2．B群(*H. pylori* 感染はあるが萎縮はない)

C群に比べ，胃がんのリスクは高くないが，時間経過でC群になる可能性が高い群である．C群に比べ，除菌による胃がん予防効果は明瞭である[7]．除菌を行った後，ある程度の画像診断(内視鏡もしくはX線)による経過観察が必要である．しかし，除菌の効果が大きい群なので，今後のデータによって，できるだけ効率的な経過観察を考えるべきである．ある年齢以下で除菌すれば，経過観察の必要がない可能性もある．

3．C群(感染，萎縮とも陽性)

B群に比べ，胃がんのリスクが高く，除菌の効果は少ないとされている．萎縮の程度や，対象者がきちんと経過観察のために来院してくれるかなど，個々のケースによる対応が必要になる．経過観察がきちんとできそうなケースでは，除菌の必要性は必ずしも大きくない．しかし，経過観察を受けないと思われる例では除菌による胃がんリスクの低下が，本人にとっても，医療経済の面からもメリットになる可能性がある．

4．D群(萎縮あるが感染陰性)

限局した感染がありうるので除菌すべきという意見もあるが，経過観察を中心にすべきである．

わが国の将来の胃がん—おわりに

H. pylori 感染率は低下を続けており，あと40年もすれば，感染率の低い世代ががん年齢となって，胃がんはまれな疾患となるが，現在は過渡期にある．

胃がん検診が不要な対象へのX線検査などの実施を避け，限られた医療資源を有効に活用するうえで，*H. pylori* 感染診断と血清PG値の組み合わせは有用である．議論のあるカットオフ値については，地域がん登録データなどを活用して早急に最適値を決めるべきである．このデータにより，同時にリスクの篩い分け能の評価が可能である．

除菌の適用については，胃粘膜の状況に加え，対象者の受療行動も考慮して決める必要がある．除菌について将来の食道下部腺がん，噴門部がんのリスクの上昇[8]など，マイナス面については十分検証されていないところもあり，データの蓄積と検討が必要である．

これまで触れなかったが，*H. pylori* は感染症であるので，小児期の感染防止も重要で，周囲の感染者を除菌することによる感染防止の可能性を定量的に明らかにする研究も重要である．

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Summary

Gastric Cancer Prevention by *Helicobacter pylori* Eradication until Now and Japanese Gastric Cancer Control Strategy from Now On

Shogo Kikuchi*

Patients with *H. pylori* infection are at a 21 times increased risk of developing gastric cancer than those without any history of *H. pylori* infection. Eradication of *H. pylori* may be effective for gastric cancer prevention, if it is employed before "germs" of gastric cancer grow so that it can be detected by endoscopic examination. The progression of mucosal atrophy weakens the preventive effects of eradication.

In Japan, rates of both mortality and incidence of gastric cancer have decreased, so that the adult population consists of those at high and those at low risk of gastric cancer. It is inevitable to evaluate gastric cancer risk for individual subjects to provide prevention. A combination of the *H. pylori* infection test and the serum pepsinogen test may be useful for evaluation. Indications for eradication therapy should be decided considering behavior of each subject in addition to the expected risk reduction effect.

Key words: *Helicobacter pylori*, eradication, serum pepsinogen, risk of gastric cancer, prevention

