

No Impact of Repeated Endoscopic Screens on Gastric Cancer Mortality in a Prospectively Followed Chinese Population at High Risk¹

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Background. Gastric cancer (GC) is the leading cause of cancer deaths in China. Our study prospectively evaluated the impact of repeated endoscopic screens on GC mortality in a high-risk population in China.

Methods. Between 1989 and 1999, a population-based gastroscopic screening was conducted in 4,394 residents of Linqu County, China, a region with the highest rates of GC worldwide. Residents ages 35 to 64 years received initial gastroscopies with biopsies in 1989. Repeated endoscopies were performed in 1994 and 1999. Cancer occurrences and deaths were actively monitored throughout the entire period until July 2000. Mortality from GC was compared with expected values based on mortality rates obtained for Linqu in the 1990–1992 Chinese Cancer Mortality Survey.

Results. Between March 1989 and July 2000, 39,303 person-years were accumulated; 85 new GCs occurred, 29 (34.5%) were in early stage. Fifty-eight cases (68%) were identified at one of the screens. The number of observed deaths from GC (37) was close to the expected (36.8). The standardized mortality ratio was 1.01 (95% CI 0.72–1.37) for the entire cohort, 1.13 (95% CI 0.77–1.57) for males, and 0.65 (95% CI 0.26–1.32) for females.

Conclusions. Despite high population coverage with repeated screens, no reduction in GC mortality was observed in this high-risk population in China.

Key Words: stomach neoplasms; gastroscopy; mortality; China.

INTRODUCTION

Despite a recent decline in gastric cancer (GC) death rates in many countries, GC is still the leading cause of cancer mortality in China and second cause of cancer deaths worldwide [1, 2]. A number of risk factors have been associated with the development of GC, but effective strategies for primary prevention are not yet available. In Japan, mass screening by X-ray examination was introduced in 1960 to reduce GC mortality through early detection and subsequent curative treatment [3]. Yet, the effectiveness of the Japanese screening program in reducing GC mortality, implemented as a community service for all persons aged 40 years and older, remains controversial [4]. Most reports on its success rely on time-trend analyses in GC incidence and mortality or on retrospective analyses using a case-control design [5–7]. While the drawbacks of the previous retrospective studies are recognized, little prospective data are available. In a recent preliminary report from a prospective cohort in Japan, no reduction in GC mortality was observed in the screened versus unscreened groups over a 40-month period of follow-up [4]. In this study, screening participation was ascertained by self-report and not prospectively observed. The accuracy of recall for cancer screenings, however, is limited [8].

The participation rate in the voluntary Japanese program is relatively low. Although more than 4 million individuals are screened each year, this number reflects

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only about 14% of the eligible population [4]. In order to evaluate the potential impact of such a screening program on GC mortality more accurately, a population-based screening with higher screening coverage would be ideal.

While GC screening is widespread in Japan, no systematic screening programs have been established in China despite similarly high GC mortality rates in many regions of the country. In Linqu County, a rural area of Shandong Province in China, GC mortality rates are among the highest in the world [9]. In this region, age-adjusted mortality from GC exceeded 55 deaths per year per 100,000 population in 1990–1992 (unpublished rate communicated by Dr. J. Ma). The high death rates from the disease, as well as the homogeneity and stability of the Linqu population, render this region ideal for population-based studies on GC. Between 1989 and 1999, a population-based screening with repeated gastroscopic exams was conducted among 4,394 adult residents in Linqu [10].

Herein we report the effect of repeated follow-up gastroscopies on GC mortality in this prospectively screened and closely followed Chinese population at high risk.

METHODS

Study Population

Our data arise from a cohort study conducted by the National Cancer Institute (NCI) and the Beijing Institute for Cancer Research (BICR) in Linqu County, a rural area in Shandong Province, China, described previously [10,11]. In brief, an endoscopic screening program for GC was launched among 3,399 residents in 14 randomly selected villages of Linqu in 1989/1990, representing 83% of residents aged 35–64 years. The 14 villages were selected at random from four randomly selected townships in Linqu County [9,12]. After providing informed written consent, those willing and healthy enough to participate underwent physical and gastroscopic examinations. Individuals with significant clotting disorders, high blood pressure, liver disease, or chronic obstructive pulmonary disease were excluded. Gastroscopies were performed with fiber-optic gastroscopes (Olympus) by three gastroenterologists. The gastric mucosa was examined macroscopically and biopsies were taken from seven standard sites: four from the antrum, one from the angulus, and two from the body. Additional biopsies were taken in case of suspect lesions elsewhere. The biopsies were fixed in formalin solution, embedded, and stained with hematoxylin and eosin. Three senior pathologists at BICR performed histopathological analyses of the biopsies according to a protocol proposed by the Chinese Association of Gastric Cancer [13]. The classification criteria for superficial gastritis

