図5：*Hp*SA，ペプシノゲン法判定と内視鏡的胃粘膜萎縮

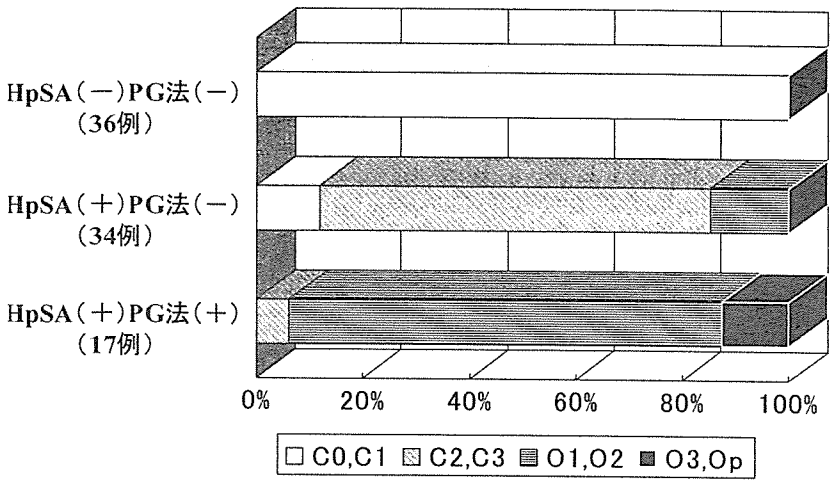

表3：*Hp*SA，ペプシノゲン法判定と内視鏡診断

	消化性潰瘍	過形成性ポリープ	胃底腺ポリープ	逆流性食道炎
HpSA(−)PG法(−)(36例)	0例	0例	3例	12例
HpSA(＋)PG法(−)(35例)	11例	2例	0例	4例
HpSA(＋)PG法(＋)(17例)	1例	1例	0例	0例

とopen typeでのOD値を比較するとopen typeで有意に高く興味深い。抗原量が多いほど萎縮を進展させるのであろうか。今後の検討で，OD値により胃疾患の頻度が異なることが明らかにすることができればスクリーニングにおいてさらに有用となる可能性がある。

さて，今回1泊2日ドック受診者に対して，1日目に採便容器を渡し2日目に回収したが，回収率が35.6％と低く問題点と考えられた。検診に広く用いる場合には前もって郵送などが必要であり，血清抗体や尿中抗体よりも手間がかかることが予想される。しかし，大腸癌検診においては，免疫学的便潜血検査が広く普及しており，これと同時に採取すれば検診に応用可能である。そのためには免疫学的便潜血検査と同一検体で検査できるように改良することも望まれる。

*Hp*検査による胃癌検診は，久道の報告[10]では胃癌死亡率抑制に対する有効性は示されていない。これは，*Hp*感染率の高さやきちんとした疫学的検討がなされていないためと考えられる。本邦における*Hp*感染率は現在50％程度であるが，今後低下することが予測されており，実際現在でも30歳代以下の世代での感染率はかなり低くなっている。動物実験や臨床成績から*Hp*感染と胃癌発生の関連は明らかになっており，将来においては*Hp*感染者のみ画像診断による胃癌検診を行う方法が成り立つ可能性もあると思われる。そのためには，今後検診の立場から大規模調

査を行い，*Hp*検査を用いることにより胃癌死亡抑制効果があることを示す必要がある。

*Hp*除菌による胃癌発生抑制効果が期待されており[16]，今後更なる大規模研究が必要であるが，検診の場で*Hp*SAを用いて*Hp*感染者を厳密に抽出し，若い世代で除菌治療を行えば，胃癌の1.5次予防に役立つ可能性も期待される。

V おわりに

今後の胃検（健）診において背景胃粘膜の把握は重要であり，PG法により胃粘膜萎縮を拾い上げるとともに*Hp*検査を併用すれば，胃癌の高危険群のみならず胃疾患の低危険群も明らかにすることができる。*Hp*SAは精度の良好な検査法であり，その利用法の工夫により検診への応用も可能と考えられる。背景胃粘膜を理解した上で精度の良好な画像診断を行うことにより効率の良い胃検（健）診とすることができる。

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Investigation of *Helicobacter pylori* stool antigen test in comparison with gastric endoscopy and serum pepsinogens

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Summary

We investigated the *Helicobacter pylori* stool antigen (*Hp*SA) test in comparison with gastric endoscopy and serum pepsinogens(PGs). Ninety-four people (60 males and 34 females; mean age 53.1 y.o., range 35-74 y.o.) were recruited in human dry dock of Matsue Red Cross Hospital. The stool antigen test was performed using the *Hp*SA ELISA (Premier Platium *Hp*SA, Meridian Diagnostics). According to manufacture's instructions, an absorbance at 450/630 nm of <0.100 and _0.120 was defined as negative and positive, respectively. Serum pepsinogens were measured by enzyme immunoassay. We defined those subjects as positive for PG as those who had levels of PG I lower than 70ng/ml and a PG I/II ratio of less than 3.0. The *Hp*SA positive rate in 92 cases except 2 cases after *Helicobacter Pylori* (*Hp*) eradication was 59.8%. Two cases after eradication were both *Hp*SA negative. In 37 *Hp*SA negative cases, endoscopical atrophic pattern were all C0 & C1. On the other hand, in 52 *Hp*SA positive cases, endoscopical atrophic pattern were C0 & C1 in 4 cases (7.7%), C2 & C3 in 28 cases (53.8 %), O1 & O2 in 18 cases (34.6%), and O3 & Op in 2 cases (3.8%). PG II level was higher in *Hp*SA positive than in *Hp*SA negative, significantly ($p<0.01$). PG I/II ratio was lower in *Hp*SA positive than in *Hp*SA negative, significantly ($p<0.01$). There was no PG method positive case in 37 *Hp*SA negative cases, but 17 cases (32.7%) were PG method positive in 52 *Hp*SA positive cases. In conclusion, gastric mucosa of *Hp*SA negative cases was healthy without gastric atrophy, and *Hp*SA test may be useful for screening of gastric cancer.

検査・診断

血清ペプシノゲン測定はどのような胃癌の発見に役立つのか?

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はじめに

血液中のペプシノゲン pepsinogen(PG)値は，胃粘膜の健康状態を簡便に評価するものとして血液検査による胃癌スクリーニング法(ペプシノゲン法，PG 法)にも応用される[1]．ここでは，PG 法の原理を概説し，臨床における血清 PG(sPG)測定の有用性と留意点について述べたい．

血清 PG 値の意義

1. 血液中の PG の由来

PG はペプシンの前駆体で，本来は胃の内腔に分泌され，ペプシンに変化して蛋白分解酵素として働くものであるが，PG の 1% 程度が血液中に認められる．PG は免疫学的にペプシノゲン I (PGI)とペプシノゲン II(PGII)に大別される．PGI は胃底線領域(主細胞および副細胞)に存在し，PGII はその他にも噴門腺，幽門腺，ブルンネル腺にも広く存在する．

2. 胃粘膜の状態と sPG 値の変動

胃の炎症，潰瘍，癌，MALT リンパ腫など多くの疾患が *Helicobacter pylori*(*H. pylori*)菌の感染と密接な関連性があるとされている．

健常な胃に *H. pylori* が感染すると，胃粘膜の炎症を起こし，sPG 特に sPGII が増加し，PGI と PGII の比(PGI÷PGII の値，I/II 比と略す)は低下する(**図 1a**)．この変化は除菌や炎症の改善により前値へと復し，sPGII の低下や I/II 比の増加が認められる．

一方，*H. pylori* 感染が持続し，慢性に経過すると，最終的に胃粘膜の萎縮をきたすが，萎縮の状態では，sPGI が低下し，I/II 比はさらに高度の低下を示す(**図 1b**)．sPGI は胃酸分泌とよく相関し，I/II 比は萎縮の程度が進むほど低下する．

このように血清 PG 値は胃粘膜の炎症や萎縮を反映し，胃粘膜の健康度を示す指標と考えられる．特に I/II 比の増加は炎症や萎縮の改善を示し，その低下は悪化を示す指標となる．

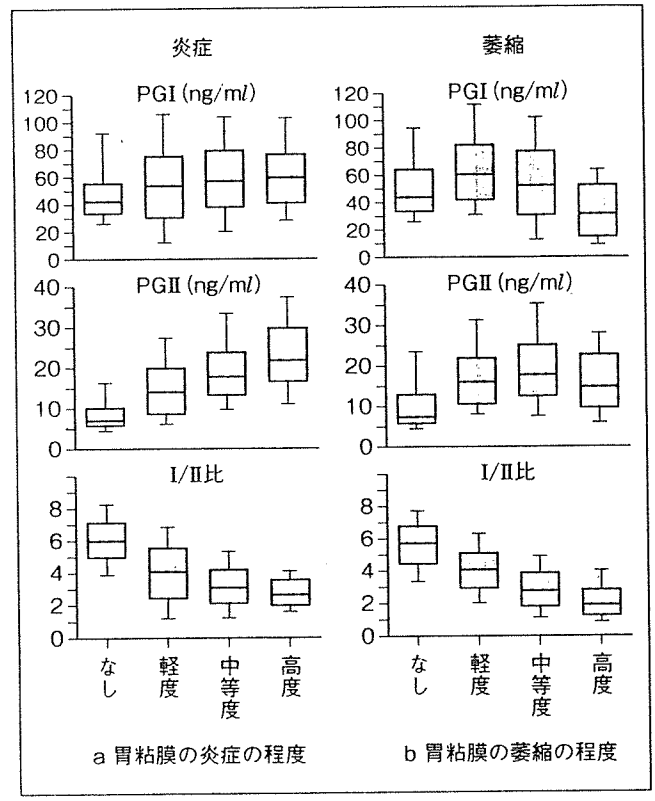

図 1　胃粘膜の炎症・萎縮と血清 PG 値の変化

3. 血中 PG 値と胃癌高危険群の診断

胃癌のほとんどは *H. pylori* 感染による胃粘膜の持続的炎症を基盤として発生すると考えられており，特に，萎縮性胃炎は胃癌の高危険群として知られている．前述のように，sPGI 値および I/II 比が低下した場合，萎縮性胃炎と診断でき，胃癌高危険群の抽出が可能である．