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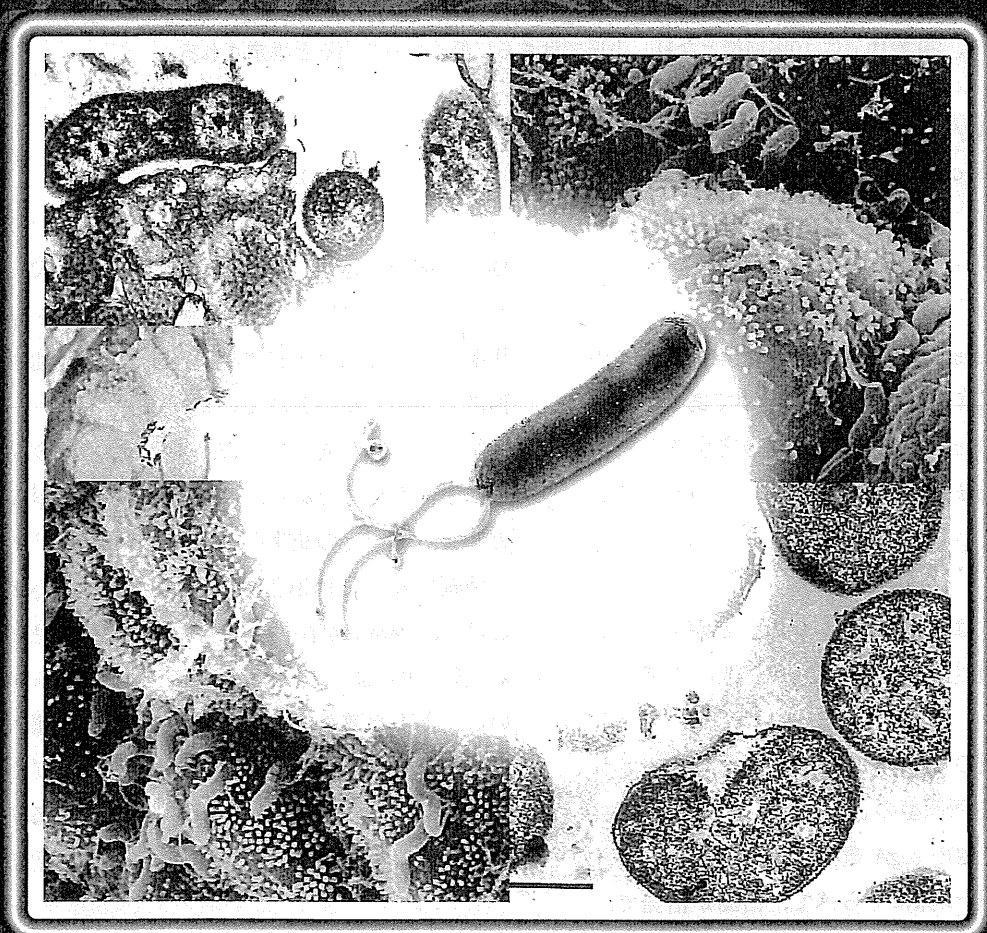
The Comparison of the Helicobacter Studies in Korea and Japan

韓国と日本の Helicobacter 研究の類似点と相違点



特別寄稿 マーストリヒトIV/フローレンス コンセンサスレポート
日本語訳 全文掲載

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◀ Special Issue ▶

The Comparison of The *Helicobacter* Researches in Korea and Japan
韓国と日本の *Helicobacter* 研究の類似点と相違点

日本における *Helicobacter pylori* の疫学
—Epidemiology of *Helicobacter pylori* in Japan—

菊地正悟*

わが国の *Helicobacter pylori*（*H. pylori*）は，病原性の強い東アジア型が大部分であるが，西欧型も一部混在する．感染率は，年々低下しており，出生時期の影響が大きく，成人以降での感染の獲得や消失は多くないと考えられる．地域差や除菌の影響が排除されていないが，現在は，50 歳代で 50%を割り込み，20 歳代では 10%前後となり，小児ではさらに低くなっていると推定される．

KEY WORDS
Helicobacter pylori（*H. pylori*），*H. pylori* 感染（有病）率，東アジア型，出生コホート

はじめに

わが国の *Helicobacter pylori*（*H. pylori*）感染の実態については現在データ収集されているが集計中であるので，これまでの報告によって現在の状況を推定するとともに，わが国の *H. pylori* の特徴を文献的にレビューする．

1．わが国の *H. pylori* の特徴

わが国の *H. pylori* は特徴として，ほとんどが東アジア型の *cagA* 遺伝子をもち[1]，大部分で *vacA* 遺伝子が *s1a/m1* である[2)3)]．