(SG), chronic atrophic gastritis (CAG), intestinal metaplasia (IM), dysplasia (DYS), and GC were described in detail and published along with photographs in an earlier paper [9]. Each biopsy was assigned a diagnosis based on the most severe lesion in the individual slide, and each subject was given a global diagnosis based on the most severe histology among all the biopsies. All 3,399 participants of the baseline screen in 1989/1990 were subsequently followed with close monitoring of death and cancer occurrences.

A repeat gastroscopic screening was offered to all cohort members in 1994 to determine the progression of precancerous gastric lesions that had been observed at baseline. Two thousand seven hundred ten subjects participated in this repeat examination. Subsequently, 2,416 became part of an intervention trial that was launched in 13 of the 14 villages in Linqu in 1994 [10]. The 2,416 subjects from the initial cohort were supplemented with 995 new individuals who had entered the eligible age range of 35–64 years. Each of the 3,411 individuals in this intervention trial received a gastroscopy with biopsy in 1994. Starting in 1995, three interventions were begun to determine if (1) treatment with amoxicillin and omeprazole to eradicate *Helicobacter pylori*; (2) dietary supplementation with vitamin C, vitamin E, and selenium; or (3) supplementation with garlic extract could reduce the high prevalence of gastric precancerous lesions in this population. In the intervention trial, *H. pylori* IgG and IgA antibody concentrations were measured using an enzyme-linked immunosorbent assay [14]. A subsequent gastroscopic examination was performed in 1999. Three thousand one hundred ninety-four of the 3,411 intervention trial participants underwent gastroscopy with biopsy in the spring of 1999. Evaluation of the intervention trial is ongoing.

Thus, three gastroscopic screenings were performed between 1989 and 1999 at approximately 4.5-year intervals. A subset of 689 high-risk individuals with pronounced premalignant lesions at baseline received an additional interim gastroscopy in 1992. In all screens, the same histopathological and endoscopic procedures were applied. A total of 4,394 residents were screened, including 3,399 from 1989/1990 and 995 from 1994. Figure 1 summarizes the numbers of residents examined at each screen.

The study was approved by the Institutional Review Board of the NCI and the BICR (separate approval for both parts in 1989 and 1994).

Follow-up and Documentation of Cancers and Deaths

A total of 4,394 cohort members were followed. For each cohort member, the observation period started at the date of initial endoscopy and ended at the date of

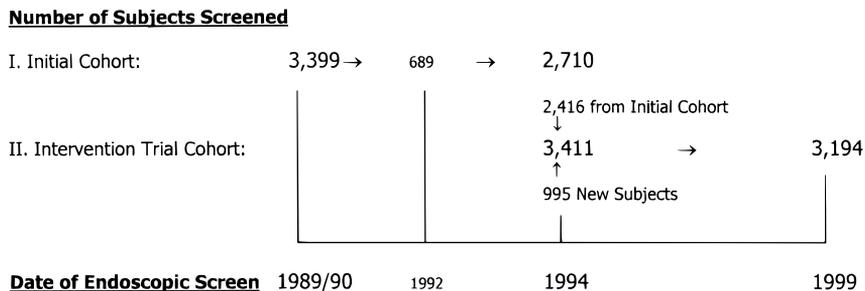


FIG. 1. Numbers of subjects with completed endoscopic exam at each of the screens. 2,416 subjects were members of both cohorts. In 1992, an additional interim endoscopy was performed on 689 subjects who had been identified as high risk with pronounced precancerous lesions at the initial screen in 1989/1990.

