Research on the application value of R-glutamyltranspeptidase in the prevention and treatment of esophageal cancer completed by Zhao Zhi Guo's research team won the second prize of Scientific and Technological Progress Award of Henan Province
- 39 2005 Fan Qing Xia's research team completed the "Prediction of chemotherapy sensitivity through the examination of esophageal cancer P53, PCNA, EGFR, TS and ERCC1 genes" won the second prize of Scientific and Technological Progress Award of Henan Province
- 40 2005 Dong Zi Ming's research team completed the "study on DNA polymerase β gene mutation in esophageal cancer" won the second prize of Scientific and Technological Progress Award of Henan Province
- 41 2005 Zheng Yu Ling's research team completed the "Study on the curative effect mechanism of Douroot-guan Shitong Oral Liquid in the treatment of esophageal cancer" won the second prize of Scientific and Technological Progress Award of Henan Province
- 42 2007 The "Interventional treatment of elderly esophageal cancer" completed by Song Tai Min's research team won the second prize of Scientific and Technological Progress Award of Henan Province
- 43 2007 Ji Zhen Yu's research team won the second prize of Science and Technology Progress Award of Henan Province for "Research on factors and mechanisms affecting the photodynamic efficacy of early esophageal cancer and precancerous lesions"
- 44 2008 He Fu Cheng research team completed the "differentiation related gene NDRG1 expression in esophageal cancer and induced differentiation treatment" won the second prize of Scientific and Technological Progress Award of Henan Province
- 45 2010 Wang Li Dong's research team found that PLCE1 and C20orf54 are important susceptibility genes for esophageal cancer in Chinese people, and the results were published in the top international journal Nature Genetics^[38]
- 46 2010 CHINA S&T NEWSLETTER reported that Wang Li Dong's research team studied esophageal cancer susceptibility genes PLCE1 and C20orf54^[76]
- 47 2010 Mai Ling's research team won the second prize of Scientific and Technological Progress Award of Henan Province for "Research on the apoptosis mechanism of esophageal small cell carcinoma"
- 48 2011 Wang Li Dong's research team's research paper on esophageal cancer susceptibility gene PLCE1 and C20orf54 was written in the "China Medical Science and Technology Development Report"^[77]
- 49 2011 Gao She Gan's research team won the second prize of Science and Technology Progress of Henan Province for "Study on photodynamic Treatment of Esophageal Cancer and its mechanism"
- 50 2011 Chen Kui Sheng's research team won the second prize of Science and Technology Progress Award of Henan Province for "research on the relationship between PI3K/Akt/mTOR signal transduction pathway and the occurrence and development of esophageal cancer"
- 51 2012 Wang Li Dong's research team discovered that NOTCH1 is an important causative gene for esophageal cancer, and the research results were published in Cancer Discovery^[42]
- 52 2012 Wang Li Dong's research team identified five esophageal squamous carcinoma susceptibility loci, rs10931936, rs13016963, rs9288318, rs10201587, and rs7578456, which are located on chromosome 2, q33, in the CASP8 /ALS2CR12/ TRAK2 region of chromosome 2, and were published in the journal Human Molecular Genetics^[78]
- 53 2012 Qin Yan Ru's team published a paper on esophageal squamous cell carcinoma RNA sequencing research in Gastroenterology
- 54 2012 Qin Yan Ru's research team published a paper on the molecular mechanism of esophageal squamous cell carcinoma growth and metastasis in the Gastroenterology^[79] and Gut^[80]
- 55 2012 Liu Hong Chun's research team completed the "study on the relationship between TPX2 and esophageal squamous cell carcinoma invasion and metastasis" won the second prize of Science and Technology Progress Award in Henan Province
- 56 2012 Ge Hong's research team won the second prize of Science and Technology Progress Award of Henan Province for "research on the correlation between apoptosis and radiosensitivity and prognosis of esophageal squamous cell carcinoma"
- 57 2012 Qi Yu's research team won the second prize of Science and Technology Progress Award of Henan Province for "research on the mechanism of Srcasm negative regulation of Src family tyrosine kinase Fyn in esophageal squamous cell carcinoma"
- 58 2012 Feng Re research team to complete the "P38 lightning in DTT and the role of cisplatin induced apoptosis of esophageal Eca109" won the second prize of Science and Technology Progress Award in Henan Province
- 59 2013 The research team led by Qin Yan Ru won the second prize for scientific and technological progress in Henan Province for their study on the functions of RBMS3SOX6PCAF and PLCE1 genes in esophageal squamous cell carcinoma

