

## Pathogenetic effects of salted pork in an area of China with high-risk for stomach cancer

Yuan Yuan, Hui-Zhi Lin, Yin-Chang Zhang, Xuan-Jie Wang, Yie-Qiu Wu, Hua Gao, Lan Wang, Yan-Hou Liu, Fang Lu, Su-Qing Lou

Yuan Yuan, Hui-Zhi Lin, Yin-Chang Zhang, Yie-Qiu Wu, Hua Gao, Lan Wang, Cancer Institute, China Medical University, Shenyang 110001, Liaoning Province, China

Xuan-Jie Wang, Traditional Chinese Medicine Hospital of Zhuanghe City

Yan-Hou Liu, Fang Lu, Su-Qing Lou, The People's Hospital of Zhuanghe City

Yuan Yuan, female, born on October 28<sup>th</sup>, 1956 in Jinzhou, Liaoning Province, graduated from the Faculty of Medicine, China Medical University in 1982. Associate Professor, engaged in the etiologic analysis and early diagnosis of gastric cancer, with more than 40 published papers

Author contributions: All authors contributed equally to the work.

Supported by The "Eighth 5 year plan" National Science and Technology Foundation (85-914-01-10).

Original title: *China National Journal of New Gastroenterology* (1995-1997) renamed *World Journal of Gastroenterology* (1998-).

Correspondence to: Yuan Yuan, MD, Cancer Institute, China Medical University, Shenyang 110001 Liaoning Province, China  
Telephone: +86-24-3866766-6351

Received: November 17, 1996  
Revised: January 31, 1997  
Accepted: March 1, 1997  
Published online: June 15, 1997

### Abstract

**AIM:** To study the pathogenetic effects of salted pork (SP) (a special food in Zhuanghe City, a region of northern China that is a high-risk area for stomach cancer) on stomach cancer, and a provide scientific basis for the primary prevention of stomach cancer in this high-risk region.

**METHODS:** This study consisted of three distinct parts. The first part involved a study of SP mutagenicity and employed both the Ames test and micronuclei assay using *V79* cells. The second part included a study of SP's effect on the gastric mucosa of residents in the Zhuanghe area who had consumed SP for more than ten years. Additionally, these studies involved an analysis of the dose effect relationship between SP and pathological changes in gastric mucosa, with a total of 300 cases analyzed. The third part of this study involved an observation of the mucosal lesions from experimental dogs by both gastroscopy and mucosal biopsy. Six healthy male dogs were selected, three were fed with SP, and the others served as controls.

**RESULTS:** This study revealed that SP extract could mutate *Salmonella typhimurium* TA<sub>98</sub> and induce an increase in both the micro

nuclei rate (MNR) and micro nuclei cell rate (MNCR) of *V79* at a dose range of 20-80  $\mu$ L/mL. There were significant dose-effect relations between SP and either MNR or MNCR. Pathological changes in the gastric mucosa of local residents who had consumed SP were significantly different from those of the control group. In people who had consumed SP for ten years, mucosal lesions were found that contained evidence of necrosis and erosion; In those who consumed SP for ten-20 years, both hyperplasia and dysplasia were seen in addition to the above lesions. In individuals who had consumed SP for 20-30 years, severe dysplasia and malignant changes were found. Furthermore, SP had damaging effect on the gastric mucosa of dogs that were fed SP. The mucosal lesions became more severe with increased feeding time.

**CONCLUSION:** SP is a strong mutagen and long-term SP exposure may result in repeated gastric mucosal damage and repair, ultimately leading to severe dysplasia and malignancy.

**Key words:** Stomach neoplasms/etiology; Meat; Mutagenicity; Gastric mucosa/pathology

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Yuan Y, Lin HZ, Zhang YC, Wang XJ, Wu YQ, Gao H, Wang L, Liu YH, Lu F, Lou SQ. Pathogenetic effects of salted pork in an area of China with high-risk for stomach cancer. *World J Gastroenterol* 1997; 3(2): 93-94 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v3/i2/93.htm> DOI: <http://dx.doi.org/10.3748/wjg.v3.i2.93>

### INTRODUCTION

Zhuanghe City is an area in northern China with an elevated occurrence of stomach cancer. The mortality of stomach cancer is 49.6/100000 for males and 22.2/100000 for females. Epidemiological investigations found that there was a close relationship between the high mortality of stomach cancer and the dietary habits of local residents. Salted pork (SP) is a special food consumed in this area<sup>[1]</sup>. In order to understand the pathogenetic effect of SP on stomach cancer, we studied three distinct aspects of SP: Its mutagenicity defined as the effect of SP on the gastric mucosa of local Zhuanghe residents who had consumed SP for more than ten years, the dose-effect relationship between SP and pathological changes of the gastric mucosa and the mucosal lesions of experimental dogs fed with SP.

### MATERIALS AND METHODS

#### Test of salted pork mutagenicity

SP samples were collected from residents in Mingyang town,

**Table 1 Ames test on salted pork**

Samples	Mutagenicity (rev/g TA <sub>98</sub> )	
	-S <sub>g</sub>	+S <sub>g</sub>
Salted pork		
-NaNO <sub>2</sub>	8640	13000
+NaNO <sub>2</sub>	8810	14900

**Table 2 Micronuclei test of salted pork-induced V<sub>79</sub> cells**

Samples	-S <sub>g</sub>		+S <sub>g</sub>	
	MNR	MNCR	MNR	MNCR
Extract of salted pork (0 mL/L)	13	12	9.0	8.0
Extract of salted pork (20 mL/L)	19	17	5.0	5.0
Extract of salted pork (40 mL/L)	19	17	8.5	8.5
Extract of salted pork (80 mL/L)	27	20	6.0	5.0
Methyl nitrate nitrosoguanidine (5 mg/L)	96	86		
Aflatoxin B1 (0.01 mg/L)			19.0	18.0

MNR: Micro nuclei rate; MNCR: Micro nuclei cell rate.