death or emigration or on July 30, 2000, whichever came first. Deaths, cancer occurrences, and emigration status were actively monitored throughout the entire period. Village doctors were contacted every 3 months to update follow-up information. In case of a new cancer or death, diagnostic information was reviewed by the BICR and local pathologists and field staff physicians. Death and cancer abstract forms were completed and computerized based on the information gathered. GCs were diagnosed as such if histopathological confirmation was available or overtly malignant behavior of the tumor (infiltrative growth, metastasis) was present. For this study, the following information was extracted from the abstract forms: date of birth, gender, earliest date of diagnosis, date and cause of death (GC/other), basis for diagnosis (histology/other), tumor location, histological type, and modality of treatment (surgical/nonsurgical). For GC cases, field staff was contacted to confirm that the cancer was diagnosed at screen or became clinically evident intercurrently. Since tumor stage was not included in the abstract forms, it was compiled from available endoscopy, histopathology, and/or surgical reports by field staff physicians. Detailed postoperative pathological stages classified according to the TNM system were not available. Tumor stages were therefore recorded as localized, regional, distant, or unstaged neoplasms in accordance with the stage categories used in the Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review of the NCI [15].

Statistical Analysis

Mortality from GC and from all causes in the cohort was compared with expected values based on rates obtained for Linqu County in the 1990–1992 nationwide cancer mortality survey [1]. Constant county rates up to the year 2000 were assumed. Sex-, calendar year-, and 5-year period age-adjusted mortality rates in this reference population were multiplied by the person-years under observation in the screened cohort in order to compute the number of expected deaths. The observed number of deaths in the cohort was then divided

by the expected number to obtain the standardized mortality ratio (SMR). To test for statistical significance, 95% confidence intervals (CI) were calculated for the SMR under the assumption that the observed number of deaths followed a Poisson distribution [16].

Survival time was calculated in months after diagnosis until the end of follow-up (July 30, 2000) or death due to GC. Deaths due to other causes were treated as censored. Survival curves were calculated according to Kaplan and Meier [17]. Survival rates were expressed as cumulative 5-year net survival, in percentage, with their respective 95% CI. Statistically significant differences were determined by the two-sided log-rank test [18].

Descriptive and survival analyses were performed with the statistical software package SAS (Version 8.0, SAS Institute, Cary, NC). Mortality analyses were conducted with Epicure (EpiWin Version 1.2, HiroSoft International Corp., Seattle, WA).

RESULTS

Four thousand three hundred ninety-two of the 4,394 subjects were included in the analyses; 2 cohort members were omitted because of missing birth dates. A total of 39,303.4 person-years were observed; 260 cohort members died (189 male) and 310 (7.05%) were lost to follow-up.

All cohort members received at least one screening examination, 3,674 (84%) were examined at least twice, and 2,440 (56%) had three endoscopic exams at intervals of approximately 4.5 years. Five hundred twenty-six (12%) individuals received four endoscopic exams. This last group includes the high-risk subgroup with an additional gastroscopy in 1992.

During the approximately 11.5-year follow-up, 85 GC cases were identified. Fifty-eight (68%) were diagnosed at one of the screens, while 27 cases became clinically evident in between the screens (intercurrent cases). Table 1 summarizes clinical and pathological characteristics of all 85 GC cases detected between Spring 1989 and Summer 2000. Among the 58 screen-detected cancers, 26 (45%) had localized disease at diagnosis,

TABLE 1
Characteristics of All Gastric Cancer Cases from the Linqu Cohort

Characteristic	<i>n</i> (%) ^a
Number of cases (<i>n</i>)	85
Diagnosed	
At endoscopic screen	58 (68%)
Intercurrently	27 (32%)
Age (years)	
Median	60
IQR ^b	50–65
Male gender	66 (77.6%)
Tumor type	
Adenocarcinoma	70 (82.4%)
Leiomyosarcoma	1 (1.2%)
Not specified	14 (16.5%)
Tumor location	
Cardia	7 (8.2%) ^c
Body/fundus	13 (15.3%)
Angulus	11 (12.9%)
Antrum/pylorus	49 (57.6%) ^d
Not specified	5 (5.9%)
Tumor stage ^e	
Localized	29 (34.1%)
Regional	14 (16.5%)
Distant	35 (41.2%)
Unstaged	7 (8.2%)
Treated by surgery (incl. palliative)	62 (72.9%)

^a Due to rounding percentages may not add up to 100%.

^b IQR, interquartile range.

^c Includes one case with overlapping tumor growth into gastric fundus/body.

^d Includes seven cases with overlapping tumor growth into gastric body.