- 60 2014 The research team led by Wang Li Dong discovered three new susceptibility loci for esophageal squamous cell carcinoma, rs7447927, rs1642764, and rs35597309, located on the TMEM173 gene on chromosome 5 q31.2, the ATP1B2/TP53 gene on chromosome 17 p13.1, and the HLA class II gene on chromosome 6 p21.32. These findings were published in the journal *Nature Genetics*^[81]
- 61 2014 The "Genome wide Association Analysis and Functional Research on Chinese Esophageal Cancer" completed by Wang Li Dong's research team won the first prize for scientific and technological progress in Henan Province
- 62 2014 Qin Yan Ru's research team published a research paper on the mechanism of esophageal squamous cell carcinoma metastasis in the *Journal of Gastroenterology*^[82]
- 63 2015 The research team led by Wang Li Dong has won the first prize of Zhejiang Provincial Science and Technology Progress Award for their research on the molecular characteristics and key technologies for comprehensive treatment of esophageal squamous cell carcinoma, as well as its clinical application
- 64 2016 Wang Li Dong's research team discovered three susceptibility sites for gastric cardia adenocarcinoma, rs10074991, rs2294693, and rs4072037, located in the PRKAA1 gene on chromosome 5 p13.1, the UNC5CL/TSPO2 gene region on chromosome 6 p21.1, and the MUC1 gene on chromosome 1 q22, respectively. This achievement was published in the *Gastroenterology*^[83]
- 65 2016 Qin Yan Ru's research team published a research paper on the function of esophageal squamous cell carcinoma stem cells in the journal *Nature Communications*^[84]
- 66 2017 Wang Li Dong's research team won the first prize of Henan Provincial Science and Technology Progress Award for the comparison of genomic feature spectrum variations between esophageal squamous cell carcinoma and cardia adenocarcinoma
- 67 2017 Wang Li Dong's research team's "Construction of Precision Medical Big Data Platform for Common Malignant Tumors such as Esophageal Cancer in Henan Province" project has received major special funding from Henan Province
- 68 2018 Wang Li Dong's research team has established a new high-throughput functional research method for tumor susceptibility genes and susceptibility loci, and the research results have been published in the journal *Nature Communications*^[41]
- 69 2018 The provincial government approves Professor Wang Li Dong as a counselor of the Henan Provincial Government
- 70 2018 The research paper on rapid rehabilitation of esophageal cancer by Li Yin's research team has been published in the journal *Annals of Surgery*^[85]
- 71 2018 Qin Yan Ru's research team published a research paper on the signaling pathway of esophageal squamous cell carcinoma metastasis in the journal *Nature Communications*^[86]
- 72 2018 The State Key Laboratory for Prevention and Treatment of Esophageal Cancer jointly built by the province and the ministry passed the consultation between the province and the ministry
- 73 2019 The Ministry of Science and Technology of the People's Republic of China approved the construction of the State Key Laboratory for Prevention and Control of Esophageal Cancer jointly built by the province and ministry, appointed Professor Wang Li Dong as the director, and Professor Zhang Li Rong, Liu Hong Min, Zhang Jian Ying, Zhang Yi and Liu Kang Dong as the deputy directors
- 74 2019 The 60th anniversary commemoration of the Linzhou Esophageal Cancer Prevention and Control Research Base and the China Cancer Prevention and Control Research Summit Forum were held in Linzhou
- 75 2019 Academician Wang Long De, Qu Ling Bo, Luo Zhen Fang, and Professor Wang Li Dong jointly unveiled the Linzhou Prevention and Treatment Research Base of the State Key Laboratory for Prevention and Treatment of Esophageal Cancer jointly built by Zhengzhou University
- 76 2019 Professor Wang Li Dong presides over the press conference for the publication of the third edition of the journal "Esophageal Diseases" and the monograph "Esophageal Cancer"
- 77 2019 The Tumor Genetics Professional Committee of Henan Anti-Cancer Association has been established, with Professor Wang Li Dong serving as the chairman
- 78 2019 In 15 hospitals in high incidence areas of esophageal cancer such as Henan, Hebei and Shanxi, the construction and awarding of on-site research bases of the State Key Laboratory for prevention and treatment of esophageal cancer jointly built by the province and the ministry were completed
- 79 2020 The First Meeting of the Academic Committee for the National Key Laboratory for Esophageal Cancer Prevention and Control Co-constructed by Sichuan Province and the Ministry of Education
- 80 2020 The research project on "the basis and clinical application of immunotherapy for malignant tumors" completed by Zhang Yi's research team has won the first prize in Natural Science of Henan Province