沖縄県では西欧型の *cagA* 遺伝子をもつ株が検出されている[1]．大分県でも西欧型の *cagA* 遺伝子をもつ株が検出される．東アジア型の *cagA* 遺伝子をもつ株は，西欧型の *cagA* 遺伝子をもつ株にくらべて，活動が活発で，強い炎症を惹起し，萎縮を進行させやすいことが報告されている[1]．東アジア型と西欧型が混在する沖縄県では，胃癌患者からは東アジア型が，十二指腸潰瘍患者からは西欧型が多く検出されている[4]．

従来からわが国に多い *H. pylori* は，東アジア型の *cagA* 遺伝子をもつ株であり，高塩食品の摂取が多いことなどと相まって胃癌の発生が多かったと考えられている．

沖縄県などで西欧型の *H. pylori* が検出されていることは，*H. pylori* が海外から持ち込まれることを示している．後述するように，わが国の *H. pylori* 感染率は低下している．上下水道などの社会基盤が大きく毀損するといった特別な事態がない限り，感染の増加は否定的である．しかし，従来の株とは，感染性などが異なる *H. pylori* が海外から入って広まる可能性は，完全には否定できない．

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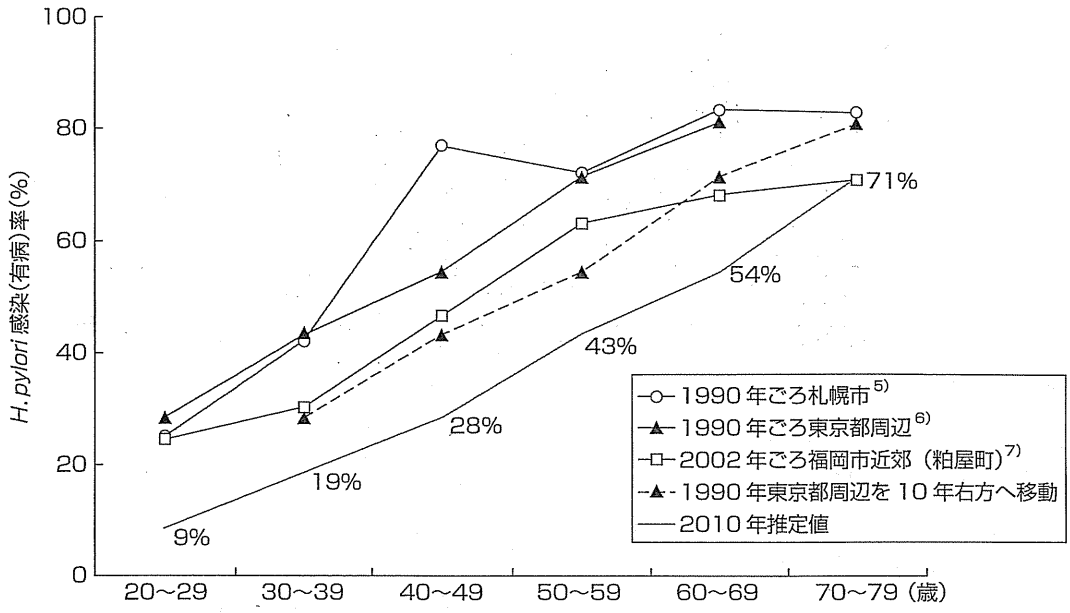

図❶ 2010 年のわが国の *H. pylori* 感染率の推定方法

①1990 年の東京周辺の値を 20 年右へ移動し，2010 年の 40〜79 歳の推定値とする．
②札幌市の 1990 年の 10〜19 歳の値を，2010 年の 30〜39 歳の推定値とする．
③2010 年推定値の 40〜49 歳と②の値を直線で結び，左へ同距離伸ばして 2010 年の 20〜29 歳の値とする．
（Asaka M *et al*, 1992[5], Kikuchi S *et al*, 2000[6], Fujimoto Y *et al*, 2007[7] より引用）