^e For stage definition see footnote to Table 2.

whereas only 3 (11%) of the intercurrent cases had localized disease. The distribution of tumor stages across screens was heterogeneous (Table 2). While 69 and 76% of those diagnosed at screen in 1989/1990 and 1994, respectively, had localized disease, stage distribution was less favorable among those diagnosed at screen in 1999. However, with 40% distant and 45% regional cancers, the stage distribution was still considerably

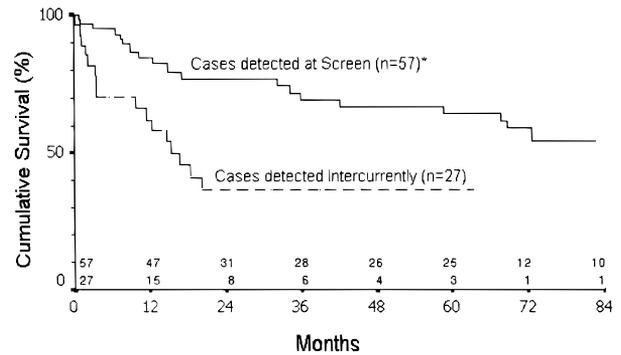


FIG. 2. Kaplan–Meier curves of GC cases from the Linqu cohort comparing the survival of cases detected at screen with the survival of cases detected intercurrently ($P = 0.0049$, log-rank test). The numbers above the *x* axis indicate the numbers of follow-up cases (diagnosed at screen, upper row; diagnosed intercurrently, lower row). *One case with leiomyosarcoma was omitted from the analysis.

more favorable at the 1999 screen than for intercurrent cases. Figure 2 compares the survival of screen-detected GC cases with the survival of cases diagnosed in between the screens. Corresponding to their considerably worse stage distribution, the intercurrent cases exhibited a clearly inferior survival. The screen-detected cases had a cumulative 5-year survival of 63.7% (95% CI 49.9–77.6%) as opposed to only 36.4% (95% CI 17.2–55.7%) for the intercurrent cases; the difference between the two curves was statistically significant (two-sided log-rank test, $P = 0.0049$).

Table 3 reports the observed and expected deaths, the SMRs, and the 95% CI for all causes of death and for death from GC. Compared to expected numbers based on rates for Linqu County, mortality from all causes was significantly reduced among the cohort subjects. This held true for both sexes; especially among females, mortality from all causes was reduced by over 40%. For GC, however, the number of observed deaths among the screened cohort members was close to the expected. The SMR in both sexes combined and for males was close to 1; the SMR for women was slightly

TABLE 2
Stage Distribution of Gastric Cancer Cases from the Linqu Cohort by Time of Diagnosis

Time of diagnosis	<i>n</i>	Tumor stage ^a			
		Localized	Regional	Advanced	Unstaged
Screen 1989/1990	13	9 (69%)	2 (15%)	2 (15%)	None
Screen 1992 (high-risk only)	8	2 (25%)	None	4 (50%)	2 (25%)
Screen 1994	17	13 (76%)	None	1 (6%)	3 (18%)
Screen 1999	20	2 (10%)	9 (45%)	8 (40%)	1 (5%)
Intercurrent	27	3 (11%)	3 (11%)	20 (74%)	1 (4%)

^a The following stage definitions were applied (adapted from the SEER Cancer Statistics Review [14]); localized, a neoplasm confined entirely to the stomach without serosal involvement regardless of nodal involvement; regional, a neoplasm that extends beyond the limits of the stomach and invades the surrounding tissue; advanced, a neoplasm that spreads to parts of the body remote from the primary tumor; unstaged, a neoplasm with insufficient or unavailable information to assign a category.

TABLE 3

Risk of Death from All Causes/Gastric Cancer among the Screened Cohort Members in Comparison with the Linqu General Population

Cause of death	Observed	Expected ^a	SMR ^b	95% CI
Gastric cancer				
1989–2000	37	36.8	1.01	0.72–1.37
Males	31	27.5	1.13	0.77–1.57
Females	6	9.2	0.65	0.26–1.32
1989–1994	11	11.4	0.97	0.50–1.66
1995–2000	26	24	1.08	0.72–1.55
All causes				
All	260	363.7	0.71	0.63–0.81
Males	189	236.1	0.80	0.69–0.92
Females	71	127.6	0.56	0.44–0.70

^a Expected numbers based on rates from the 1990–1992 Chinese Cancer Mortality Survey.