内視鏡検査を行った 5,838 名(男性 2,139 名，女性 3,699 名)における胃癌の発見率(有病率)と I/II 比の関係をみると(**図 2**)，I/II 比が低いほど胃癌の発見率が高く，I/II 比が 1 以下の男性では，4% 以上の発見率であった[2]．

0910-1551/04/¥100/頁/JCLS

- 血清 PG 値は胃粘膜の炎症や萎縮を反映して変動する.
- 胃粘膜の炎症では，特に PGII が増加し，PGI と PGII の比(I/II 比)は低下する.
- 胃粘膜の萎縮では，PGI が低下し，I/II 比は高度の低下を示す.

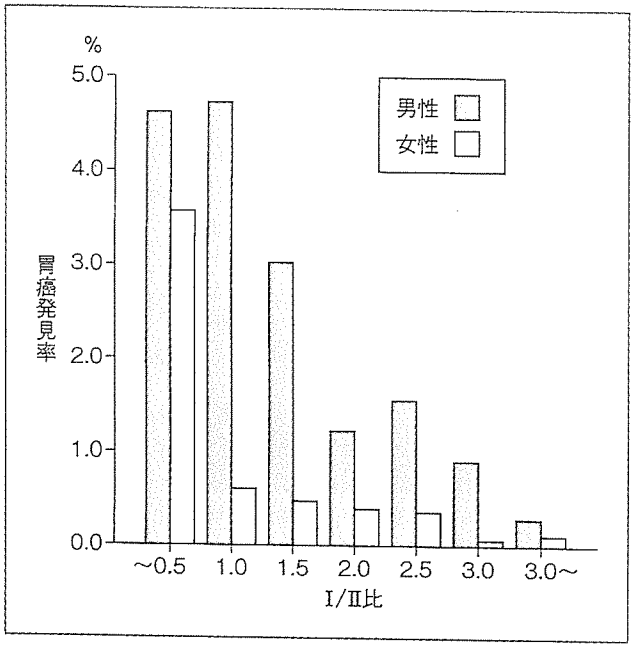

図2　PG 値と胃癌の発見率(有病率)の関係

血液による胃健診・PG 法の方法

1. PG 法の胃癌スクリーニングとしての意義

PG 法でスクリーニングを行う場合は，基準値[sPGI 70 ng/m*l* かつ I/II 比 3] 以下を陽性とし，要精密検査と判定する(**図 3a**)[1]．さらに，sPGI および I/II 比が低いほど萎縮が強いと判定され，陽性の中を細分し，[sPGI 50 ng/m*l* 以下かつ I/II 比 3 以下] を(2+)，[sPGI 30 ng/m*l* 以下かつ I/II 比 2 以下] を(3+)とする.

健常者での年代別の陽性率は，年齢とともに高くなる(**図 3b**)．PG 法の精度管理上，対象，事後措置などにいくつかの留意点がある.

2. PG 法の対象

血液検査による簡便な高危険群の設定であるが，判定に影響を与えるような sPG が変化する状態がいくつか知られている．すなわち，1) プロトンポンプ阻害薬を服用中の者(sPG 値が高くなる)，2) 胃切除後の者(sPG 値が低くなる)，3) 腎不全の者(sPG 値が高くなる)などがある．これらの状態の者には，PG 法は不適当である[1].

3. 胃癌における陽性率

基準値を用いての胃癌発見精度は，内視鏡をゴールドスタンダードとした検討で，感度 80%，特異度 70%，陽性反応的中度 1.5% とされている[3]．PG 法の感度は，胃癌のなかでもより萎縮性胃炎を背景としてもつ隆起型，分化型胃癌で高く，未分化型，陥凹型，潰瘍形成を伴うもので低いことが知られている．また，有症状例よりも，無症状例のほうが胃粘膜萎縮の強いものが多く，感度も高い.

4. PG 陽性者の事後措置

PG 陽性者には原則として内視鏡検査による精密検査を行う．また，その後も定期的に精密検査を行うことが望ましい(管理検診)[1]．内視鏡検査であれば，1～2 年に 1 回を原則とするのがよい．初回に胃癌が発見されなくとも，その後の経過中に発見される場合がある.

5. PG 法による胃癌スクリーニングの成績

地域における PG 法のわれわれの経験では，延べ 49,029 名の受診者の中から，72 名の胃癌が発見された．胃癌発見率は 0.15% であり，間接 X 線法と同等以上の発見率であり，さらに早期癌割合は 72.2% と高率であった．また，同時に胃腺腫も 0.11% 発見された.

PG 法と間接 X 線法同時受診者で発見された胃癌の特徴を方法別にみた(**図 4**)．PG 法では X 線法に比べ，UML はほぼ均等，前壁，大彎の割合が高く，分化型のものが多かった.

6. PG 陰性癌対策

sPG は胃粘膜全体の状態を評価するものであり，限局性病変の有無を示してはいない．したがって，PG 法で陰性でも，胃癌がないということ

- PG 低値群を胃癌の高危険群として抽出でき，I/II 比が低い程胃癌発見率が高い．
- PG 法では［sPGI 70 ng/m*l* かつ I/II 比 3］以下を陽性とし，原則内視鏡検査による精密検査を行う．
- PG 値に影響を与える状態として，1）プロトンポンプ阻害薬服用，2）胃切除後，3）腎不全などがある．