2．わが国の成人の *H. pylori* 感染率

1）現在の感染率

正確な *H. pylori* 感染率を把握するためには，無作為抽出した対象者の同意を得て感染診断をおこなうことが理想である．しかし，わが国ではこのような方法による感染率の報告はない．一般健診受診者を対象とした研究は，いくつか報告されている．代表的な研究の結果をグラフ化したのが図❶である．1990 年ごろ札幌市[5]と東京都周辺[6]で収集された対象の感染率は，40 歳代を除いてよく一致している．2002 年の福岡市近郊（福岡県粕屋町）のデータ[7]は，1990 年の東京のデータを右に 10 年移動させたものに近い値をとっている．このような結果から，わが国の *H. pylori* 感染率は，出生時期の影響が大きく，成人以降での感染の獲得や消失は多くないと考えられる．言い換えると出生コホートの感染率が持続すると考えてよいといえる．このため，図❶に示したような方法で 2010 年の感染率を推定した．10 歳以上では新規感染はまれなので，2010 年の 30 歳以上では 1990 年の東京周辺もしくは札幌市の値を用いた．札幌市の 1990 年の 0〜9 歳は，おもな感染時期である 5 歳以下を含むので，その後も感染があると考えられる．このため，直線による推定をおこなった．細かな推定ではないが，最近のわが国の *H. pylori* 感染率は，図❶の 2010 年推定値からそれほど遠くない値であると考えられる．

消化性潰瘍などに対して保険診療による除菌がおこなわれるようになっているので，実際には除菌が成功裏におこなわれた分を差し引かなければならない．しかし，除菌実施状況にも地域差があるので，図❶の推定値はこれを考慮せず，除菌に成功した例を感染者に含めた値となっている．

2）感染率の地域差

同じ福岡県でも，福岡市に隣接する粕屋町と山村である星野村（現八女市）では，各年代の感染率とも星野村のほうが 10%以上高い[7]．他の地域でも，都市部にくらべ農山村部では一般に感染率が高いようである．上下水道の整備などの時期に影響されると考えられる[8]．また，

除菌がおこなわれるようになったので，除菌に熱心な医療機関がある地域で感染率が低くなるという，医療による地域差もあると考えられる．

3．わが国の小児の感染率

外来を訪れた無症状の小児の 1995 年ころの感染率は，1 歳未満で 4%，1～4 歳で 10%，5～9 歳で 20%，10～14 歳で 25%，15～19 歳で 30%であった[9]．また，2001 年ごろの出生児が 2 歳で感染率 3.7%になったという結果[10]や，1998 年ごろの出生児が 5 歳で感染率 11%になったという結果[11]が報告されている．

海外と同様にわが国でも 5 歳以上での感染はまれと考えられている．最近の学会報告では 10 歳以下の小児の感染率は 2～5%程度とされている．

おわりに

わが国の *H. pylori* 感染率は年々低下している．地域差や除菌の影響が排除されていないが，最近の推定値（図❶）では，50 歳代で 50%を割り込み，20 歳代では 10%前後となり，小児ではさらに低くなっている．

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A new approach for elimination of gastric cancer deaths in Japan

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We explore a strategy for the elimination of gastric cancer deaths in Japan. Most gastric cancer is due to *H. pylori* infection in Japan. The effect of *H. pylori* eradication therapy on gastric cancer prevention in younger people is excellent, but it declines along with advancing age. Therefore, a test-and-treat approach to *H. pylori* infection is recommended in younger people, while for people aged 50 years or older a combination of countermeasures for *H. pylori* eradication that includes primary prevention and secondary prevention by endoscopic examination will reduce gastric cancer deaths, since this method will increase early detection if the disease occurs. In this paper, I described a new strategy of elimination of gastric cancer deaths in Japan due to such a high quality of diagnosis and treatment for gastric cancer. If this strategy succeeds, the incidence of gastric cancer in Japan may decrease much longer than 10 years.

