Serum biomarker-based screening of the risk groups of stomach cancer: Preliminary results of a feasibility study in Finland

Mide kanseri risk gruplarının "serum biomarker" temelli taraması

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Background and Aims: *Atrophic gastritis and acid-free stomach are the single most significant risk conditions for gastric cancer. In a pilot study (2012), we assessed i) the feasibility of a population-based screening for atrophic gastritis by a biomarker test (GastroPanel; Biohit Oyj, Helsinki), and ii) how to best organize this type of screening.* ***Materials and Methods:*** *In autumn 2012, all middle-aged men and women (aged 51–65 years) from four relatively small municipalities in South-Western Finland were invited for atrophic gastritis screening with the GastroPanel assay. The screening protocol was designed and implemented by a nationally operating large private supplier of medical and screening services (Health Care Finland, Ltd). The costs of the screening were included among the regular costs of the primary health care, which in Finland are the responsibility of the municipalities.* ***Results:*** *In the screened cohort, low (25 µg/l) pepsinogen I; levels were detected in 5% of the participating men, Helicobacter pylori infection was present in about 20%, and 29% of the screened subjects were referred for further medical examinations. A diagnostic gastroscopy was performed for 3.6% of screened subjects, with low pepsinogen I. These patients were referred for medical surveillance in local hospitals. In the final analysis, the effectiveness of this pilot screening program will be assessed by standardized mortality rate of gastric cancer,comparing the screened and not screened population, and by potential years of life lost and the rate of potential years of life lost for gastric cancer during several years of follow-up.* ***Conclusions:*** *In the short-term, the number of subjects with low pepsinogen I turned out to correspond the a priori assumptions of their frequency. The on-going annual surveillance of these patients by gatsrocopies should reduce the incidence of gastric cancer by 60%, standardized mortality rate due to gastric cancer by 50%, and the potential years of life lost -rates (premature deaths) due to stomach cancer by 70%. The number of individuals with Helicobacter pylori - infections was higher than expected. Taken together, this type of screening by serum biomarker test (GastroPanel) followed by endoscopy should result in a remarkable decrease in gastric cancer mortality and its cost-effectiveness is assumed to be high, since this is a once in the life-time screening by a biomarker.*

Key words: Screening, population-based, gastric cancer, serum biomarkers, pepsinogens, gastrin-17, *Helicobacter pylori*

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Giriş ve Amaç: *Atrofik gastritis ve gastrik anasidite gastrik kanser için en belirgin ve temel risk faktörüdür. Biz 2012 yılında yaptığımız pilot çalışmada i) Bir biyolojik belirteç ile atrofik gastritis ve toplum tabanlı taramanın fizibilitesini ve ii) Böyle bir tarama programının en iyi nasıl organize edileceğini değerlendirdik.* ***Gereç ve Yöntem:*** *2012 sonbaharında Güney Batı Finlandiya'nın birbirine benzer dört küçük bölgesinden tüm orta yaşlı kadın ve erkekler (51-56 yaş arası) GastroPanel testi ile atrofik gastritis taraması için davet edildiler. Tarama protokolü dizayn ve uygulaması ulusal düzeyde faaliyet gösteren Health Care Finland Ltd.tarafından yapıldı. Tarama programı giderleri Fnlandiya'da idarenin sorumluluğunda olan birinci basamak için uygun bir tetkik gideri olarak görüldü ve karşılandı.* ***Bulgular:*** *Tarama yapılan kohort grubun %5'inde serum pepsinojen I düzeyi düşük (25 µg/l) bulundu. Tarama yapılanların %20'sinde Helicobacter pylori (+)'ti ve tarama yapılan grubun %29'u ileri tıbbi tetkikler için yönlendirildi. Düşük pepsinojen saptanan gruba diagnostik gastroskopi yapıldı (%3,6). Bu hastalar tıbbi takip için yerel hastanelere sevk edildi. Tarama programının etkinliği; taranan ve tarama yapılmayanlardaki mide kanserine bağlı ölüm oranları ve gastrik kanser için takip edilenlerin potansiyel yaşam yılı kaybı ve oranları ile karşılaştırılarak değerlendirilecektir.* ***Sonuç:*** *Gastroskopi yapılan hastaların yıllık gözetimi; gastrik kanser insidansını %60, gastrik kansere bağlı mortaliteyi %50 ve mide kanserine bağlı (erken ölümlerde) potansiyel yaşam yılı kaybını %70 azaltacaktır. Yapılan taramada Helicobacter pylori enfeksiyonu beklenenden yüksek bulunmuştur. GastroPanel ile taramanın endoskopi ile takibi mide kanseri mortalitesinin belirgin şekilde azalmasını sağlar ve bu test ömür boyu bir kez yapıldığından maliyet etkin kabul edilmektedir.*