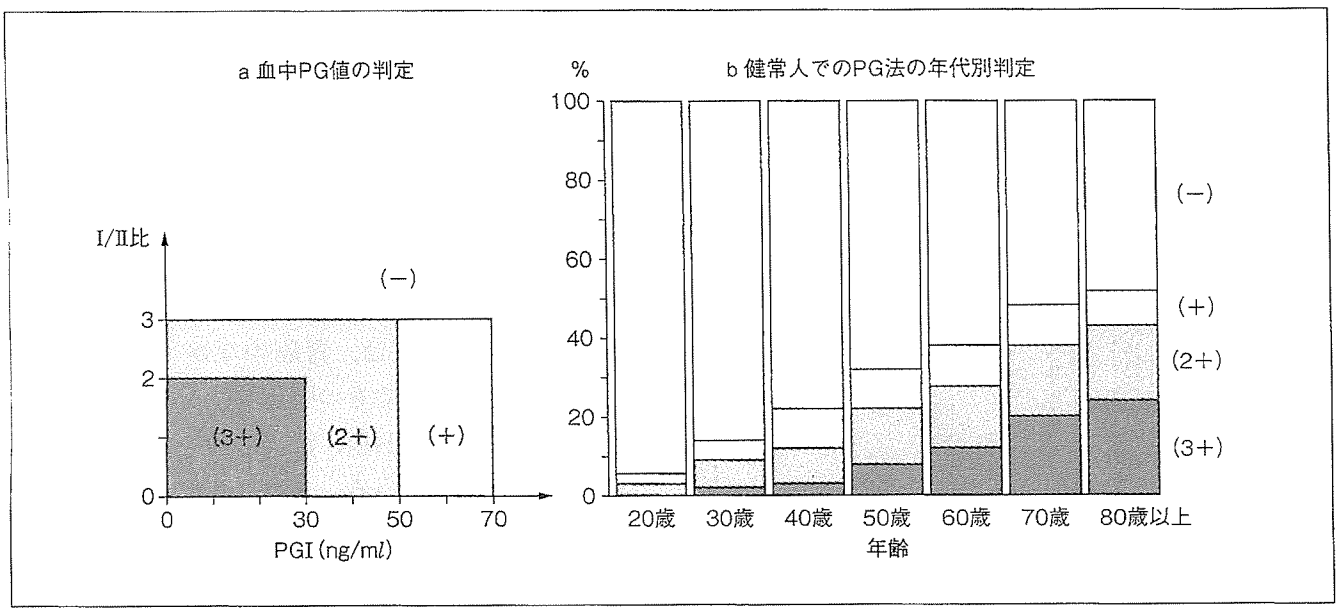

図 3　PG 法の判定と健常人における PG 法判定の年齢別結果

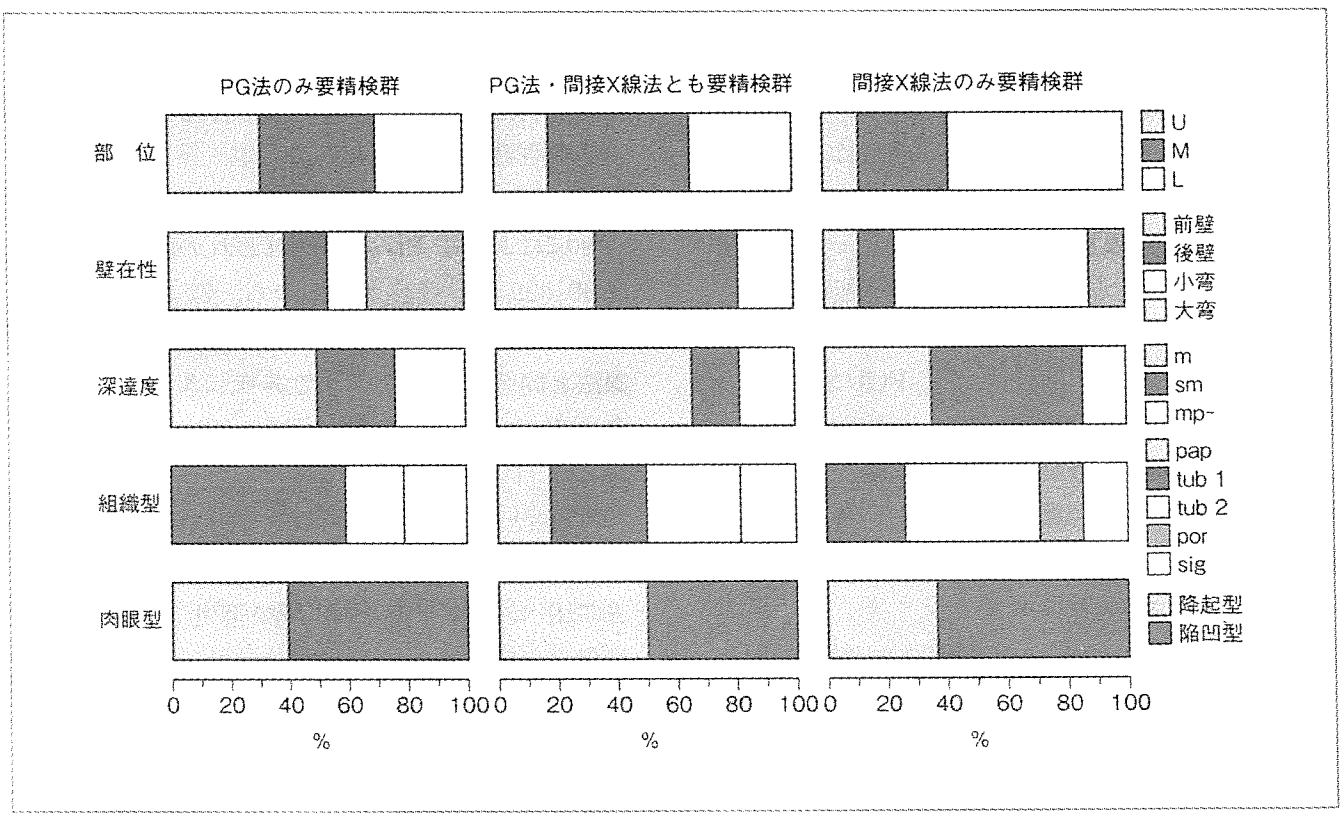

図 4　PG 法・間接 X 線法同時受診者における判定別発見胃癌の比較

- PG 法は胃癌のリスクを示し，陰性癌も低頻度であるが存在する．
- 明らかな消化器症状のある者は，PG 法にかかわらず，一度は精密検査を受けるべきである．
- PG 法では胃癌発見精度向上のため，X 線法との組み合わせを推奨している．

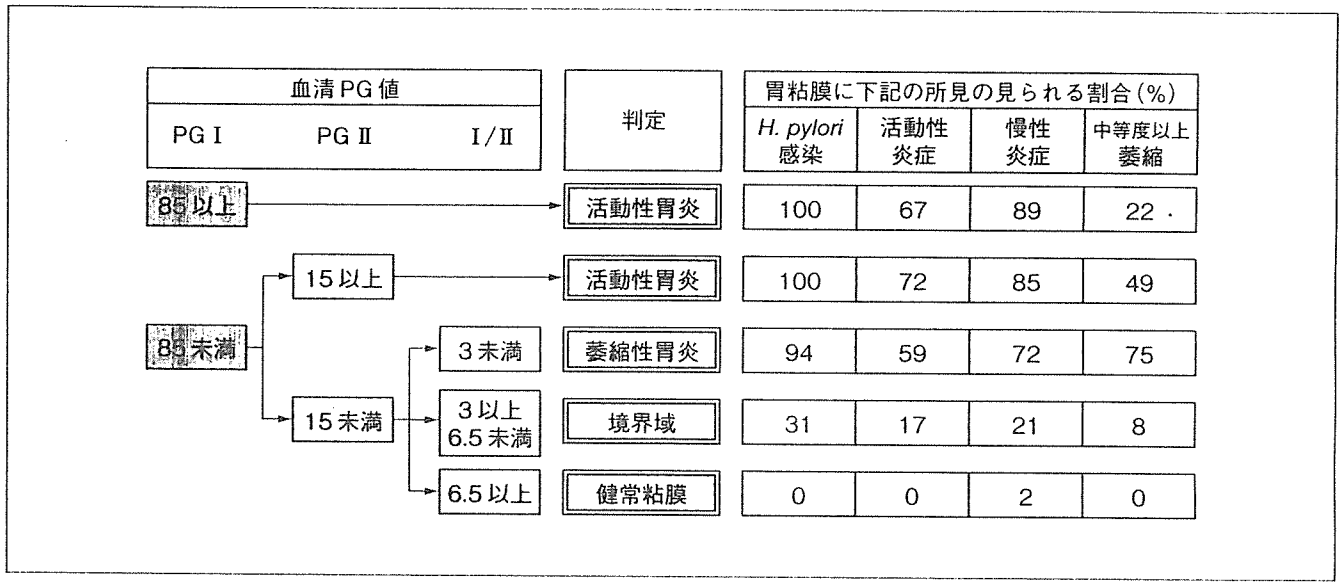

図5　PG 値による胃粘膜の状態の推定

ではなく，そのリスクが低いということである(図2)．PG 陰性胃癌の存在は常に考慮し，説明と問診を十分に行う必要がある．

また，明らかな上部消化器症状のある者や食道，胃，十二指腸疾患で治療中の者は，sPG にかかわらず，一度は精密検査を受けるべきである．

胃癌スクリーニングとして計画する場合には，精度向上のため，X 線法との組み合わせを推奨している[1,3]．その方法は，「同時併用法(PG 法と X 線検査を同時に行い，一方でも陽性なら精密検査)」もしくは「二段階法(PG 法をまず行い，陰性なら X 線検査，陽性なら内視鏡検査)」，「異時併用法(PG 法と X 線検査を交互または一定の間隔で交替を繰り返す)」がある．これらの組み合わせで，X 線検診単独施行の場合よりも，多くの胃癌が発見可能となる．また，PG 陰性胃癌の診断には，*H. pylori* 感染状況や便潜血検査も参考になる．

臨床における有用性

1. 測定の意義

臨床の現場で sPG を測定することは，胃癌高危険群の判定として PG 法の個別検診への応用が可能である．また，X 線検査の感度が 100% でないことから，組み合わせて補完的に用いることもよい．

胃粘膜の健康度の把握は，胃の健康診断，内視鏡検診の必要性の客観的な根拠にもなる．また，除菌後などの胃炎の推移のチェックにも使用できる．

血中 PG 値の変化によって存在が疑われる状態として，高値の場合には，急性胃粘膜病変，十二指腸潰瘍，Zollinger-Ellison 症候群，プロトンポンプ阻害薬の服用や腎不全などがあり，低値の場合には，胃粘膜萎縮を背景にもつ胃腺腫，胃癌，悪性貧血や胃切除後の状態なども考えられる．なお，高 sPGI 血症の十二指腸潰瘍は再発率が高いことも知られる．

● 血清 PG 値で，胃粘膜の炎症，萎縮，*H. pylori* 感染の状態が評価できる．
● PGI が 85 以上または PGII が 15 以上では，全例 *H. pylori* 感染が見られた．

2. sPG による胃粘膜の状態の評価

sPG を測定した場合の，胃粘膜の健康度評価を図 5 に示す．これは，内視鏡検査と sPG 測定，*H. pylori* 抗体測定，胃粘膜組織の炎症，萎縮，*H. pylori* を評価した 283 例での検討結果である[4]．sPGI が 85 以上または sPGII が 15 以上では，全例 *H. pylori* 感染がみられた．sPGI が 85 未満，sPGII が 15 未満，I/II 比が 6.5 以上では *H. pylori* 感染はみられなかった．このように sPG の測定で，胃粘膜の *H. pylori* 感染，炎症，萎縮の推定が可能であった．

また，井上は PG 法陰性で *H. pylori* 感染もない場合，胃癌の低リスクとしている[5]．

おわりに

以上，血液による胃健診，PG 法と臨床現場での測定の有用性について述べた．血液検査のため，簡便に，他の検査とも組み合わせやすく，精度管理も容易で，胃の状態が客観的に把握できるなど，多くの利点をもち，その原理が熟知されて行われることが，肝要かと思われる．

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Jpn J Clin Oncol 2006;36(5)301–308
doi:10.1093/jjco/hyl022

Comparison of Observed and Expected Numbers of Detected Cancers in the Research Center for Cancer Prevention and Screening Program