Gastric cancer is the second most common cause of cancer deaths worldwide.[1] Until the early 20th century, Europe and the United States suffered a high incidence of gastric cancer. The 20th century also witnessed that the incidence of gastric cancer rapidly decreased coincidently with the changes in life style, sanitation and the widespread adoption of refrigeration for food preservation. Currently, three East Asian countries, Japan, China and Korea, account for about 60% of new gastric cancers. Early studies of the possible cause of gastric cancer emphasized dietary factors such as excessive intake of salt or nitrates and hereditary factors. The culture of *Helicobacter pylori* (*H. pylori*) in 1983[2] resulted in research focused on proving the causal relationship between *H. pylori* infection and gastritis and gastric cancer. As a result, in 1994, *H. pylori* was classified as a definite carcinogen by the International Agency for Research on Cancer (IARC) of the World Health Organization.[3] Since that time, many clinical studies have been conducted to examine how eradication of *H. pylori* might contribute to the prevention of gastric cancer. Because of a low incidence of gastric cancer, the relatively short duration of available studies and the general lack of risk stratification, statistically significant decreases were infrequently reported. In 2008, a multicenter clinical study was conducted in Japan to examine the incidence of new gastric cancer after endoscopic mucosal resection in high-risk patients with early gastric cancer who were randomly allocated to eradication of *H. pylori* group.[4] The study showed that *H. pylori* eradication resulted in a reduction in the incidence of new gastric cancers by approximately one-third, thus demonstrating the efficacy of *H. pylori* eradication in reducing the incidence of gastric cancer. The study also confirmed that eradication could not completely prevent metachronous gastric cancers and that periodic follow-up for gastric cancer would be required even after eradicating *H. pylori* in high-risk patients.

In Japan, gastric cancer screening has long been done by using barium contrast images.[5] However, evidence that *H. pylori* infection played an important role in the development of gastric cancer and that *H. pylori* eradication could prevent or reduce the incidence of gastric cancer suggested the need for a new strategy to eliminate gastric cancer in Japan. The new strategy could be one that combined primary prevention by *H. pylori* eradication with secondary prevention using surveillance of high-risk patients. Japan is currently at the forefront of devising methods and procedures for the elimination of gastric cancer based on the current high level of knowledge and technology and experience in gastric cancer screening. Here, we briefly describe the history of gastric cancer prevention in Japan and introduce the changes in *H. pylori* therapy and a new program that combines primary prevention and secondary prevention that will be soon introduced in Japan.

Key words: gastric cancer prevention, *H. pylori* eradication, endoscopic surgery, early gastric cancer
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Previous Preventative Measures for Gastric Cancer in Japan

The prevention of cancer, including gastric cancer, has primarily focused on secondary measures for early detection of cancer, rather than on primary prevention aimed at elimination of the causes in Japan. Indirect barium contrast imaging has been used as the screening method for gastric cancer; however, despite the long interest and emphasis, the

screening rate was only 9.6% in 2010.[6] Screening for gastric cancer based on barium contrast imaging also does not have a high sensitivity for detecting early cancer[7] and is associated with considerable exposure to radiation. Furthermore, targeting all people aged 40 years or older for screening is a major problem as people aged below 50 years account for only about 3% of all patients with gastric cancer in Japan.[6,8] Moreover, *H. pylori*-negative patients with minimal or no atrophy of the gastric mucosa are very unlikely to develop gastric cancer,[9–11] and thus, these patients are unlikely to benefit from annual barium contrast screening and are still exposed to the adverse effects of radiation.

The most serious disadvantage with Japan's attempts to prevent gastric cancer was the inability to implement primary prevention, which is understandable as the cause of gastric cancer had not been identified in the 1970s when programs of screening for this cancer were begun. However, we now know that more than 95% of gastric cancers are due to *H. pylori* infection in Japan and Korea.[10,11] As a general rule for cancers caused by infections, such as liver cell cancer and cervical carcinoma, primary prevention based on preventing the infection or early eradication before significant damage is done is preferred over screening (*i.e.*, primary prevention is superior to secondary prevention). Primary preventative measures for gastric cancer have yet to be started in Japan, and Japan has relied on barium contrast screening for 30 years. A decrease in the age-specific mortality rate of gastric cancer has been experienced from 1970 to 2010 in both sexes in Japan. However, this seems most likely to reflect the decrease of incidence rate of gastric cancer known to have occurred in both sexes in Japan during the same period.[8] The aging of the population has increased the population at risk, and thus the number of patients dying from gastric cancer has remained unchanged at around 50,000 per year.[12] The lack of a reduction in the total number of deaths despite the decline in age-standardized mortality rates provided important evidence to the Japanese Government that current programs were not effective in the prevention of gastric cancer deaths.