- 81 2020 The "Key Technologies and Application for Early Detection and High-Risk Group Warning of Esophageal Cancer" completed by Wang Li Dong's research team won the first prize in Henan Medical Science and Technology Award
- 82 2020 The research team led by Qin Zhi Hai has won the First Prize of Henan Medical Science and Technology Award for their work on "Inhibiting Tumor Growth by Targeting Immune Negative Regulatory Inflammatory Factors in the Tumor Microenvironment"
- 83 2020 The "DNA self-assembly nanotechnology for drug delivery systems targeting esophageal cancer," jointly developed by Wang Li Dong's research team and Wang Yanfeng's research team, won the second prize of the Science and Technology Award from the Henan Provincial Department of Education
- 84 2020 The research team led by Wang Li Dong, focusing on the "Multidimensional Omics Characteristic Spectrum and Application Research of Esophageal Cancer," has been approved as a project included in the Central Guidance for Local Science and Technology Development Special Project [Cross-regional R&D Cooperation (Free Exploration)]
- 85 2020 The research team led by Wang Li Dong, with their project titled "Esophageal Cancer Specific Cohort Study: Genetic Cohort of Esophageal Cancer Families," has been approved for the National Key R&D Program
- 86 2020 The major projects of Henan Province undertaken by Wang Li Dong's research team successfully passed the final acceptance
- 87 2020 Zhang Jiaying's research team "Research and development and application of key technologies for early immunity and molecular diagnosis of common malignant tumors based on precision Medicine" was funded by Henan Provincial Science and Technology Major Special Project (post-subsidy fund)
- 88 2020 Henan Province Science and Technology Department approved the Xinyang Guangshan People's Hospital and the Central Plains scholar Professor Wang Li Dong cooperation to build the Central Plains scholar workstation
- 89 2020 Lu Jing's research team's "Molecular Mechanism and chemoprevention of esophageal Cancer" project was funded by Henan University Science and Technology Innovation Team Support Program
- 90 2020 Wang Li Dong and Li Xiu Min 's team found that as a novel modulator of Hippo signal transduction, regulating the activity or gene expression level of PARK2 may be a new strategy for the treatment of esophageal cancer, the results were published in Theranostics
- 91 2021 Henan Provincial Party Committee Work Conference special report "Three generations of the State Key Laboratory for Esophageal Cancer Prevention and Control" Relay "Care for Esophageal health"
- 92 2021 Wang Li Dong's team found that extra-chromatin DNA, located in the cytoplasm, is closely linked to gastric cardia cancer according to a study published in Nature Communications^[87]
- 93 2021 Education Times carried out a special report on the State Key Laboratory of Esophageal Cancer Prevention and Treatment jointly built by the province and the Ministry "hoping to" turn esophageal cancer into a minor disease like a cold " " .
- 94 2021 Hou Gui Qin's research team found that chloroquine (CQ) can improve the anti-tumor efficacy of SFN in esophageal squamous cell cancer by enhancing the Caspase pathway activated by sulforaphane (SFN), published in Acta Pharmaceutica Sinica B^[88]
- 95 2021 Liu Kang Dong's research team found that targeting integrin $\alpha\beta 3$ with indomethacin can inhibit esophageal cancer recurrence, the research results were published in Clinical and Translational Medicine^[89]
- 96 2022 Liu Hong Min's research team "Epigenetic regulation of HDAC6 and SHP2 on immune escape of esophageal cancer and intervention of targeted small molecule inhibitors" was supported by the National Natural Science Foundation of China Regional Innovation and Development Joint Fund
- 97 2022 Wang Li Dong and Gao She Gan's research team won the first prize of the Medical Science and Technology Award of the Chinese Association of Research Hospitals
- 98 2022 Liu Kang Dong's research team "Mechanism research of histone post-translational modification molecules in esophageal cancer" was funded by the Henan Provincial Leading Talents Project of Henan Provincial Science and Technology Department
- 99 2022 The research team of Wang Li Dong completed the analysis of histopathological types and clinicopathological characteristics of 272, 437 patients with primary esophageal malignancies, the largest sample size so far, and the research results were published in the Chinese Journal of Internal Medicine^[90]
- 100 2023 Dong Zi Gang 's research team found that TAGLN2 and CRNN may be high-risk candidates for the precancerous stage of the esophagus, the results of which are published in Nature Communications^[91]
- 101 2023 The Third Youth Academic Forum and 2023 Academic Exchange Meeting of the State Key Laboratory of Esophageal Cancer Prevention and Treatment jointly built by the province and Ministry were held in Linzhou