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Received September 7, 2005; accepted February 12, 2006; published online May 30, 2006

Background: The Research Center for Cancer Prevention and Screening program is a one-arm prospective study designed to evaluate the effect of multiple modalities for cancer screening. Basic programs consist of screening tests for cancer of the lung, esophagus, stomach, colon, rectum, liver, gall bladder, pancreas and kidneys, in addition to prostate cancer screening for males and breast, cervical, endometrial and ovarian cancer screenings for females.
Objective: To investigate the possibility of overdiagnosis, we compared the observed numbers with expected numbers based on the model.
Methods: We calculated the expected number of cancers on the basis of negative or positive history of screening tests within the previous year, based on assumed sensitivity and sojourn time. Observed numbers of screen-detected cases for stomach, colorectal, lung, prostate and breast cancer were compared with expected numbers.
Results: From February 2004 to January 2005, 3786 participants were enrolled in our study. The overall cancer detection rate was 5.8% (119/2061) for males and 4.1% (71/1725) for females. No statistically significant difference was found between observed and expected cases for colorectal cancer screening, gastric cancer screening for females and lung cancer screening for males. Observed numbers of breast, prostate and lung cancer for females exceeded those expected ($P < 0.05$).
Conclusions: Although cancer screening programs in the present study increased the detection of potentially curable cancers, these modalities, particularly lung, breast and prostate screening, might detect cancers which would not necessarily be clinically significant. We should therefore weigh up benefit and harm for such cancer screening programs.

Key words: cancer screening – detection rate – sensitivity – sojourn time – overdiagnosis

INTRODUCTION

In an attempt to prevent premature death, the Health Service Law for the Aged introduced cancer screening programs in Japan for all residents over the age of 40 in 1983. Screening for gastric and cervical cancer was introduced initially, and colorectal, lung and breast cancer screening programs followed. At present, five cancer screening programs are conducted nationwide, and over 25 million people are screened annually (1). Although the research group for cancer screening in Japan recommended six cancer screening programs (2) in 2001, new modalities for cancer screening have been introduced in several local municipalities without evaluation by reliable studies. To reduce mortality from a specific cancer, effective, evidence-based screening should be conducted and appropriate management of quality assurance is required.

In 2004, the Japanese Government initiated the Third-Term Comprehensive 10-Year Strategy for Cancer Control, aimed at reducing the incidence and mortality of cancer in Japan. The Research Center for Cancer Prevention and Screening (RCCPS) was established at the campus of the National Cancer Center, Tokyo, in the same year. Although development of the new modalities is worthwhile, a systematic approach for the evaluation of cancer screening programs is required. In order to investigate the efficacy of cancer screening, programs using new modalities have been conducted. Variable cancers were detected in the past year, but might consist of overdiagnosis

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cases. To investigate its possibility, we compared the observed numbers with expected numbers based on the model.

SUBJECTS AND METHODS

Cancer Screening Programs

The RCCPS Cancer Screening Program is a one-arm prospective study designed to evaluate the effect of multiple cancer screening modalities. This is a hospital-based program and participants are enrolled on a voluntary basis. Age for the target group was 50 years and over for males and 40 years and over for females. Exclusion criteria were previous diagnosis of cancer and followed-up for pre-cancerous disease based on self-reporting. The research and screening methods were explained to all participants using written materials and face-to-face presentations by health-care professionals. In addition, participants signed informed consent documents approved by the National Cancer Center. All participants responded to a questionnaire concerning life style, smoking, alcohol intake, nutrition, past history of disease including cancer, family history and previous investigations within a year. These participants will be followed using a questionnaire survey after the baseline screening year. Follow-up studies include a hospital survey to investigate medical records of cancer patients detected by cancer screening and interval cancer rates based on the participant's response. In addition, these participants are asked to attend repeat screening 5 years after the baseline.

Basic programs consisted of screenings for esophageal, gastric, colon, rectal, lung, hepatic, gall bladder, pancreatic and renal cancer. Cancer screening modalities were as follows: gastrofiberscopy (GFS) for the esophagus and stomach; total colonofiberscopy (TCF) or barium enema (BE) for the colon and rectum; computed tomography (CT) and sputum cytology for the lung; and abdominal ultrasonography (US) for the liver, gall bladder, pancreas and kidneys. The participants could choose TCF or BE based on their preferences. For males, prostate cancer screening was performed using an assay of prostate specific antigen (PSA) serum levels with a cut-off value of 2.7 ng/ml. For females, a combination of modalities was performed: two-view mammography (MMG), US and physical examination (PE) for the breasts, Pap smear for the cervix, and magnetic resonance imaging (MRI) for the endometrium and ovaries. Moreover, whole body scanning using positron emission tomography (PET) with injection of 2.78 MBq/kg fluorine-18-FDG was provided as an optional investigation. This study was approved by the Institutional Review Board of the National Cancer Center.

Comparison of Observed and Expected Detection Numbers

Numbers of subjects recruited into the program from February 2004 to January 2005 and observed numbers of detected cancers were classified by 5-year age group and by gender. In the questionnaire survey, we collected information on the following investigations performed within the previous year as follows: photofluorography, GFS, fecal occult blood test (FOBT), TCF, BE, chest radiography and MMG. We could not obtain information regarding previous investigation of CT for lung and PSA because these indicators were lack of the questionnaire.

Since screening detects cancer in a large prevalence pool, detection rate is influenced by previous investigations. Sojourn time (ST) is the duration of the detectable, preclinical phase of cancer (Fig. 1). The ST depends both on the natural history of the cancer and performance of screening modalities. Maximum lead time would therefore be achieved if screening was performed at the beginning of the ST. Although ST and sensitivity (SE) vary with age on individual cases, we used estimated mean values obtained from literatures. For simplicity of the present study, we assumed the following conditions: (i) ST and SE were constant in all age groups and (ii) SE was constant throughout ST.

We calculated the expected numbers of gastric, colorectal, lung, prostate and breast cancers in patients. The subjects are divided into three groups based on the previous history as follows: (i) subjects with no history of screening, (ii) subjects with history by the same test and (iii) subjects with history by the different test. In the first group, given that I represents underlying incidence and P target population numbers, expected numbers (E) at prevalence screening, which corresponds screening without previous investigation, can be derived from the following formula: $E = I \times (P/100\,000) \times \mathrm{ST} \times \mathrm{SE}(3)$. PSA screening is applicable to this case because previous history cannot be obtained from the questionnaire. In the second group, the expected numbers (Ex) is the sum of incidence and false-negative cases of previous investigation (Fig. 2). The sensitivity of modality1 assumed SE1 and ST1 for its sojourn time. Ex is calculated as follows: $\mathrm{Ex} = I \times (P/100\,000) \times (\mathrm{ST1}\text{-}(\mathrm{ST1}\text{-}1) \times \mathrm{SE1}) \times \mathrm{SE1}$. The modality2 was previous investigation, which is different from the modality of RCCPS screening program. Similarly, the sensitivity of modality2 assumed SE2 and ST2 for its sojourn time. These cases are the participants who have a screening history using other modalities in colorectal, gastric and lung cancer screening. When participants had history of previous investigation

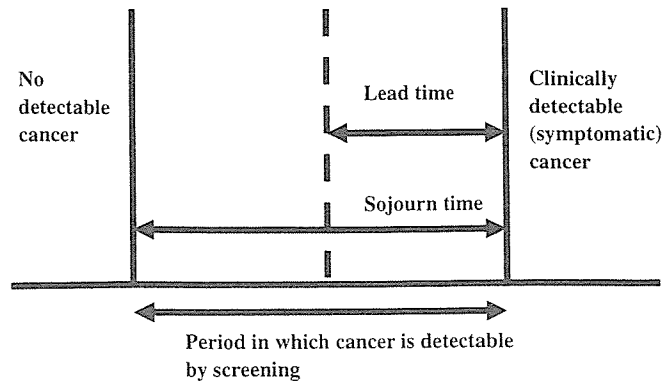

Figure 1. A graphical representation of the prognosis of clinical cancer and role of screening.