Effect of *H. pylori* Eradication on Gastric Cancer Incidence

Intervention studies that assessed the preventative effect of *H. pylori* eradication on gastric cancer have been conducted in healthy individuals worldwide.[13–17] In the United States and Europe, however, most studies were terminated before enrolling enough subjects for significant analysis because the incidence of gastric cancer is extremely low in these countries.[18,19] Overall, the annual incidence of gastric cancer has been reported to be only 0.1–0.3%[20,21] in persons infected with *H. pylori*. In contrast, the annual incidence of metachronous recurrence is reported to be in the range of 3–5% of patients who have undergone endoscopic surgery to remove early gastric cancer.[22,23] Our study evaluated recurrence of metachronous gastric cancer in 544 patients who had received endoscopic treatment. They were randomly allocated to *H. pylori* eradication or noneradication groups and were followed up with annual endoscopic examinations for 3 years. As a result, metachronous recurrence was found in nine and 24 subjects from the eradication and noneradication groups, respectively. The eradication group had a significantly lower incidence of metachronous gastric cancer with a hazard ratio of 0.339 according to intention-to-treat analysis.[4]

A large-scale cohort study was reported from Taiwan, in which about 80,000 patients with peptic ulcer were followed up for 10 years after *H. pylori* eradication therapy.[24] The patients were assigned to an early eradication group (patients underwent *H. pylori* eradication therapy at the time of diagnosis) or a late eradication group (patients underwent *H. pylori* eradication therapy at 1 year after diagnosis). As a result, the incidence of gastric cancer was markedly lower in the early eradication group than in the late eradication group ($p < 0.02$). This study is important in showing that while the effect of *H. pylori* eradication therapy in reducing the incidence of gastric cancer is obvious, earlier eradication can be more effective. These studies also suggest that *H. pylori* has a cancer promotion effect over and above its ability to cause atrophic gastritis. In 2011, a possible mechanism was described due to incomplete repair of genes damaged by *H. pylori* infection, which cleaves double-stranded DNA in the nuclei of gastric epithelial cells.[25] In addition, they demonstrated that the genetic defect remained as long as *H. pylori* infection persisted, further supporting the importance of *H. pylori* eradication in high-risk patients.

Gastric Cancer Elimination Project

It has been demonstrated that most gastric cancer is due to *H. pylori* infection (*i.e.*, a necessary but not sufficient cause), and we believe it is time for a major strategic shift in the preventative measures for gastric cancer. Preventative measures for liver cancer have been conducted with the focus on hepatitis viruses since 2002 in Japan, and this has succeeded in decreasing the mortality.[26,27] In marked contrast, annual deaths from gastric cancer have remained at around 50,000 for the last few decades, suggesting that the current preventative measures have been less than satisfactory.[8] Even though viruses and bacteria are not the same, completely different preventive measures should not be taken for liver cancer and gastric cancer when both are caused by infection. In 2012, the section on Current Status of the Basic Plan to Promote Cancer Control Programs of the Japanese Government issued a new plan to determine Cancer Control Programs for next 5 years in Japan, including those caused by microorganisms such as human papillomavirus associated with the development of cervical carcinoma, hepatitis viruses associated with liver cancer, human T-cell leukemia virus Type I associated with adult T cell leukemia and *H. pylori* associated with gastric cancer. For *H. pylori*, the benefits of bacterial eradication should be examined based on findings from Japan and abroad.[28]

Meanwhile, the Japanese Society for Helicobacter Research published a guideline recommending that all *H. pylori*-

infected people receive bacterial eradication therapy.[29] In response to this, the Japanese government has expanded coverage by the national health insurance scheme. In addition to gastroduodenal ulcer, three other indications for *H. pylori* treatment including mucosa-associated lymphoid tissue (MALT) lymphoma, postendoscopic surgery for early gastric cancer and idiopathic thrombocytopenic purpura (ITP) have been newly designated. Japanese insurance coverage for *H. pylori* eradication therapy for an indication other than gastroduodenal ulcer is the first in the world.