102	2023	Henan Provincial Science and Technology Department, Nanyang City Science and Technology Bureau, the First Affiliated Hospital of Zhengzhou University and the First People's Hospital of Nanyang City held the unveiling ceremony of the Zhongyuan Scholars Workstation of the First People's Hospital of Nanyang City
103	2023	Guangshan People's Hospital Zhongyuan scholars workstation project successfully passed the acceptance defense review
104	2023	On the 95th anniversary of the First Affiliated Hospital of Zhengzhou University, Professor Wang Li Dong was awarded the Outstanding Contribution Award
105	2023	The State Key Laboratory for the Prevention and Treatment of Esophageal Cancer jointly built by the province and Ministry held the annual Summit Forum on the Prevention and Treatment of Esophageal Cancer in 2023 and the Academic Thought Seminar on the prevention and treatment of esophageal cancer in three generations and 65 years
106	2023	The database and biobank of the State Key Laboratory for the Prevention and Treatment of Esophageal Cancer have been certified by the International ISO9001 Quality Management System
107	2023	Gao She Gan's research team "Mechanism and application of porphyromonas gingivalis induced microecological imbalance to promote the occurrence and development of esophageal cancer" won the first prize of Scientific and Technological Progress of Henan Province
108	2023	Liu Hong Yan's research team "Establishment and clinical application of Major birth defect screening and diagnosis system" won the first prize of Science and Technology Progress in Henan Province
109	2023	Wang Qi Ming's research team "Innovation and application of new technologies for the diagnosis and treatment of refractory non-small cell lung Cancer" won the first prize of Science and Technology Progress in Henan Province
110	2023	Li Xiu Min's research team "Discovery and application of new markers for early screening of esophageal cancer" won the second prize of Science and Technology Progress of Henan Province
111	2024	The State Key Laboratory of Esophageal Cancer Prevention and Control Project chaired by Professor Wang Li Dong was awarded the "Double First-Class" construction by Zhengzhou University in 2024 – 2025
112	2024	The results of a comparative study of capecitabine monotherapy or XELOX (capecitabine + oxaliplatin) versus PF (cisplatin + fluorouracil) regimen in the radical concurrent chemoradiotherapy of locally advanced esophageal squamous cell carcinoma led by the Gao She Gan Research team were published in the Journal of Clinical Oncology (JCO) ^[92]
113	2024	Li Xiu Min's research team "Research and development and clinical application of methylation detection kit for early diagnosis of esophageal cancer" won the major special project of Henan Province Biology and New Medicine Industry R&D Joint Fund of 5 million yuan in 2024

4 Important scientific issues and prospects of esophageal cancer research

4.1 The research background of esophageal cancer prevention and control and the understanding of the 65 years prevention and control research in the high incidence area of Linxian

Esophageal cancer is a malignant tumor with Chinese characteristics. There are great differences in the prevalence, histology and risk factors of esophageal cancer between Chinese and Western populations, which lead to different scientific issues and difficulties in sharing the research results of esophageal cancer between Chinese and Western scholars. There are about half a million new esophageal cancer patients in the world every year, more than half of which occur in

China. The incidence of esophageal cancer is 100 times higher than that in Western countries, while the 5-year survival rate is only about 15%. Squamous cell carcinoma is the main histological type of esophageal cancer in China, accounting for 97%. The main risk factors are vitamin deficiency (especially riboflavin, vitamin A and folic acid) and nitrosamine exposure. In Western population, esophageal adenocarcinoma is the main type (80%), and the main risk factors are obesity and reflux esophagitis. The epidemiological characteristics of esophageal cancer in China are significant regional distribution differences (the incidence in high and low risk areas was 500 times different) and obvious familial clustering (40% of patients with positive family history), suggesting that environmental and genetic factors play an important role in the development of esophageal cancer, but these two characteristics are not obvious in Western population. The database of ep-

idemiological information and the sample bank of esophageal precancerous lesions accumulated by population census, follow-up and prevention research in high incidence areas are the important basis for elucidating the mechanism of esophageal cancer in China^[6].