Anahtar Kelimeler: Tarama, toplum tabanlı, gastrik kanser, serum biyomarker, pepsinojenler, gastrin-17, *Helicobacter pylori*

Geliş Tarihi: 30.08.2013 • **Kabul Tarihi:** 30.08.2013

BACKGROUND AND OBJECTIVES

Gastric cancer (GC) remains to be among the most common cancers, with high mortality worldwide. In 2010, the number of new cases in Finland was 628 (both genders included) (1). The life expectancy of patients with GC is short, unless the disease is diagnosed at an early stage. The five-year cumulative survival ratio for male patients diagnosed with GC in Finland in 2002–2009 was only 23% (1).

It is estimated that approximately one half of all GCs will develop from atrophic gastritis (AG) and acid free stomach (2) – via so-called "Correa cascade". Identification of AG should be considered as a hallmark (warning sign) of GC, that should prompt endoscopic examination, which enables early diagnosis and treatment of the premalignant lesions while at asymptomatic stage (2,3). Furthermore, there is strong evidence (4-6) that low levels of serum pepsinogen I (SPGI) (and SPGI/II ratio) is a reliable biomarker of AG of the corpus, thus providing an accurate tool for non-endoscopic screening of AG and acid-free stomach (7). The optimal predictive value of SPGI for GC is likely to be achieved if biomarker screening is performed among middle-aged individuals (8-12).

Biomarker screening enables identification of the subjects at high risk for GC (8-11). Accordingly, an appropriately designed population-based screening by these stomach-specific biomarkers is capable of detecting the subjects with early pre-cancer lesions or conditions, i.e., AG, with or without on-going Helicobacter pylori (HP)-infection (8,9).

In 2012, a feasibility study was conducted to assess the value of GastroPanel (GP; Biohit Oyj, Helsinki, Finland) test in detection of the subjects with advanced AG, and accordingly at risk for GC. The screening protocol was developed by Health Care Finland Ltd, following the structure of their on-going mammographic screening programme. The present communication reports the key observations of this pilot study, focused on estimation, of the efficacy of GP-screening among middle-aged subjects, (followed by medical surveillance of all subjects with implicated AG), in reduction of mortality from GC and/or in prolongation of life.

MATERIAL and METHODS

In the target municipals, all eligible men and women (age groups 51-65 years) were invited by mail to the local communal health centre for blood sampling for the GP test by experienced laboratory nurses (Health Care