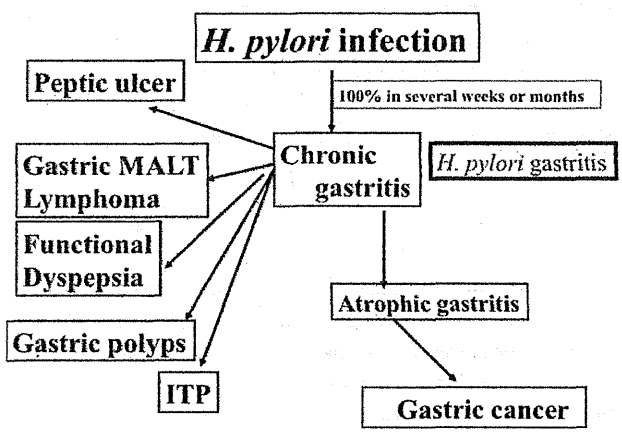

Figure 1. Progress of *H. pylori* infection. *H. pylori*-related chronic gastritis is leading to peptic ulcer, gastric MALT lymphoma, functional dyspepsia, gastric polyps, ITP, atrophic gastritis and gastric cancer.

Currently, the Japanese Minister of Health, Labour and Welfare has been asked to extend insurance coverage to chronic gastritis by the presidents of the Japanese Society of Gastroenterology, the Japan Gastroenterological Endoscopy Society and the Japanese Society for Helicobacter Research, raising expectations that approval of the request will be granted, as the final target to eradicate gastric cancer is to eliminate chronic gastritis due to *H. pylori* infection. The Japanese medical insurance is a universal health insurance system covering all citizens with freedom of choice of medical institution and high-quality services with low costs.[30] This insurance covers 90% of payment of medical expenses in persons aged above 75 years, 80% of payment at 70 to 74 years and 70% of payment less than 69 years. We are currently negotiating with the Japanese Government to expand the application of medical insurance to chronic gastritis. Hopefully, this will be approved in 2013 for patients with *H. pylori*-related chronic gastritis with endoscopy used to confirm the diagnosis of chronic gastritis.

When *H. pylori* eradication therapy for chronic gastritis is covered by national health insurance, different measures should be taken for people aged below 20 years and people aged 50 years or older. Bacterial eradication in persons aged below 20 years may achieve prevention of diseases such as peptic ulcer, gastric MALT lymphoma, functional dyspepsia, gastric polyps, ITP, atrophic gastritis and gastric cancer associated with *H. pylori*-related chronic gastritis (Fig. 1). We reported that incidence of gastric cancer after eradication of *H. pylori* increases along with advancing age (Fig. 2).[31] Thus,