^b SMR, standardized mortality ratio = observed deaths/expected deaths.

reduced, but not significantly so (Table 3). When we calculated the SMRs separately for the periods 1989–1994 (initial cohort) and 1995–2000 (intervention trial cohort) in order to identify a possible impact of the interim exam in 1992 or the intervention after 1994 on GC mortality, no difference in the period-specific SMRs for GC was found. As observed for the entire period, mortality from GC was not reduced within the two separate periods.

DISCUSSION

The large population-based follow-up screening in Linqu County reported here is the first systematic screening for GC in China. Although the screening conducted in this population took place in the context of various protocols and was not specifically designed as a screening intervention to reduce GC mortality, the fact that the population was repeatedly screened and closely followed offered an opportunity to examine effects of screening on GC mortality. Unfortunately, our data show no reduction in GC mortality in this repeatedly screened population over a more than 10-year period of follow-up.

In Linqu, three endoscopic screens were performed, in 1989/1990, 1994, and 1999. In addition, an interim exam was conducted in a high-risk subgroup in 1992. Over 80% of the cohort members participated in at least two screens at approximately 4.5-year intervals, yet a reduction in GC mortality was not observed. Our prospective findings, even though not directly comparable, contrast with retrospective data from Japan that suggest a sustained reduction in GC mortality by more than 50% in screened versus unscreened groups for up to 5 years after a one-time screen [7].

Since tumor stage is the most important prognostic

factor following diagnosis of GC [19], a reduction in GC mortality through screening can be expected only if the overall proportion of early stage tumors is increased. In our cohort, only 34% (29/85) of all GCs were still localized at diagnosis. Although the stage distribution among cases diagnosed at screens 1989/1990 and 1994 was quite favorable, only 10% of the GCs were still localized at the 1999 screen. A relatively large number of 27 cases was diagnosed intercurrently, mainly in prognostically unfavorable advanced stages. Compared to those diagnosed at screen, their survival was considerably worse. Since screening coverage was high in this study and the same population was repeatedly examined, the low yield of cancers detected with localized disease suggests that screening intervals of approximately 4.5 years were in fact too wide. Too many cancers were diagnosed in late stages; a reduction in GC mortality was not observed.

Under ideal conditions with complete coverage and repeated screens in sufficiently narrow intervals, the number of intercurrent cases should reflect only the accuracy of the screening method. It is possible that some cancers were missed by the endoscopic exams. Small lesions, especially with a more infiltrative growth pattern, may be difficult to identify by gastroscopy [20]. Due to the standardized approach with biopsies and histopathological analyses for all screened subjects, however, it is unlikely that many cancers were missed. In fact, among the 27 intercurrent cases, only 5 became clinically evident within a year after the previous screen.

In the baseline survey in 1989/1990, less than 2% of the population had a normal gastric mucosa or SG only. Approximately 45% had CAG, 33% IM, and 20% DYS. In 1994, the odds of developing GC within the 4.5 years of follow-up were more than 100-fold higher among those with DYS compared with those with SG or CAG [11]. Although some observers might assume that nearly everybody in this population had been infected with *H. pylori* at some point in view of the extensive histopathology, the overall prevalence of *H. pylori* based on IgG or IgA elevations among trial participants was 66.9% in 1994, before the beginning of the intervention [10]. Prevalences were 63.3, 63.2, and 76.8 for 1996, 1997, and 1999, respectively.

A recent study followed nonconcurrently a group of patients with endoscopical diagnosis of early GC in whom surgery had been delayed or not been performed [21]. The median time until progression to advanced GC was estimated to be 44 months. Thus, assuming a constant rate of development of new cancers over time, screening intervals of about 4.5 years are likely to be too long for early detection of GCs especially in the case of tumors with a more rapid growth in a high-risk area.

For individuals with more advanced precancerous lesions detected at an earlier screen (1992 subgroup), even a 2-year interval might have been too wide.

A possible reason for failure to demonstrate an effect of screening on GC mortality would be ineffective treatment following cancer detection. In Linqu, the standard treatment for GC cases with localized and regional disease was surgical resection of the tumor and lymphatic drainage. The 5-year survival proportions for patients with localized and regional disease in this cohort, 92.4 (95% CI 82.3–100%) and 53.6% (95% CI 18.4–88.7%), respectively, are comparable with the favorable stage-specific survival rates reported from Japan [22]. Therefore, inefficient surgical treatment cannot explain the observed nonreduction in GC mortality.