Important scientific issues in esophageal cancer research; early detection is the key to reduce the incidence and mortality of esophageal cancer; Early detection refers to asymptomatic patients with severe precancerous lesions and patients with early cancer (Tis-1NOM0). At present, 90% of patients with esophageal cancer are diagnosed at an advanced stage. The main reason for this outcome is that patients have no specific symptoms at the early stage, and there is a lack of molecular targets for early warning and screening of asymptomatic high-risk populations. Traditionally, "asymptomatic population in high-risk areas, over 40 years old, male, smoking, drinking, and positive family history" has been generally defined as "high-risk or high-risk population of esophageal cancer", which is also the main target of early screening for esophageal cancer. At present, chromoendoscopy and mucosal biopsy are important screening methods for early detection of esophageal cancer. However, the application of endoscopic screening in the asymptomatic population has been limited due to its trauma, high cost, and low efficiency (for example, the detection rate of early cancer is only about 2% in routine endoscopic screening in high-risk areas, and about 90% of asymptomatic high-risk populations are "companion examinations"). Clearly, the definition of high-risk population should be combined with the latest results of modern multi-dimensional omics research, molecular typing and histological classification (severe precancerous lesions), and the precise definition of high-risk population.

4.2 Changes in the definition of high-risk population for esophageal cancer

Since 1959, due to the progress of research technology and the accumulation of research on the molecular mechanism of multi-stage evolution of esophageal cancer, the understanding of the high-risk population of esophageal cancer has been more comprehensive and systematic, and the definition of high-risk population of esophageal cancer has also changed significantly. From

1950 to 1970, the definition of high-risk population mainly included: ① from high-risk areas, ② male, ③ age > 40 years, ④ positive family history, ⑤ smoking, and ⑥ drinking; from 1980 to 2000, the ⑦ markers of cell and/or precancerous lesions in biopsy tissue were added.; from 2000 to now, we have gradually added ⑧ molecular typing based on multi-dimensional omics, ⑨ liquid biopsy (mainly including tumor-related gene proteins, autoantibodies, SNPS and metabolomics indicators, etc.) and ⑩ intelligent medical risk models based on biological computing^[6, 70, 71, 93].

4.3 Accurate prediction of the progression of precancerous lesions

The morphological changes of esophageal precancerous lesions were mainly atypical hyperplasia of epithelial cells. In recent years, this lesion has been classified as intraepithelial neoplasia in the world. Precancerous lesions are characterized by bidirectional instability: they develop into cancer, remain unchanged for many years, or regress to mild lesions^[94, 95]. Obviously, it is difficult to predict the progression of precancerous lesions from morphological changes alone. There have been many reports on the molecular changes of precancerous lesions, but there is still no marker that can accurately predict the progression of precancerous lesions. Most of the previous studies verified multiple related molecules found in single or combined tumor tissues in precancerous tissues, and there was a lack of genome-wide profiling of precancerous tissues, which may be one of the main reasons for the difficulty in accurately predicting the progression of precancerous lesions. In addition, because most precancerous lesions are mucosal biopsy tissues, the number of lesion cells is very small, and the amount of effective DNA is also small, which leads to the slow progress of omics research on precancerous lesions. In recent years, with the progress of molecular biology technology, satisfactory sequencing data can be obtained with 50 – 200ng of whole genome DNA. Western scholars have made important progress in whole genome exon sequencing of biopsy tissue of Barrett's esophageal precancerous lesions with severe dysplasia^[96]. Accurate molecular prediction of the progression of precancerous lesions to cancer is the key to identify high-risk populations and

precise prevention and treatment, thereby reducing the incidence of Barrett's precancerous lesions.

4.4 Molecular typing and targeted therapy

For example, although the 5-year survival rate of early-stage esophageal cancer (T1N0M0) is significantly better than that of intermediate-advanced esophageal cancer (80% vs 20%), about 3% of intermediate-advanced esophageal cancer patients survive more than 10 years^[91, 97]. However, about 3% of patients with advanced esophageal cancer survive for more than 10 years even after exploratory surgery finds that radical resection cannot be carried out and gives up surgical treatment. After radical surgical treatment, 8% of early cancer patients died within one year, and the main cause of death was short-term explosive extensive blood metastasis of large organs^[98]. It is difficult to explain the paradox that those with a high risk of death have a good prognosis, while those with a low risk have a poor prognosis from a clinical perspective. Multiomics molecular variation and the use of multidimensional omics signature profiles to classify diseases (molecular typing) may help elucidate this phenomenon. At present, there is no targeted therapy for esophageal squamous cell carcinoma and gastric cardia adenocarcinoma at home and abroad. The lack of multi-center large cohort specific molecular profiling verification and molecular classification is the key to restrict the targeted therapy, which further leads to the difficulty in improving the 5-year survival rate.