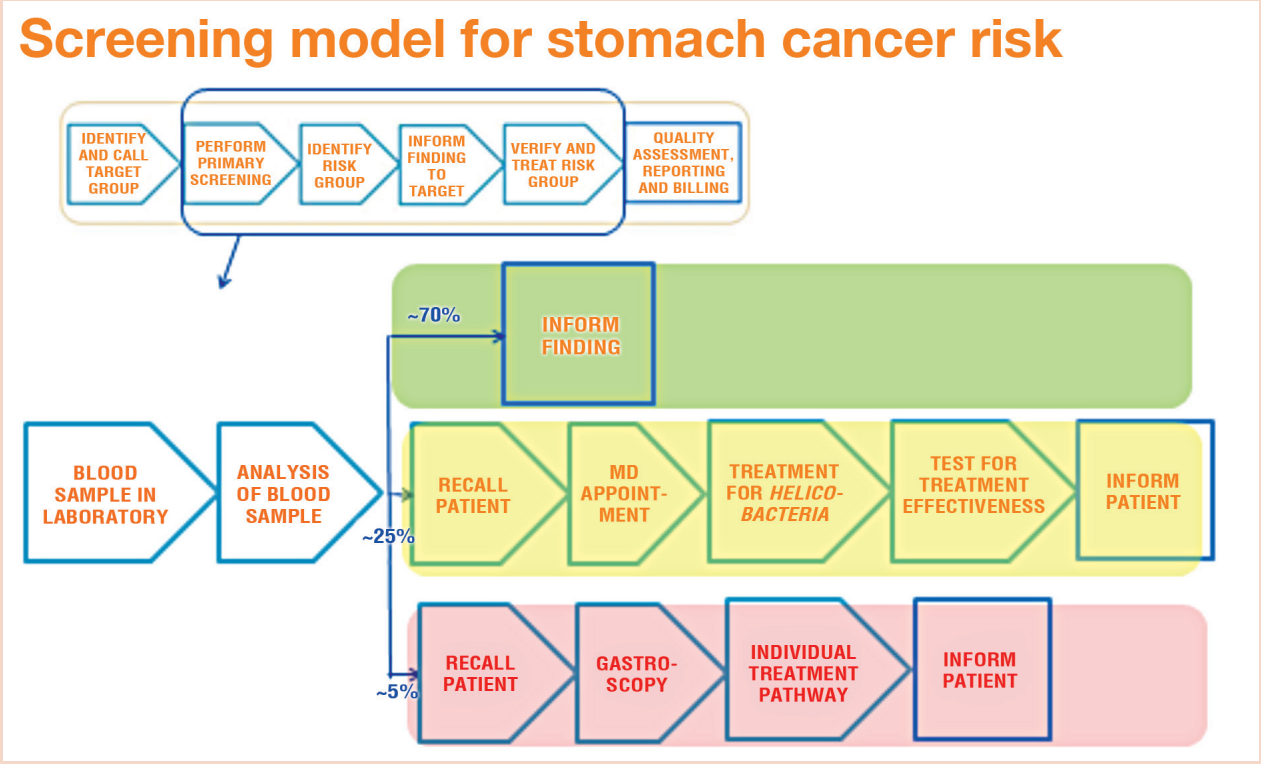

Figure 1. Screening model for gastric cancer screening

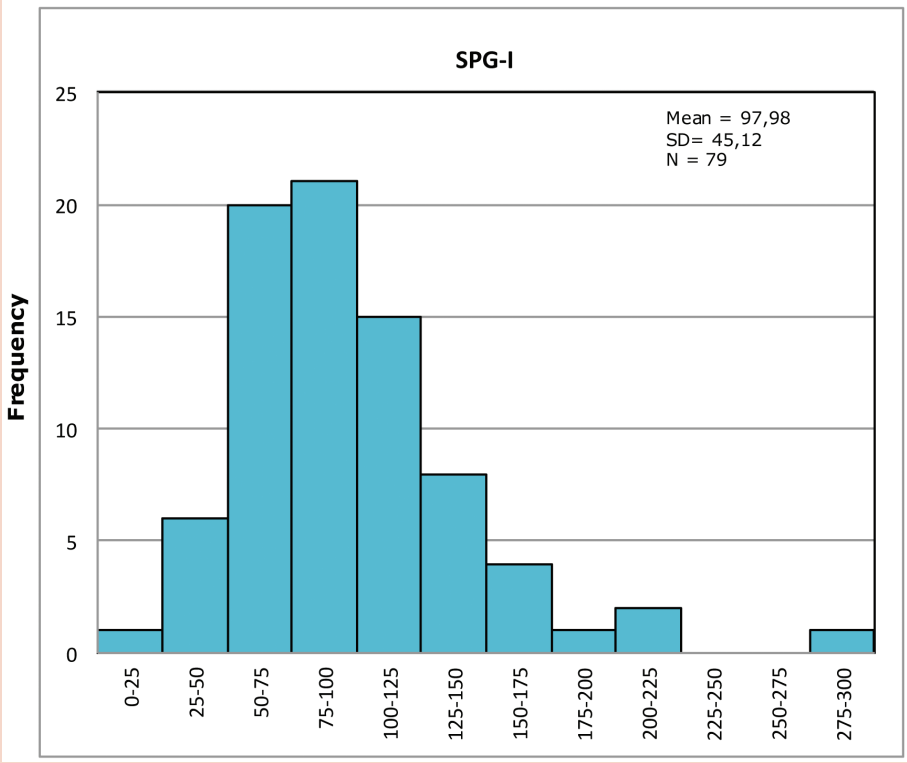

Figure 2. Distribution of SPGI levels in the screened population

Finland Ltd). Following the manufacturer's instructions, fasting sera were collected in EDTA tubes, and stored at -70 0C until analyzed. In this study, only two of the four GP-biomarkers (serum pepsinogen I and Helicobacter pylori) were analyzed using the specific ELISA tests provided by Biohit Oyj. All subject who had low SPGI levels (25 µg/l cut-off) were contacted by phone and invited to gastroscopy, unless they had any contraindications. All individuals with HP-infection were referred to receive medical treatment from the municipal health care.