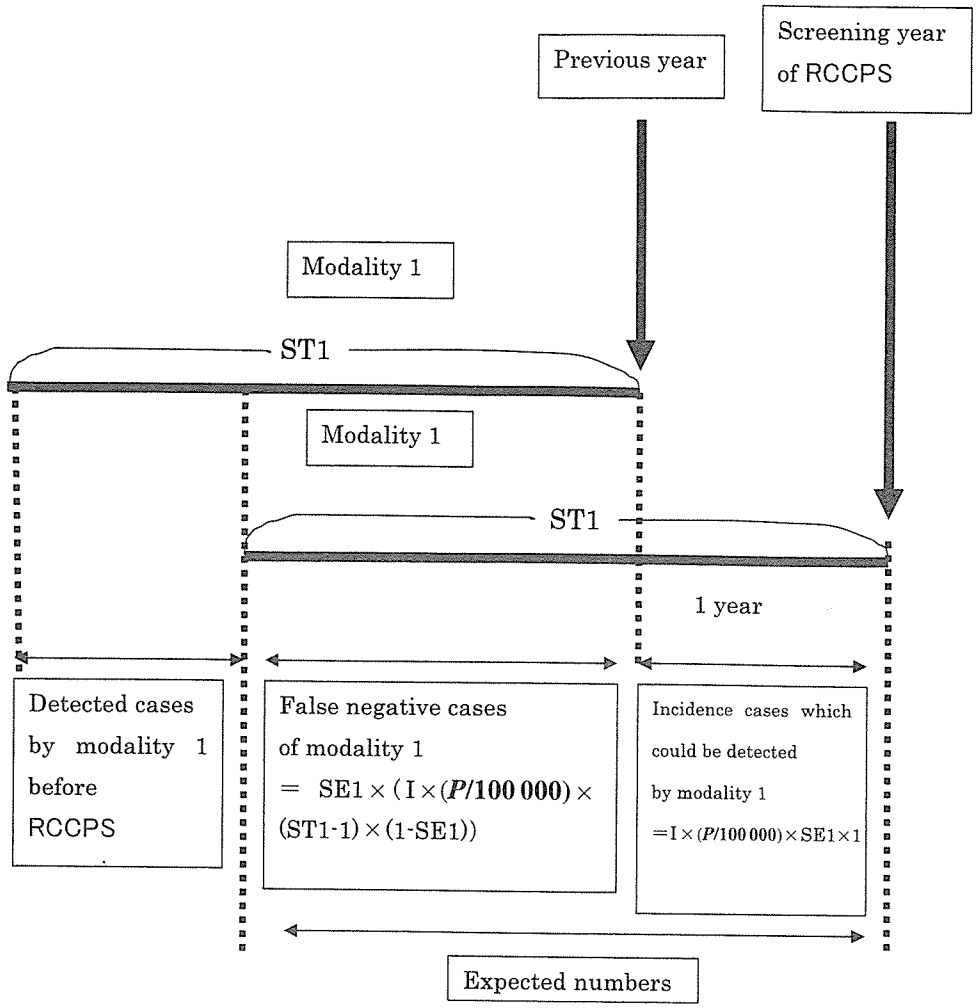

Figure 2. Calculation of expected numbers with previous examination using same modality. RCCPS: Research Center for Cancer Prevention and Screening; I: Incidence; P: Target population numbers; SE: Sensitivity; ST: Sojourn time.

using modality2, the expected number (Ey) including false-negative cases of previous screening is as follows: Ey = $I \times (P/100\,000) \times (ST1-(ST2 \times SE2)) \times SE1$ (Fig. 3).

The incidences of gastric, colorectal, lung, prostate and breast cancer were obtained from estimations calculated by cancer registries (4), while the ST and SE of breast cancer screening were assumed based on published reports (3,5–9). The ST or lead time of prostate cancer screening was determined from published articles and it ranged from 5 to 15 years (10–17). In other modalities, SE has been reported without adjustment for ST (18–20). In the baseline analysis, SE was assumed as follows: 70% for GFS; 70% for BE; 70% for TCF; 80% for CT; 80% for the combination of MMG, US and PE; 70% for MMG; 70% for PSA; 50% for chest radiography; 50% for FOBT; and 60% for photofluorography. ST was assumed as follows: 5 years for GFS; 5 years for BE; 10 years for TCF; 5 years for CT; 5 years for a combination of MMG, US and PE; 4 years for MMG only; and 10 years for PSA screening. In colorectal cancer screening, ST of immunological FOBT was assumed to be 2 years [published reports which reported the range from 2 to 4.70 years using various estimation models (21–23)]. The ST of chest radiography is 1 year based on previous reports (24,25). No references to ST of photofluorography could be found; this was assumed to be 3 years in the present study. We estimated E of detected cancers and compared these with observed numbers (O) to calculate the ratio O/E. The observed and expected numbers of detected cancer were compared using the chi-squared test. A sensitivity analysis was used to assess the effect of varying individual model parameters during the construction and testing of the models; this was performed to assess the effects of changes in our assumptions regarding ST and SE. We conducted a sensitivity analysis in the cases in which difference of the ratio O/E was significant.

RESULTS

Table 1 presents the distribution of all participants by 5-year age group and by gender. From establishment of the study in February 2003 to January 2004, 3786 participants were enrolled: 2061 males and 1725 females. In both genders, most participants (over 25%) were in the 60- to 64-year age

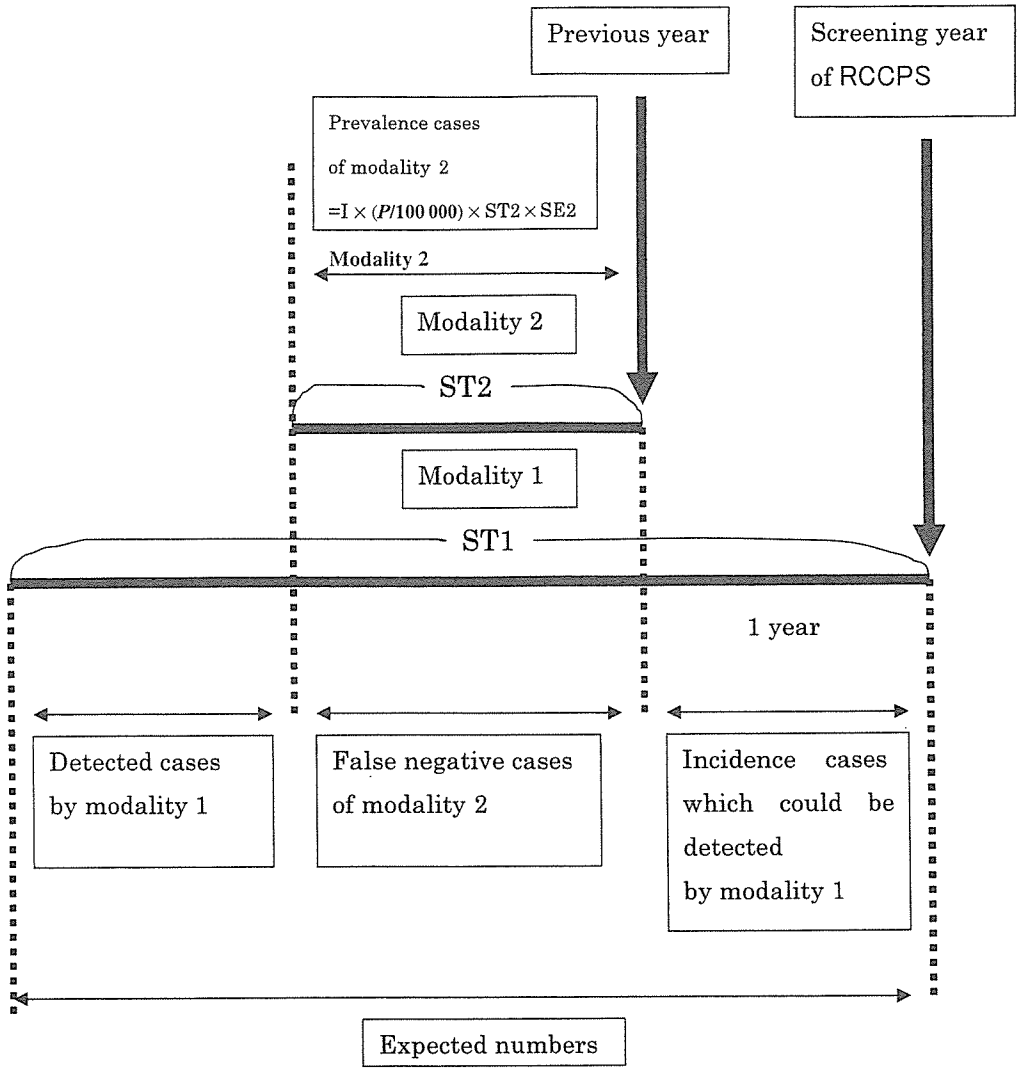

Figure 3. Calculation of expected numbers with previous examination using different modalities. RCCPS: Research Center for Cancer Prevention and Screening; I: Incidence; P: Target population numbers; SE: Sensitivity; ST: Sojourn time.

groups. Of participants over 70 years of age, 5.5% (114/2061) were males and 3.9% (67/1725) were females. Almost 90% of participants came from the Tokyo metropolitan area and the seven surrounding prefectures. Regarding colorectal cancer screening, TCF was performed in 83.6% (1723/2061) of male participants and 77.8% (1342/1725) of female participants, and the remaining 15.4% (317/2061) of male and 19.9% (343/1725) of female participants had BE. PET scans were performed for 79.0% (1629/2061) of males and 74.3% (1282/1725) of females. In the first year of the RCCPS programs, 190 cancers were detected (Table 2). The detection rate for all cancers was 5.8% (119/2061) for males and 4.1% (71/1725) for females. Approximately twice as many males as females had undergone TCF within the previous year (Table 3). In contrast, GFS had been performed in similar numbers of males and females. The frequency of MMG within the previous year was 18.5% (317/1712).