Mortality from all causes of death was substantially reduced among members of the cohort. For both sexes combined, it was reduced by nearly 30%, for males by about 20%, and for females by more than 40%. Two main reasons may be responsible for this observation. First, only those individuals healthy enough to undergo endoscopy were included in the cohort; those with underlying illness were excluded. Second, participation in the screening might have led to an increased health consciousness and the close follow-up by medical personnel might have contributed to the reduced overall mortality.

Some limitations of our data should be considered. The number of GC cases from Linqu was relatively small and the period of follow-up was limited. Thus, although the estimated SMR was 1.01, the 95% CI of 0.72–1.37 admits the possibility of a 28% reduction in risk. Only a larger study with more GC events can increase the precision of our estimates. Our data are of observational character and were not primarily collected to evaluate the effect of repeated screens on GC mortality. The study design with two overlapping cohorts, an interim endoscopy in 1992, and an intervention since 1995 complicates the interpretation of the results. However, one would expect that an intervention implemented to reduce the progression of gastric premalignant lesions and a supplementary screen in a high-risk subgroup would rather result in an additional reduction in GC mortality, which was not the case. The period-specific SMRs equaled the overall SMR, which was close to 1 (Table 3).

For purposes of comparison, we referred to death rates obtained for Linqu County in the most recent cancer mortality survey in China. These rates are based on a nationwide retrospective survey conducted in 1990–1992. In Linqu, the surveyed population averaged approximately 750,000 residents per year [1]. This survey relied on a passive reporting system and on clinical diagnoses without histopathological confirmation in the majority of cases; thus, underreporting and misclassification may have led to underestimated GC

mortality rates in Linqu. Such underestimates would bias the SMR for GC toward 1, because the cohort members in our study were under active surveillance. However, a sensitivity analysis in which we gradually increased the Linqu rates for GC showed that at least 13 more expected GC deaths corresponding to an increase of 37% in the Linqu County rates would have been needed to yield a marginally significant reduction in the SMRs for GC (data not shown). It seems unlikely that so many GC deaths were missed by the survey. Also, the expected deaths were calculated under the assumption of constant county rates up to the year 2000. To check this assumption we compared the rates to the preceding survey conducted in 1975–1977 and found that age-adjusted mortality rates were nearly identical in 1990–1992. Thus, the assumption of stable county rates seemed plausible.

Despite these limitations, this study has several advantages over previous reports on GC screening. The effect of repeated screens on GC mortality was prospectively evaluated in an unselected, very stable, and homogeneous population at high risk. Actual participation was observed and not indirectly identified through self-reports or examinee files as in other studies [4,5,7]. All cohort members were screened at least once and were subsequently followed, regardless of participation in subsequent screens. This allowed for inclusion of screen-detected, as well as intercurrent GC cases in the analysis. The high degree of screening coverage minimized the possibility of self-selection bias inherent in retrospective analyses of programs with relatively low coverage, in which participation may be influenced by symptoms or, conversely, an increased health consciousness. Also, screening was performed by endoscopy with biopsy, a method with considerably higher diagnostic accuracy than radiography, yet more invasive and costly [23,24]. Consistent endoscopic and pathologic techniques were used throughout the entire period.

In conclusion, the results of our study suggest that repeated endoscopic screens in 4- to 5-year intervals do not result in a reduction of GC mortality in a population at high risk for GC. Despite employment of a screening method with high diagnostic accuracy and optimal screening coverage, the screening intervals appeared to be too long in order to detect a large number of tumors in prognostically favorable early stages. An intensified endoscopic surveillance program—especially for individuals with high-grade precancerous lesions—might have given more favorable results.