4.5 Key molecular markers of recurrence and metastasis, sensitivity to chemoradiotherapy and prognosis

Recurrence and metastasis and resistance to chemoradiotherapy are the main factors leading to high mortality of esophageal cancer. The multi-center large-scale verification was conducted by using the omics characteristic spectrum, and the relationship between omics and clinical phenotype was correlated and analyzed, so as to determine the key molecular markers of recurrence and metastasis, sensitivity to radiotherapy and chemotherapy, and prognosis. Molecular classification is another key issue for implementing precision medicine and improving survival rate. The establishment of embassy and large cohort database of clinical

diagnosis and treatment, pathology and follow-up and tissue specimen bank is the key basis for achieving the above goals. Up to now, there has been no report on clinical large cohort and specimen bank of esophageal squamous cell carcinoma and gastric cardia adenocarcinoma abroad. In recent years, many hospitals and scientific research institutions in China have established corresponding databases and specimen banks, but most of them are in the initial stage, especially the follow-up data needs a long time to accumulate.

4.6 Development trend and application prospect in the field of prevention and treatment of esophageal cancer

Intelligent medical research for esophageal cancer based on biological computing will be a new trend in the field of esophageal cancer prevention and treatment. In recent years, high-throughput technology has developed rapidly, accumulating a variety of biomedical data such as genome, epigenome and transcriptome. There are more and more biomedical databases, including Cancer Genome Atlas (CGA) database, National Center for Biotechnology database, protein interaction database, and biological metabolic pathway database. According to statistics, the total amount of biomedical data generated in the world every year has reached EB level, which provides conditions and basis for in-depth understanding of the mechanism of cancer occurrence and development and biological processes. Biological computing is an emerging research field of information processing in biotechnology. It has many advantages, such as distributed, discrete, algorithmic, scalable, readable and parallel properties, which are suitable for modeling and simulation of biological systems, and has attracted wide attention in the biomedical community. At present, as a cross-cutting research field of biotechnology, computer science and clinical medicine, bio-computing is committed to the development of high-performance computing models and algorithms, which is an important tool for exploring cancer diagnosis and treatment.

The occurrence and development of esophageal cancer is a pathological process involving multiple genes, and the changes of molecular pathology run through the whole process of carcinogenesis. It is of

great application value to develop molecular indicators for monitoring the occurrence and development of esophageal cancer. Therefore, the study of biomarker mining methods to accurately find the molecular markers of each subtype and precancerous state of esophageal cancer from the pathological model of esophageal cancer has important research value for the early detection, prevention and prediction of esophageal cancer.

Traditional disease prediction models are not sufficient for early detection of esophageal cancer. At present, there are some problems in the research of disease prediction models: first, the prediction models ignore tumor heterogeneity; Second, most prediction models are based on linear models and decision tree models, which are difficult to describe the dynamic process of disease occurrence and development. Third, some important factors are more or less missed in the current prediction models. Based on the high-throughput data of esophageal cancer, constructing a personalized and systematic early prediction model of esophageal cancer based on living environment, dietary habits, age, gender and other factors is the key to accurately predict the occurrence and development of esophageal cancer and improve the survival rate of patients with esophageal cancer. With the development of high-throughput technology, the accumulation of big data makes it possible to use biological computing methods to predict the occurrence of esophageal cancer. Related scientific problems mainly include: how to construct a model that can reflect the multi-process and heterogeneity of esophageal cancer based on short sequence high-dimensional data; How to effectively identify the biomarkers for each subtype of esophageal cancer; How to establish a multi-factor personalized prediction model for early detection of esophageal cancer by comprehensively considering the influencing factors of esophageal cancer such as tumor markers, gender, age, race, region, and dietary habits^[99].

