

# Screening for Gastric Cancer: Is endoscopy the best option?

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Gastric cancer is the second most frequently occurring type of cancer in men, and the fourth in women in our country. It is the leading cause of cancer mortality according to the *Instituto Nacional de Cancerología de Colombia* (2005), which makes this type of work of primordial importance. Attempts at early diagnoses will always be crucial and important crucial in order to change the today's reality in which 80% of these lesions are diagnosed in later stages.

In this issue of the magazine, Dr. Emura et al (7) presented the results of two massive campaigns in Bogotá which used endoscopy to screen for premalignant lesions and gastric cancer. 650 patients were evaluated using a standardized protocol for systematic endoscopy with the use of chromoscopy, electronic-optical narrow band imaging (Olympus) and indigo carmine supravital stain. Premalignant gastric lesions (atrophic gastritis, intestinal metaplasia and dysplasia) were found in 30% of the patients in the study. Two cases of early gastric cancer were found as well.

The country with most experience in screening for gastric cancer is Japan, with the emergence in 2008 of guidelines for screening based on systematic review and evaluation of methods used over the past 40 years (1). The objective was to evaluate methods in light of available evidence and experience in recent years.

Around 1960, photofluorography to screen for gastric cancer started to be used in the prefecture of Miyagi. This practice was adopted as a public health strategy throughout the country. In 1983 a Health Service law was introduced for gastric cancer screening for all residents aged 40 and older. In 2004, 4.4 million people participated for a screening rate of 13% (2). Fluoroscopy is recommended based on results of case-control and cohort studies. Other methods used include endoscopy, serum pepsinogen and testing for antibodies to *H. pylori*. All used in the clinical setting as opportune methods of screening. These concepts were outlined by Tashiro in 2006 (5).

At this point, I think it is important to remember that two types of screening exist: population screening referred to in the article by Dr. Emura (7) is applied to a geographically defined population. It has a program covering most of the population of that area, which, if not complete, covers a representative sample of the study population as determined by an appropriate sampling. Thus, results of this type of study retain their external validity and can be used later in health policy making. The other type is opportune screening performed within the clinical setting. The primary objective of this type of study is measured in decreases of the incidence and mortality and thus implies monitoring. Continuing with the analysis of population screening studies, our key outcome is mortality. Patients in this type of study should be followed up on for at least 5 years.

The target population in screening studies should be asymptomatic with an average risk of gastric cancer. This means that individuals with family histories or known risk factors must be excluded from these studies. When undertaking a screening program, the population in which sampling will be done must first be defined. For this there are different methods, all of which apply only to asymptomatic patients. Screening tests must be highly sensitive, easy to apply, noninvasive and inexpensive (8).

With this in mind a pubmed search of literature on screening for gastric cancer from 2000 to 2010 was conducted. Search terms of "screening-gastric-cancer-neoplasm-pre-malignant lesions" were entered and found 17,043 items. None of these items refers to either chromoendoscopy, or the narrow band imaging (NBI) as screening tests. There are two Japanese studies of screening that are systematic literature reviews (1 and 5). From this research found the following:

1. Photofluorography (Level of evidence: 1 ++). There are no controlled clinical studies on this topic, but we found 5 case-control studies and two cohort studies. Despite their limitations, the main confounding variables were taken into account in the evaluation of the studies. One case-control study was conducted in Venezuela and the other in Japan. These showed a decrease of 40% to 60% in gastric cancer mortality using photofluorography screening. The sensitivity of photofluorography was between 60% and 80%, while its specificity was between 80% and 90%. The only reported adverse effect was exposure to radiation which was negligible.
2. Endoscopy (Level of evidence 2): There are no studies evaluating the efficacy of screening endoscopy in Japan. There is a Chinese study (6) which showed no changes in mortality rates. There are only two studies reporting on the accuracy of endoscopy as a diagnostic tool rather than as a screening tool. The populations had dyspepsia, and various gastrointestinal symptoms. There was no mortality data for the patients screened, nor were side effects of endoscopy reported.
3. Serum pepsinogen (Level of evidence 2) (3): Available data to date are low quality. There is insufficient evidence for use outside of the diagnosis of atrophic gastritis, but DR. Mikki has been working hard using an index that could have greater value, and also working on using gastrin and /or antibodies to H. pylori for screening (4).
4. Antibodies against H. pylori (Level of evidence: 2-): In combination with pepsinogen.