The long-term evaluation of the screening program will be based on follow-up of deaths of all men invited for screening. The short- and long-term cost-effectiveness analyses will carried out by the epidemiologists of the University of Eastern Finland jointly with the economic and accounting experts of the Finnish Consulting Group. In the long-term evaluation, the standardized mortality rates (SMR) and potential years of life lost (PYLL) up to age 80 will be estimated for GC and all cancers combined. PYLL is an established measure of premature deaths.

RESULTS

The protocol for the screening of the risk of GC was developed by Health Care Finland Ltd (Terveystalo), consisting of six main steps (Figure 1), which are further divided into twelve specific processes.

The costs of this pilot screening study were covered by the municipalities, and the unit cost/price of the screening was calculated for each invited person. The unit cost was a standard cost per an invited individual, including the costs incurred by each of the twelve steps, regardless of the observed unit costs for individual patients. From the municipal financial point of view, the total amount of costs was obtained by multiplying the unit costs by the number of inhabitants included in the target age cohorts invited for screened.

Of the invited 374 persons, 86 percent participated in the screening. In addition, 41 residents outside the target age cohort agreed to participate spontaneously, and cover the costs by themselves.

A random sample of 79 subjects were included in the present analysis. The mean SPGI was 97,98 µg/l with SD=45,1. Altogether, 3/79 (3,9%) subjects had SPGI levels below the 25 µg/l cut-off. (Figure 2). Diagnostic gastroscopy was performed for all individuals having SPGI values below this threshold.

Among these 79 persons, the mean HP-antibody levels was 26,77 EIU, with SD=41,0. HP-antibodies were within normal range in 51 patients (Figure 3). In the whole co-

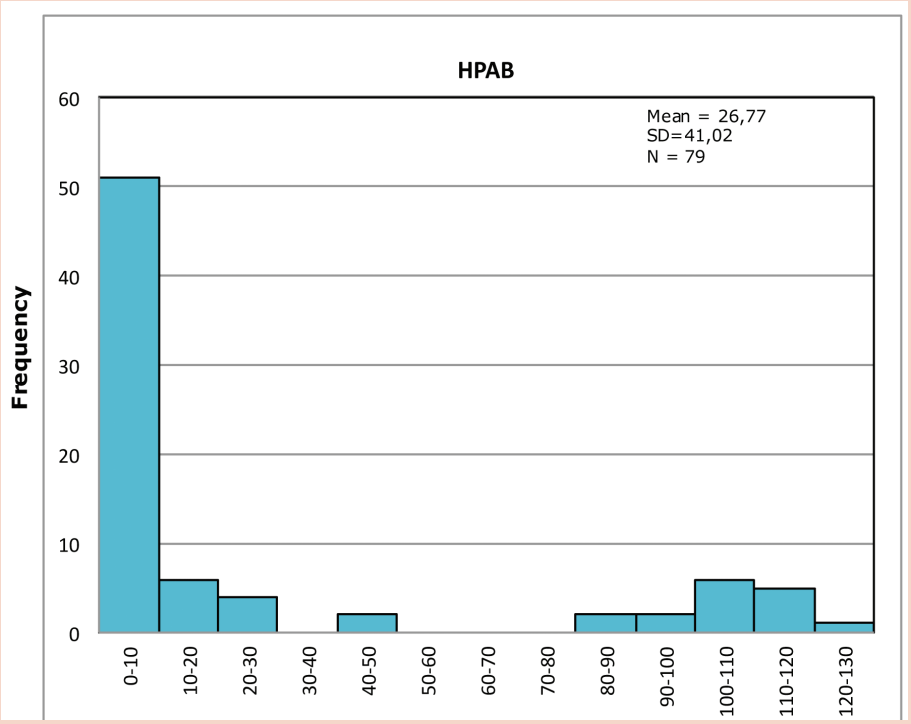

Figure 3. Distribution of *H. pylori* antibody levels in the cohort

hort, 36% had elevated HP-antibody levels. Of the 79 subjects in this analysis, 66 had HP-antibody levels below 50 EIU, the rest being interpreted as having an HP-infection.