The cycle research strategy of "high-risk population-laboratory-high-risk population" was established. Future studies on esophageal cancer will make full use of the advantages of China's esophageal cancer case resources, focus on solving major clinical scientific problems (accurate prediction of precancerous lesion pro-

gression, recurrence and metastasis, sensitivity to chemoradiation and key molecular markers of prognosis), and adopt multidimensional omics integration and association analysis with clinical phenotype big data to obtain precancerous lesion progression and esophageal cancer omics characteristic spectrum. Multi-center scale verification was conducted to obtain key molecular markers that can be used to accurately predict the progression of esophageal prelesions, recurrence and metastasis, sensitivity to radiotherapy and chemotherapy, and prognosis, which will provide important technical support for the accurate diagnosis and treatment of esophageal cancer. The accumulation of big data in omics and clinical epidemiology will lay an important foundation for the realization of precision medicine (prevention and treatment) of esophageal cancer. It is also the main field of esophageal cancer research in China that is expected to make major breakthroughs in the future.

At present, there is no standardized guideline for early detection, prevention and treatment of esophageal cancer in high-risk population. Based on the new model of "environment-genetic-gene interaction" in the pathogenesis of esophageal cancer, the molecular classification criteria for high-risk population were established, and the molecular targets for early warning screening, early detection, early diagnosis and individualized prevention and treatment were determined. The high-risk population was identified by using a drop of blood to detect these molecular signatures, and then the high-risk population was examined by chromoendoscopy and biopsy. It will greatly improve the detection rate of patients with early cancer and precancerous lesions, so as to provide important technical support for the final reduction of the incidence and mortality of esophageal cancer. Using this idea, Wang Li Dong's research group tested the susceptibility gene loci and autoantibodies in peripheral blood of 11 000 asymptomatic residents in high risk areas of esophageal cancer, and identified 660 high-risk groups. Then, pigmented endoscopy and mucosal biopsy were performed on these high-risk groups, and 234 patients with esophageal cancer were found. Compared with 2% (234/11 000) of the traditional asymptomatic population, the detec-

tion rate of early esophageal cancer was increased by nearly 18 times (234/660). More and more omics findings are enriching the new model of "environment-genetic-gene interaction" in the pathogenesis of esophageal cancer. These studies lay an important foundation for the further establishment and improvement of standardized guidelines for early detection, prevention and treatment of esophageal cancer in high-risk population.

Chemoprevention: After the high-risk population has been identified, the intervention and chemoprevention of precancerous lesions has become one of the focuses to reduce the incidence of esophageal cancer. Individualized prevention is designed to Design different prevention strategies based on the multi-dimensional omics characteristics and the molecular mechanism of high susceptibility in the early stage of the multi-stage evolution of esophageal cancer.

Cell and gene therapy and targeted drug therapy: it is difficult to further improve the therapeutic effect of esophageal cancer by relying solely on traditional surgery, radiotherapy and chemotherapy. The combination of new treatment methods and traditional treatment is the key to improve the 5-year survival rate of patients with advanced esophageal cancer. The research group of Wang Yaohe and Liu Hongmin in Zhengzhou University has made important progress in cell and gene therapy and targeted drugs, and these research results have important clinical application prospects.

5 Summary

Over the past 65 years, three generations of the esophageal cancer pathological research team in Henan Province have employed a cyclical research strategy of "high-risk population-laborator-high-risk population". This approach has led to establish a large database and tissue sample bank containing clinical, diagnostic, treatment, pathology, and follow-up data for patients with esophageal cancer and precancerous lesions. Their research has clarified the molecular basis of the genetic high susceptibility to esophageal cancer, and the molecular mechanism underlying its multi-stage evolution.

The research focuses on identifying key molecular targets and establishing a theoretical system for molecu-

lar typing and early detection of asymptomatic high-risk population, with primary goal of improving the early detection rate. Using molecular genetics, molecular pathology, multi-dimensional omics technology, population surveys, and bioinformatics-based clinical phenotype and multi-dimensional omics association analysis, the team has developed an intelligent medical model system for early detection and personalized prevention and treatment of esophageal cancer.

In addition, their serial research has systematically elucidated the molecular mechanisms driving esophageal cancer progression, the early molecular changes associated with esophageal cancer transformation, and their relationship to morphological changes and prognoses of precancerous lesions. They have also further revealed the influence of environmental and genetic interaction on esophageal cancer transformation. These serial studies provide critical theoretical and technical support for the screening, early detection, and individualized prevention, as well as treatment of high-risk groups of esophageal cancer populations.

Acknowledgments

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