This review has not shown that endoscopy is a good method for screening, different from its usefulness as a diagnostic test, which obviously is increasing with the use of chromoendoscopy and NBI as noted in the article

by Emura et al. (7) It seems important to recall here the difference between screening performed in asymptomatic populations and diagnostic testing applied to individuals with symptoms.

When a screening program is designed, the selection of the population in the geographical area chosen for sampling is essential. However, there are multiple options. It is very difficult to get a representative sample of the population and avoid selection bias that subsequently limits the external validity of results (9). According to the literature, individuals were solicited through advertisements. This method introduces selection bias because most likely people or individuals who answer these calls have discomfort or symptoms (Remember that a screening program is aimed healthy individuals.) Neither the methods for choosing the geographical area in which sampling was performed, nor the sampling methods used, were reported. Moreover, I do not have clarity on the calculation of sample size (Generally it helps if one knows the required number of screened individuals for diagnosis of gastric cancer.) In addition, it is not clear what denominator was used to calculate incidence rates and/or prevalence. If we still think this was a mass screening, it still does not express how follow up was going to be conducted for individuals screened.

The purpose of this study is unclear as is the issue of whether or not chromoendoscopy was used for screening. If it was, where was its sensitivity and specificity validated in order to define whether or not it was a good screening test? Research in various different databases does not show any literature to date that supports the use of chromoendoscopy and NBI for the purpose of screening.

When a diagnostic test is chosen for screening it must have certain characteristics. It must be sensitive, and as non-invasive and inexpensive as possible. To date, these features are not known about the chosen test. As noted above, the initial Japanese studies of screening validated their tests in the cases of fluoroscopy, and pepsinogen I and II. It would be interesting to know the sensitivity and most importantly the specificity and the area under the receiver operating characteristic (ROC) curve (AUC). This would define the utility of chromoendoscopy as a diagnostic test.

Do the materials and methods express what will be realized in a cross-sectional study to determine the prevalence of gastric lesions and their relationship with H. pylori? Apparently with data obtained from two screening campaigns in Bogota. However the endoscopic technique and how to perform chromoendoscopy, biopsies and histological evaluations are all clear, which is interesting and important.

Since this is a screening study, the types of statistical tests used catch my attention. A program is used rather than a statistical package. Also the chi-square statistic is used. This is generally a statistical test used to prove a hypothesis. So, I

wonder, what is the hypothesis of this study? In this type of study I would like to know, what are the operating characteristics of endoscopy and chromoendoscopy as diagnostic tests given that the population sampled already had symptoms? Monitoring of screened patients was not recorded. How is to going to be performed? For these reasons the link with the final outcome, reduction in mortality from gastric cancer, is lost.

In the results, the pathological findings are presented as prevalences, using the number of participants in the study as the denominator. In reality, this is a relative frequency or prevalence in the study which cannot be extrapolated to the population of Bogota because the study 's design does not allow it. In other words, referring to the study:

- Mild chronic antral gastritis 21.8% (142/650)
- Moderate to severe chronic antral gastritis 77.4% (508/650)

Prevalence is a population measure: a rate where the numerator is the event and the denominator is the population defined geographically at the time when the event was recorded. Therefore, the information presented can only talk about absolute or relative frequencies. The results do not express how the measurement of the usefulness of chromoendoscopy was done nor whether the utility is economic or diagnostic, either or which would depend on the initial design of the study.

This study concludes that 1 in 325 healthy people living in Bogota has gastric cancer and 1 person out of every 33 people has a premalignant lesion. However, it is not clear where this statement comes from because there are no measurements of prevalence, nor are there expressions within the results which would statistically explain these findings. These numbers worry me. If we think that in Bogota there are 10 million people, and more than 50% of our population could have gastric cancer....! But this is meaningless because only 650 individuals were evaluated. We are back to the same thing, which is the size of the sample, and how was the population sampled! In summary, the external validity of the study does not allow such statements because

our prevalence would be 100 times or more than the prevalence in any other country in the world.

In conclusion, I consider that this effort was important, and that these lines of research should be stimulated. The methodology, the study design, and the statistical analysis have limitations. We must wait and see what the impact and utility of the use of chromoscopy will be. The conclusion is that those individuals who participated in the state had a high frequency of lesions predisposed to gastric cancer.

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