Of all screened subjects, 29% were referred to medical follow-up (treatment of HP- infection, gastroscopy, treatment of vitamin-B deficiency, etc.) on the basis of their findings in the GP-test or gastroscopy (Figure 4).

DISCUSSION

The pilot study described in this communication is the first in our country, designed for a population-based screening of middle-aged men and women. In Finland, effective screening programs are available for women, i.e., screening for cervical cancer and breast cancer. However, for the Finnish men, the only screening program is for colorectal cancer (CRC), using a FOB (fecal occult blood) test and covering age groups 60-69 years (1). The preliminary results of this pilot study indicate, that using a simple and inexpensive biomarker test (GP) for screening results in both prevention and treatment of prevalent stomach problems in the population. The GP-screening was initiated by a large screening trial in Finland, conducted in 1994-1996. The results of the long-term effectiveness of this study are not available as yet. However, the preliminary data suggests that both SMR and PYLL-rates due to GC can be considerably reduced by a population-based screening by a panel of stomach-specific serum biomarkers (GP).

Although, we were not able to record the detailed data on diagnostic and treatment procedures carried out after the 2012 feasibility study, and no follow-up of the effectiveness of this screening will be available for years, it is conceivable that several endoscopic mucosal resections of precancerous gastric conditions will be performed as a result of this initial screening (18). Substitutions of vitamin or micronutrient deficiencies related to AG and acid-free stomach have already been administered, and eradication of HP has been carried out for several of these patients. All these measures aim to prevent the progression of these early pre-cancer conditions to GC, thus eventually decreasing GC incidence and mortality, as well as PYLL values in the screened population (13-17).

Of the diagnosed GC precursors, it was estimated that 25-33% would develop into GC within the following 5-10 years, unless adequately treated and monitored. If a population-based screening for GC by a panel of serum biomarkers is considered sufficiently beneficial (18,19), the design and implementation of such a program could follow the principles of other on-going screening programs (e.g., mammography screening), exploiting the existing health services according to the WHO recommendations for screening programs.

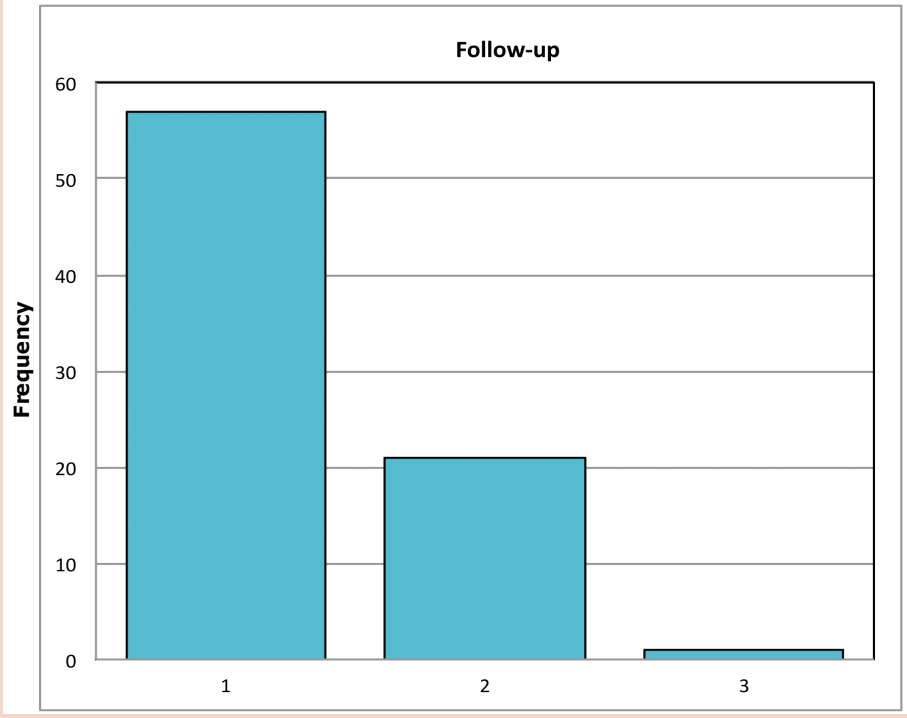

Figure 4. Proportion of cases submitted to clinical follow-up

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