Zhuanghe City. After the nitrosation treatment and filtering of SP, the Ames test and micro nuclei assay using V<sub>79</sub> cells were conducted. The experimental methods were used based on previous reports<sup>[2]</sup>.

#### **Histopathological examination of the gastric mucosa of local residents who did or did not consume SP**

Among 12000 local residents in the Zhuanghe area who had consumed SP for many years, 150 residents who consumed SP four times a week (about 1000 g) were selected as subjects for the study, including 40 who had consumed SP continuously for ten years, 60 for 20 years, and 50 for 30 years. Another 150 residents who were matched in both sex and age but had not consumed SP were selected as controls. A retrospective investigation and comparative analysis of the living habits and dietary structure during the past 30 years in the two groups were conducted, which involved gastroscopies and mucosal biopsies. Biopsies covered the antrum, gastric angle, and anterior and posterior body of the stomach, respectively. The 1200 samples of mucosal biopsies were fixed with formalin, and routine paraffin sections, H and E staining, AB/PAS, as well as HID/AB staining were performed.

#### **Histopathological examination of the gastric mucosa from experimental dogs fed with SP**

Six two-month old healthy male dogs from the same strain that each weighed 4.5 kg were chosen for the experiment. The dogs were randomly divided into test and control groups (three dogs per group). The dogs in the test group were fed three times a day with SP that had been mixed with maize gruel (150 g). The dogs in the control group were fed with fresh pork mixed with maize gruel and vegetables. Any additional feeding conditions were the same for the experimental and control groups. During pre- and inter-testing, gastroscopies and mucosal biopsies were performed on the anterior and posterior wall of both the dog's antrum and body of its stomach, respectively. At the end of the test (12 mo later), an autopsy was performed and the stomachs were dissected and opened along its greater curvature. The specimens were then fixed in formalin. Blocks of gastric wall were isolated from the cardia to the pylorus, including the anterior and posterior body, antrum, esophagus and duodenum. After routine sectioning and staining, histopathological examinations were made on the gastric mucosa samples.

## **RESULTS**

#### **Ames test of SP mutagenicity**

In this study, whether or not SP was treated with nitrosation or S<sub>g</sub> and mixed with SP, the reverted number of salmonella typhimurium TA<sub>98</sub> all increased significantly. These findings indicate that SP extract is a strong mutagen to strain TA<sub>98</sub> (Table 1).

#### **Micronuclei test of SP-induced V<sub>79</sub> cells**

The SP extract could increase both the micronuclei rate (MNR) and micronuclei cell rate (MNCR) of V<sub>79</sub> cells at a dose range between 20 mL/L-80 mL/L. There were dose-effect relations between SP and either MNR or MNCR. Up to an 80 μL dose of MNR was two times higher in the test group when compared with that of the control group (Table 2).

#### **Histopathological examination of the gastric mucosa from local residents**

Necrosis and erosion foci (55/150, 36.6%), hyperplasia and dysplasia (31/150, 20.6%), as well as metaplasia (9/150, 6%) were detected in the gastric mucosa of 150 cases within the test group; one case of severe dysplasia was suspected of having cancer and poorly differentiated carcinoma in two stomachs were detected. Owing to different time spans of consuming SP, the degree of mucosal changes revealed significant differences. The pathological changes e.g. erosion and dysplasia became more severe with increased SP consumption over the years.

Among 150 cases from the control group, only a few cases were detected as having superficial gastritis, metaplasia and atrophic gastritis.

#### **Histopathological examination of the gastric mucosa from experimental dogs**

In this study, gastroscopic and histopathological examinations were done on three experimental dogs and three control dogs at the time of pre-, inter- (feeding SP for eight months) and post-experiment (12 mo later). Compared with the control group, the gastric mucosa from the test group showed various changes, which included erosion, necrosis, hyperplasia, inflammation, etc. These mucosal lesions became more severe with increased time of SP feeding.

## **DISCUSSION**

Although a few reports have been made on the pathogenesis of food in areas at high-risk for stomach cancer, studies on SP pathogenesis have not proven fruitful. In this study, we verified that SP from Zhuanghe City, an area in northern China at high-risk for stomach cancer, showed a strong occurrence of mutagenicity and demonstrated the damaging effect of SP on the gastric mucosa of dogs. Pathological changes of the gastric mucosa from local residents who had consumed SP showed significant differences from those of the control group. In people who had consumed SP for ten years, gastric mucosal lesions, which included signatures of erosion, necrosis and inflammatory change, were seen; in those for ten-20 years, hyperplasia and dysplasia were found in addition to the above specified lesions, and both severe dysplasia and malignant changes were observed in those who had consumed SP for 20-30 years.

There were significant differences in the mucosal changes observed between the test and control groups. Within the test group, the degree of mucosal changes, particularly erosion, metaplasia, dysplasia and tumorigenesis, had a positive relationship with the duration of SP consumption. This indicated that long-term exposure to SP may result in repeated gastric mucosal damage and repair, ultimately leading to severe dysplasia and malignancy. The results of this study may provide an important scientific basis for carrying out "primary prevention" by changing dietary habits in order to decrease the incidence of stomach cancer in the Zhuanghe area.

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S- Editor: Filipodia L- Editor: Jennifer E- Editor: Liu WX



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ISSN 1007-9327