Expected numbers of detected cancers were calculated by classifying participants into groups by screening modalities for gastric, colorectal, lung, prostate and breast cancer (Table 4). In males, expected numbers of cancers were as follows: gastric cancer, 15.3 cases; colorectal cancer, 2.3 cases for BE and 21.9 cases for TCF; lung cancer, 10.9 cases; and prostate cancer, 7.0 cases. In females, expected numbers were as follows: gastric cancer, 3.7 cases; colorectal cancer, 1.1 cases for BE and 7.6 cases for TCF; lung cancer, 2.4 cases; and breast cancer, 6.2 cases. For TCF screening, observed numbers were almost equal. The observed numbers for gastric cancer were almost two times than expected numbers. But, in females, it was not significantly different. On the other hand, lung cancer was observed seven times more often in females but nearly equal in males. Prostate cancer and breast cancer were both detected over two times more frequently than expected. On the sensitivity analysis of prostate, breast and lung cancer screening for females, expected numbers of prostate and lung cancer increased in accordance with ST and SE. For prostate cancer screening, *O/E* ratio ranged between 5.36 and 16.07 according to SE values from 30 to 90% when ST was set at 5 years;

Table 1. Distribution of participants in RCCPS (February 2004–January 2005)

All participants	Sex	Age									
		40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80 years over	All
	Male	0	0	311	500	552	554	89	23	2	2061
	(%)	0.0	0.0	15.1	24.2	26.8	26.9	4.3	1.1	0.1	100.00
	Female	126	156	260	375	429	312	51	14	2	1725
	(%)	7.3	9.0	15.1	21.7	24.9	18.1	3.0	0.8	0.1	100.00
Examinees within participants											
BE	Male	0	0	48	69	91	92	13	3	1	317
	Female	25	31	46	66	86	77	7	4	1	343
TCF	Male	0	0	257	427	488	457	73	20	1	1723
	Female	97	121	208	298	337	230	40	10	1	1342
PET	Male	0	0	250	405	450	423	78	21	2	1629
	Female	78	114	196	276	334	228	41	13	2	1282

BE: barium enema; TCF: total colonoscopy; PET: positron emission tomography.

Table 2. Age distribution of screen-detected cancer and detection rate by screening modality among the participants in the RCCPS (February 2004–January 2005)

Cancer	Modality	Sex	Examinees	Detected numbers (years)										Detection rate (%)
				40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	Above 80	All	
Esophagus	GFS	Male	2040	0	0	0	0	2	5	1	0	0	8	0.39
		Female	1684	0	0	0	0	0	0	0	0	0	0	0.00
Stomach	GFS	Male	2042	0	0	0	5	11	10	2	0	0	28	1.37
		Female	1684	0	1	2	0	1	3	0	0	0	7	0.42
Colon and rectum	BE	Male	317	0	0	0	1	1	1	1	0	0	4	1.26
		Female	342	0	0	1	1	0	2	0	0	0	4	1.17
Colon and rectum	TCF	Male	1723	0	0	3	1	9	10	3	0	0	26	1.51
		Female	1342	0	0	4	1	3	6	0	1	0	15	1.12
Lung	CT	Male	2061	0	0	1	2	3	7	0	1	0	14	0.68
		Female	1697	2	1	5	5	1	3	1	0	0	18	1.06
Prostate	PSA	Male	2042	0	0	1	3	5	12	2	1	0	24	1.18
Breast	MMG + US + PE	Female	1712	2	3	2	3	2	0	2	0	1	15	0.88
Others		Male	2061	0	0	4	0	4	7	0	0	0	15	0.73
		Female	1725	1	2	2	2	1	2	1	1	0	12	0.70
All cancer		Male	2061	0	0	9	12	35	52	9	2	0	119	5.77
		Female	1725	5	7	16	12	8	16	4	2	1	71	4.12

GFS: gastrofiberscopy; BE: barium enema; TCF: total colonoscopy; CT: computed tomography;PSA: prostate specific antigen; MMG: mammography; US: ultrasonography; PE: physical examination.
Detected cancers included these cases: multiple cancers at the same organ (5 persons, 11 cancers) and multiple cancers at multiple organs (6 persons, 13 cancers).

observed numbers of prostate cancer always exceeded expected numbers at any cases if ST was changed from 5 to 15 years. For lung cancer screening for females, *O/E* ratio ranged between 6.72 and 12.10 according to SE values from 50 to 90% when ST was set at 5 years; observed numbers of breast cancer were three times more than expected at any cases if ST was changed from 5 to 10 years.

DISCUSSION

The efficacy of reducing mortality rates from cancer has been established for several cancer screening programs. Based on these studies, the research group for cancer screening in Japan recommended the following six cancer screening programs (2): photofluorography for gastric cancer, fecal occult blood

Table 3. Proportion of having previous investigations within a year by screening modalities

Examination	Modality	Previous examination within a year	
		Male (%)	Female (%)
Stomach	XP	43.5 (887/2040)	30.0 (505/1684)
	GFS	28.7 (586/2040)	23.3 (393/1684)
Colon and rectum	FOBT	52.7 (1074/2040)	40.7 (685/1684)
	BE	4.9 (99/2040)	3.0 (50/1684)
	TCF	15.4 (315/2040)	8.3 (139/1684)
Lung	Chest X-ray	73.9 (1524/2061)	62.0 (1052/1697)
Breast	MMG	-	18.5 (317/1712)

The percentage of previous examination compared males and females using the chi-squared test.
XP: gastrophotofluorography; FOBT: fecal occult blood test; GFS: gastrofiberscopy; BE: barium enema; TCF: total colonoscopy.
PSA: prostate specific antigen; MMG: mammography; US: ultrasonography; PE: physical examination.

test for colorectal cancer, chest radiography and sputum cytology for lung cancer, Pap smear for cervical cancer, a combination of physical examination and mammography for breast cancer, and hepatitis virus markers for hepatocellular carcinoma. Recently, the guideline for colorectal cancer screening has been revised, and chemical and immunological fecal occult blood tests have been recommended as population-based screening (20). Both TCF and BE could be introduced in opportunistic screening as long as well-controlled risk management is performed. Although these guidelines follow evidence-based cancer screening programs, new modalities which show no evidence of mortality reduction have rapidly been disseminated. These new modalities, such PET, CT and GFS, possess high sensitivity and are therefore anticipated to detect early cancer; however, while they are useful for cancer detection, their effectiveness in cancer screening is unclear.

The detection rates in our study were higher than those of population-based screening (20). There are two possibilities for this difference. First, for over 70% of participants, it was the first experience that they were examined by GFS, TCF, BE, CT and MMG. When screening is initiated, an apparent excess of diagnosed cancers is inevitable, because in the first round of screening a large number of cancers that would have occurred in future are diagnosed earlier. Second, the sensitivity of the modalities in our study was superior to those of population-based screening (18–20). Population-based screening programs have been conducted using chest radiography and sputum cytology for individuals at high risk of lung cancer, while similar programs using photofluorography for gastric cancer and immunological fecal occult blood testing for colorectal cancer have also been performed. Considered these conditions, we calculated the expected numbers of detected cancers in our cohort based on assumptions of sensitivity and sojourn time in several modalities. The difference of observed and expected numbers could be changed according to use of the data. We conducted a sensitivity analysis to investigate the robustness because it was possible that our conclusion would be changed according to the data used for the analysis. For example, we used incidence rates obtained from population-based cancer registries. The incidence rate from cancer registries is the weighed average of incidence among the population with and without previous history of screening. These assumptions might introduce under- or overestimation.

In the cases of prostate, breast and gastric cancer for males and lung cancer for females, the observed numbers exceeded expectation and were similar to those expected in the other cases. High detection rate is a consequence of the screening itself, i.e. overdiagnosis, especially in prostate and lung cancer for females. Overdiagnosis has been pointed out and was a major harm in both screening programs (26). Although the test was conducted using the same modality for lung cancer screening, the results were different between males and females in our study. The difference of two groups might be explained by the difference of the history of chest radiography. Strauss et al. (27) state that the overdiagnosis hypothesis is counter to virtually all known data on the natural history and biological behavior of lung cancer. In recent screening studies, both detection rate and stage I cancer by CT exceeded that of chest radiography (28,29). For the very reason, overdiagnosis could be a more serious problem for CT screening. On the other hand, the cut-off point for prostate cancer screening is controversial. PSA value of 4.0 ng/ml is a popular cut-off point for prostate cancer screening; 2.7 ng/ml was used in the present study. However, only two cases (8.3%) of the detected prostate cancers exhibited PSA levels below 4.0 ng/ml. In the European Randomized Study of Screening for Prostate Cancer, the cut-off PSA level was changed from 4.0 to 3.0 ng/ml (30). Krumholtz and colleagues (31) found a prostate cancer incidence rate of 22% in patients with 2.6–4.0 ng/ml PSA based on biopsies of 94 patients with clinical stage T1c. Recently, the prevalence of prostate cancer was reported to be 14.9% for those with PSA values below 4.0 ng/ml (32). Of these tumors, 15% contained Gleason pattern 4, indicating that high-grade cancer occasionally occurs in the presence of low PSA. Disagreement exists as to the best cut-off value for PSA. Greater detection of prostate cancer increases the risk of overdiagnosis and overtreatment, which can cause erectile dysfunction and urinary incontinence. The risk of overdiagnosis has been reported as more than 48% within a screening population with a 4-year screening interval (13). Etzioni and colleagues calculated the overdiagnosis rates of prostate cancer screening as 29% for whites and 44% for blacks, based on SEER-Medicare database (14). Men with low-grade prostate cancer (Gleason score of 2–4) have minimal risk of dying from prostate cancer during 20 years of follow-up compared with men with high-grade prostate cancer (Gleason score of 8–10) (33). On the other hand, Bill-Axelson et al. (34) reported that radical prostatectomy reduces disease-specific mortality and overall mortality compared with watchful waiting. Including selection of therapy, the efficacy of prostate

Table 4. Comparison of the observed and expected numbers of cancer by screening modality