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REFERENCES

1. Li LD, Lu FZ, Zhang SW, Mu R, Sun XD, Huanpu XM, et al. Cancer mortality trends in China 1973–1992. *Zhonghua Zhong Liu Za Zhi* 1997;19:3–9. [In Chinese]
2. Pisani P, Parkin DM, Bray F, Ferlay J. Estimates of worldwide mortality from 25 cancers in 1990. *Int J Cancer* 1999;83:18–29.
3. Hisamichi S. Screening for gastric cancer. *World J Surg* 1989;13:31–7.
4. Inaba S, Hirayama H, Nagata C, Kurisu Y, Takatsua N, Kawakami N, et al. Evaluation of a screening program on reduction of gastric cancer mortality in Japan: preliminary results from a cohort study. *Prev Med* 1999;29:102–6.
5. Hisamichi S, Sugawara N, Fukao A. Effectiveness of gastric mass screening in Japan. *Cancer Detect Prev* 1988;11:323–9.
6. Oshima A, Hirata N, Ubukata T, Umeda K, Fujimoto I. Evaluation of a mass screening program for stomach cancer with a case–control design. *Int J Cancer* 1986;38:829–33.
7. Fukao A, Tsubono Y, Tsuji I, Hisamichi S, Sugihara N, Takano A. The evaluation of screening for gastric cancer in Miyagi Prefecture, Japan: a population-based case–control study. *Int J Cancer* 1995;60:45–8.
8. Tsubono Y, Fukao A, Hisamichi S, Hosokawa T, Sugawara N. Accuracy of self-report for stomach cancer screening. *J Clin Epidemiol* 1994;47:977–81.
9. You WC, Blot WJ, Li JY, Chang YS, Jin ML, Kneller R, et al. Precancerous gastric lesions in a population at high risk of stomach cancer. *Cancer Res* 1993;53:1317–21.
10. Gail MH, You WC, Chang YS, Zhang L, Blot WJ, Brown LM, et al. Factorial trial of three interventions to reduce the progression of precancerous gastric lesions in Shandong, China: design issues and initial data. *Controlled Clin Trials* 1998;19:352–69.
11. You WC, Li J, Blot W, Chang YS, Jin ML, Gail MH, Zhang L, et al. Evolution of precancerous lesions in a rural Chinese population at high risk for gastric cancer. *Int J Cancer* 1999;83:615–9.
12. You WC, Li JY, Jin M, Yang B, Hu S, Xu G. A study of precancerous lesions in a high risk population. *Chin J Cancer Res* 1989;1:53–57. [In Chinese]
13. Chinese Association of Gastric Cancer. Classification and diagnostic criteria for the histologic gastric and duodenal biopsy specimens. Liaoning: Liaoning Pub. House, 1981.
14. Zhang L, Blot WJ, You WC, Chang YS, Kneller RW, Jin ML, et al. Helicobacter pylori antibodies in relation to precancerous gastric lesions in a high-risk Chinese population. *Cancer Epidemiol Biomarkers Prev* 1996;5:627–30.
15. Gloeckler Ries LA, Kosary CL, Hankey BF, editors. SEER cancer statistics review 1973–1996. Bethesda (MD): National Cancer Inst., 1999.
16. Breslow NE, Day, NE. Rates and rate standardization. In: *Statistical methods in cancer research, Vol. II, The design and analysis of cohort studies*. Lyon: Int. Agency for Research on Cancer, 1987. [IARC Scientific Publication No. 82]
17. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1953;53:457–81.
18. Kalbfleisch JD, Prentice RL. The log-rank test. In: *The statistical analysis of failure time data*. New York: Wiley, 1980:79.
19. Shiraishi N, Inomata M, Osawa N, Yasuda K, Adachi Y, Kitano S. Early and late recurrence after gastrectomy for gastric carcinoma. *Cancer* 2000;89:255–61.
20. Hosokawa O, Tsuda S, Kidani E, Watanabe K, Tanigawa Y, Shirasaki S, et al. Diagnosis of gastric cancer up to three years after negative upper gastrointestinal endoscopy. *Endoscopy* 1998;30:669–74.
21. Tsukuma H, Oshima A, Morii T. Natural history of early gastric cancer: a non-concurrent, long-term, follow-up study. *Gut* 2000;47:618–21.
22. Maruyama K, Sasako M, Kinoshita T, Sano T, Katai H. Surgical treatment for gastric cancer: the Japanese approach. *Semin Oncol* 1996;23:360–8.
23. Babazono A, Hillmann AL. Declining cost-effectiveness of screening for disease. The case of gastric cancer in Japan. *Int J Technol Assess Health Care* 1995;11:354–64.
24. Longo WE, Zucker KA, Zdon MJ, Ballantyne GH, Cambria RP, Modlin IM. Role of endoscopy in the diagnosis of early gastric cancer. *Arch Surg* 1987;122:292–5.