Cancer screening	Modality	Baseline analysis		Male				Female			
		Sensitivity (%)	Sojourn time (years)	Observed numbers	Expected numbers	*O/E*	*P*-value	Observed numbers	Expected numbers	*O/E*	*P*-value
Stomach	GFS	70	5	28	15.31	1.83	0.0463	7	3.69	1.90	0.3649
Colon and rectum	BE	70	5	4	2.25	1.78	0.4120	4	1.08	3.70	0.1781
	TCF	70	10	26	21.90	1.19	0.5610	15	7.64	1.96	0.1427
Lung	CT	80	5	14	10.86	1.29	0.5473	18	2.38	7.56	0.0021
Prostate	PSA	70	10	24	7.00	3.43	0.0022	–	–	–	–
Breast	MMG+US+PE	80	5	–	–	–	–	15	6.22	2.41	0.0488

The observed and predicted numbers of detected cancer were compared using the paired *t*-test. XP: gastrophotofluorography; FOBT: fecal occult blood test; GFS: gastrofiberscopy; BE: barium enema; TCF: total colonoscopy; PSA: prostate specific antigen; MMG: mammography; US: ultrasonography; PE: physical examination. *O/E* = observed numbers/expected numbers.

cancer screening programs is still unclear. Although the cancer screening programs in the present study increased the detection of potentially curable cancers, these modalities might detect tumors that would not be clinically significant. We should accordingly weigh up the benefits and harms of cancer screening using these modalities, and such information should be given to the participants of our study.

The present study is the first report from the RCCPS and has several limitations. First, our cohort of around 4000 volunteers is insufficient to observe reduction of mortality rates from specific cancer and no comparable group was included. Second, participants were volunteers who were receptive to screening by the new modalities. Hence, a self-selection bias could not be excluded. In the present study, we estimated expected numbers using a simple model based on approximate assumptions. However, to estimate correct sojourn time accurately and to modify our model accordingly, lengthy follow-up is needed. We have started follow-up studies, which include an annual questionnaire survey of participants and a hospital survey to acquire information on cancer patients. Information concerning interval cancer can be obtained through this survey, and sensitivity and sojourn time of several cancers can be reinvestigated based on the new model. In addition, we aim to investigate all participants using the same modalities after 5 years and are planning further programs to evaluate the accuracy of the screening modalities.

Acknowledgments

This study was supported by a Grant-in-Aid for the Third-Term Comprehensive 10-Year Strategy for Cancer Control (H16-cancer control-016) from Ministry of Health, Labour and Welfare of Japan. The authors thank Ms Kanoko Matsushima and Ms Junko Asai for the manuscript preparations.

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Jpn J Clin Oncol 2005;35(10)626–629

Cancer Statistics Digest

Comparison of Laryngeal Cancer Mortality in Five Countries: France, Italy, Japan, UK and USA from the WHO Mortality Database (1960–2000)

Laryngeal cancer mortality age-standardized rates (ASRs), using 1985 Japanese standard population, are shown for Japan, USA, UK, France and Italy (Fig. 1). In all of the countries, males have higher ASRs compared with females. For males, ASRs have been decreasing since 1970s in Japan and France. ASRs in the other countries have been gradually decreasing in recent years. For females in Japan, ASRs drastically decreased until 1990 and since then have been slightly decreasing. In Italy, a mild decreasing trend is observed after the middle of the 1980s. In the USA, ASRs increase until 1980. The others remained roughly flat for four decades.

Mortality trends in males are shown by age group according to year of death (Fig. 2). In Japan, the USA and the UK, decreasing trends are observed among age groups under 70 years old. In France and Italy, mortality rates are higher than in the other three countries for all age groups and there are decreasing trends after passing peaks between 1970 and 1980. Japan has the greatest difference in mortality rates between the 40–44 and 85+ age groups, while France and Italy have only a small difference between those age groups. Mortality trends in females are shown by age group according to year of death (Fig. 3). In Japan, mortality rates have been decreasing for all age groups. There is no obvious trend in the other countries.

Mortality trends in males are shown by age group according to year of birth (Fig. 4). In Japan, mortality rates decreased from the birth cohort born in 1900 onwards. In the USA, a mild decreasing trend is observed from the birth cohort born 1920. In the UK, mortality rates have been decreasing with the birth cohort born before 1920. After the birth cohort born in 1920, however, a decreasing trend is not observed. In France and Italy, mortality rates in the 40–64 age groups exhibit a peak with the birth cohort born around 1930. Mortality trends in females are shown by age group according to year of birth (Fig. 5). Decreasing trends are observed from the birth cohort born in 1900 in all of the countries except the USA. In the USA, as well as for the 40–64 age group for males in France and Italy, there is a peak in mortality rates with the birth cohort born around 1930.

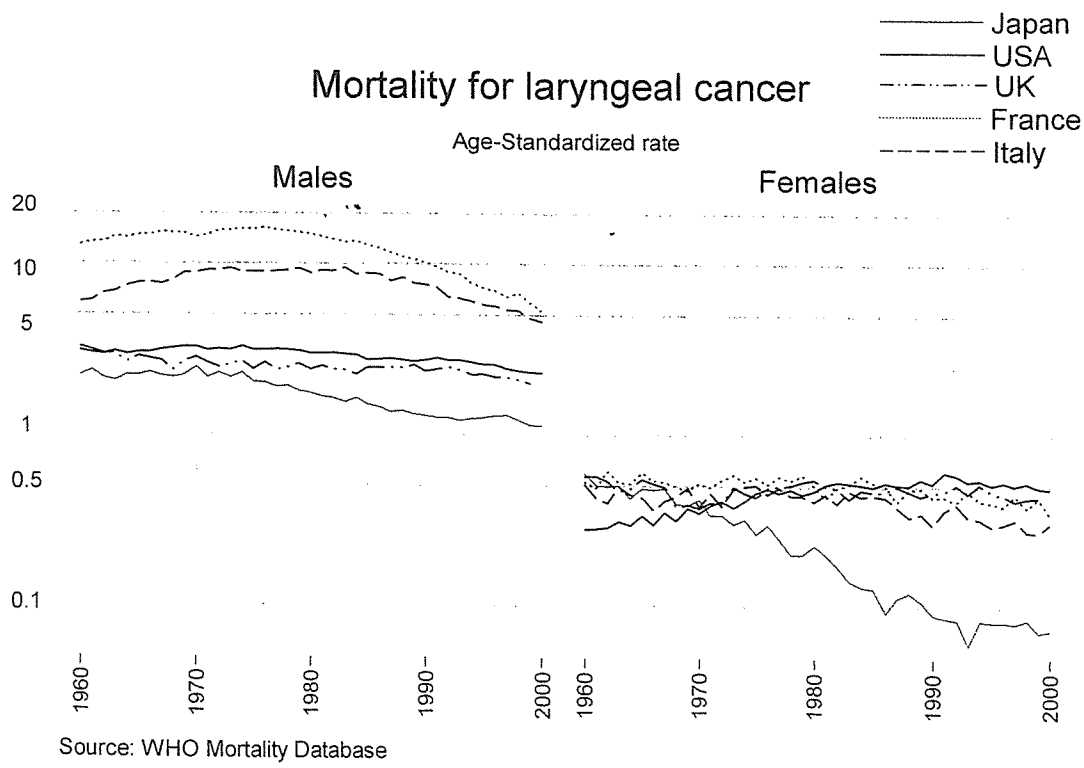

Figure 1. ASRs for laryngeal cancer for males and females: age-standardized with 1985 Japanese standard population, rates per 100 000.

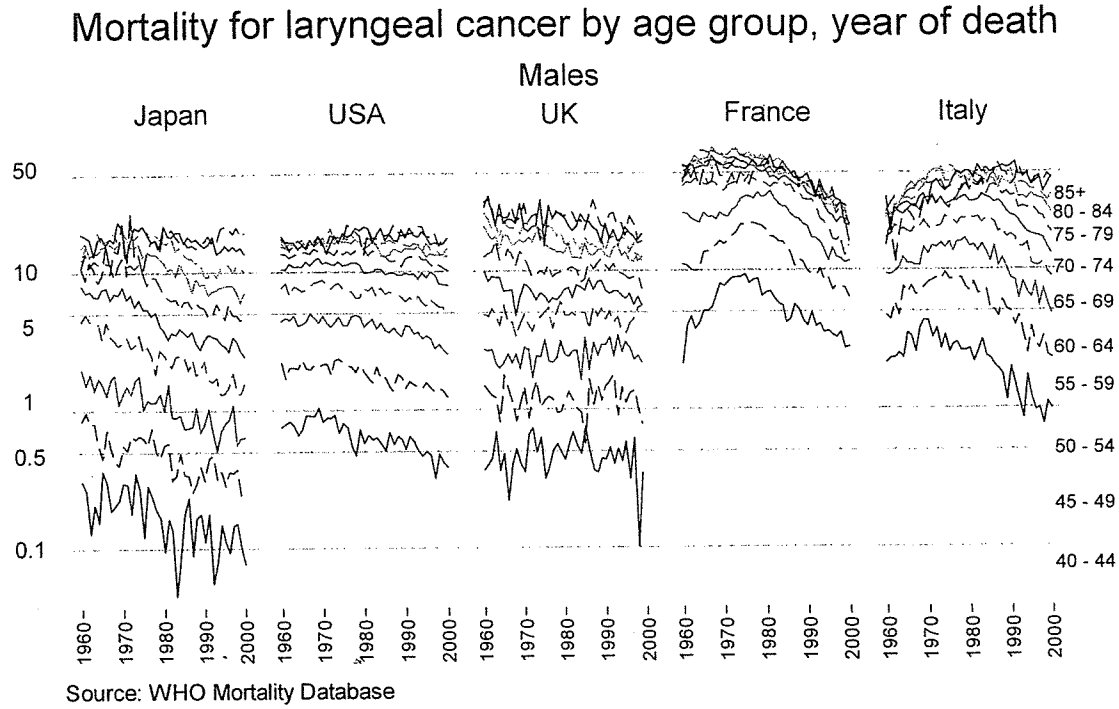

Figure 2. Age-specific rates over 40 years of age by year of death for laryngeal cancer in five countries, males, rates per 100 000.

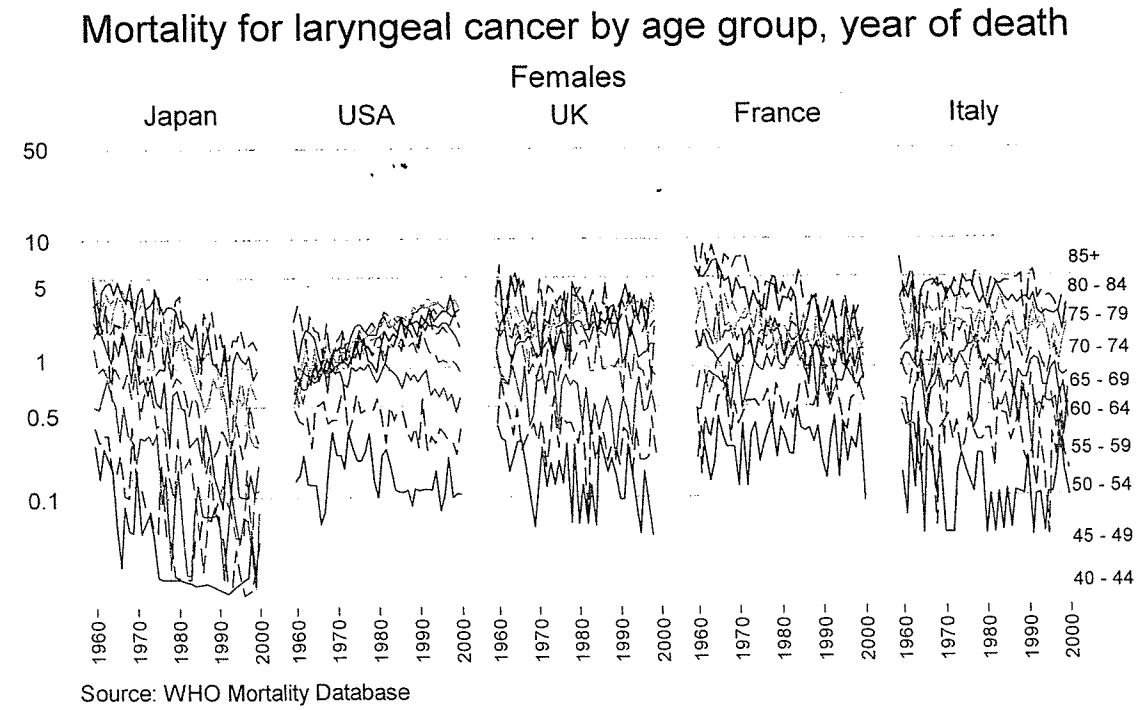

Figure 3. Age-specific rates over 40 years of age by year of death for laryngeal cancer in five countries, females, rates per 100 000.

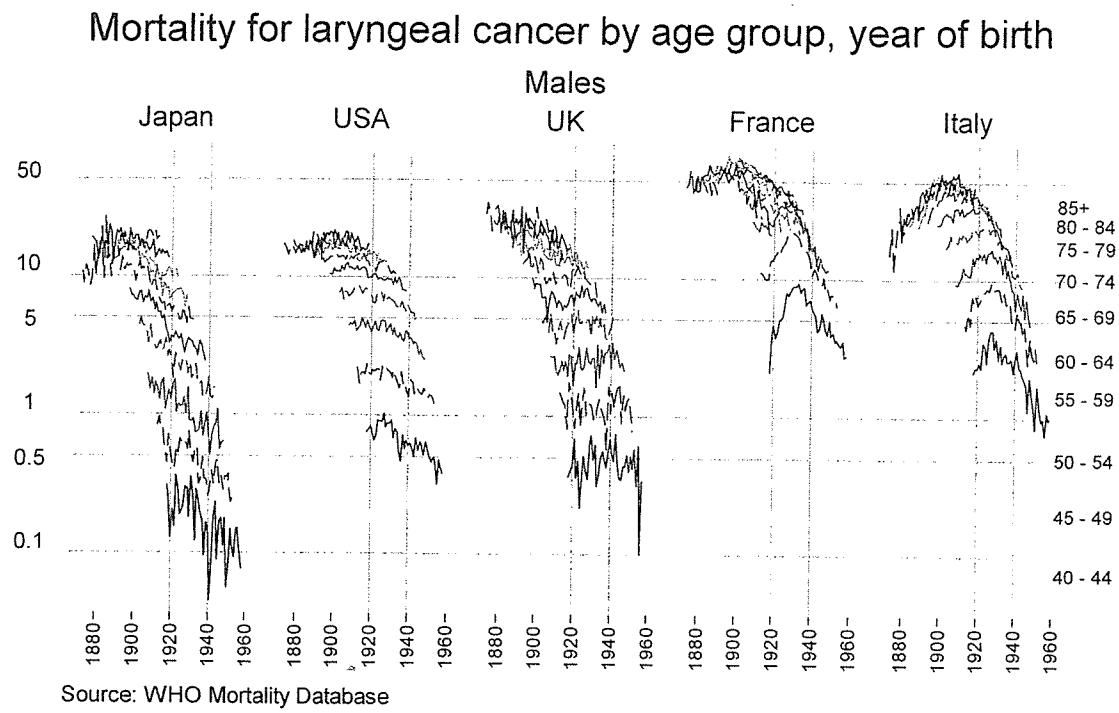

Figure 4. Age-specific rates over 40 years of age by birth cohort for laryngeal cancer in five countries, males, rates per 100 000.

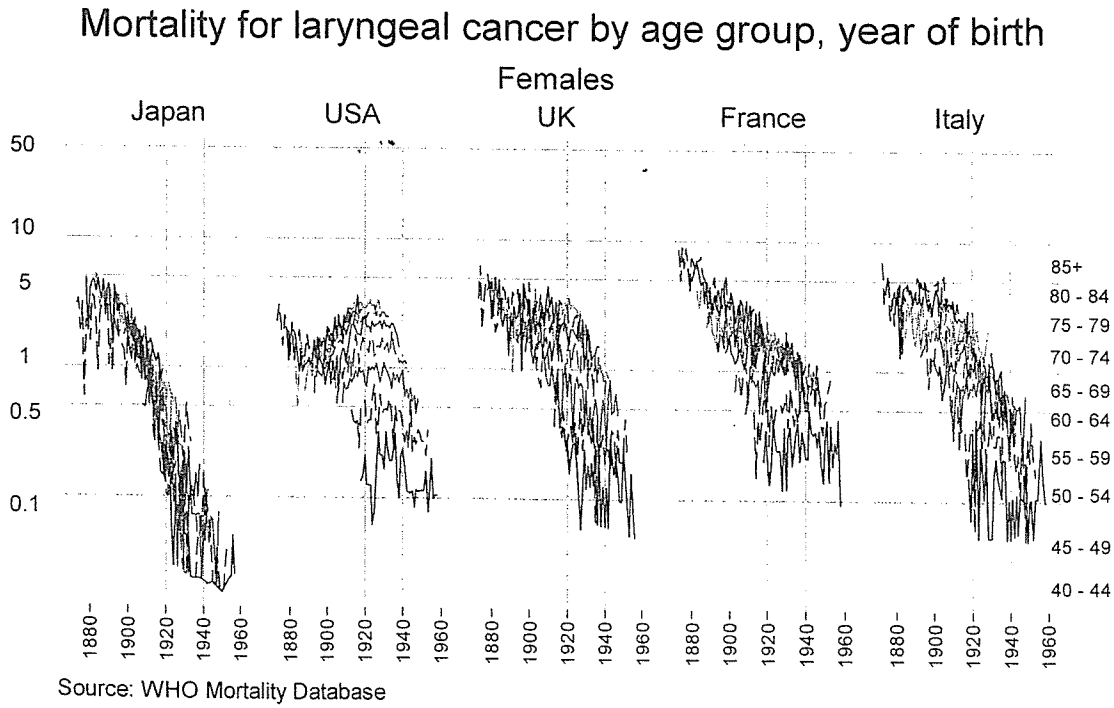

Figure 5. Age-specific rates over 40 years of age by birth cohort for laryngeal cancer in five countries, females, rates per 100 000.

Note: Original data is downloaded from WHO Mortality Database (version as of August. 2004). The data was then tabulated by I. Yoshimi with 161 (ICD-7,8,9), and C32 (ICD-10). Responsibility for this presentation and interpretation lies with the authors, not the WHO Mortality Database.

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doi:10.1093/jjco/hyi169