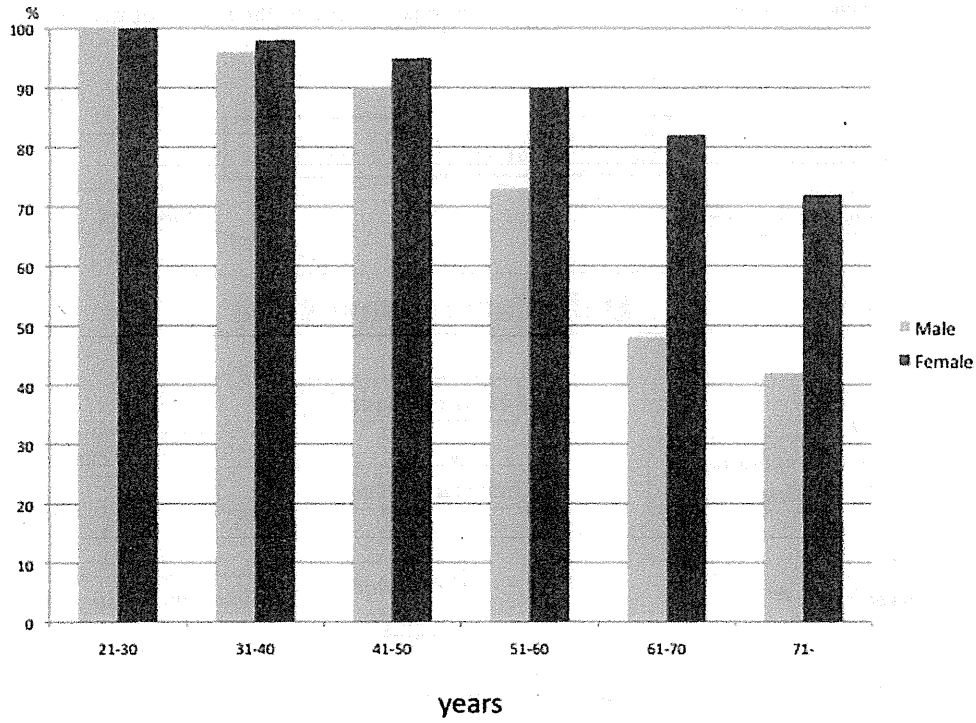

Figure 2. Possible rate of gastric cancer prevention by eradication of *Helicobacter pylori*.[31]

a test-and-treat approach is recommended for younger people that includes universal *H. pylori* testing and immediate bacterial eradication in those with a positive result (Fig. 3).

Because people aged 50 years or older frequently have atrophic gastritis and are likely to be at risk for cancer despite *H. pylori* eradication, we recommend that they will be referred for evaluation of the presence and severity of their *H. pylori*-related gastritis. Those with *H. pylori* infection should receive endoscopic examination (which will be covered by Japanese medical insurance) to evaluate for the presence and severity of atrophic gastritis. If people have a family history of gastric cancer and/or have been diagnosed as having atrophic gastritis by previous endoscopic examination, additional endoscopic examinations will also be offered in cases without *H. pylori* infection.

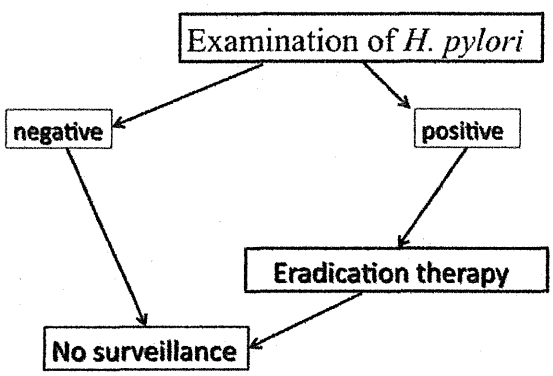

Figure 3. An approach for elimination of gastric cancer deaths in younger generation (before 20 years) in Japan.

We expect that many patients with gastric cancer will be discovered during this endoscopic examination. This project thus includes a form of endoscopic screening supported by medical insurance. Those without gastric cancer should receive bacterial eradication therapy. Persons whose endoscopic examination shows findings close to normal can be transferred to a no-surveillance group. If atrophic gastritis is found in people, a repeat endoscopic examination should be performed 1 to 2 years later and they should be considered for a surveillance program; the frequency and nature of which will depend on the results of ongoing and subsequent research on surveillance based on risk stratification (Fig. 4). As described above, the program combines primary prevention (*H. pylori* eradication) and surveillance with early cancer detection for those remaining at risk for development of gastric cancer despite *H. pylori* eradication.

Financial and Social Effects of Gastric Cancer Elimination

The cost of gastric cancer treatment in Japan is currently around 300 billion yen per year and will exceed 500 billion yen annually if measures are not taken for a decade or so. However, if the incidence of gastric cancer is reduced by *H. pylori* eradication, medical costs should be lowered substantially.[31]

Another important issue, in addition to cost, is the effect on society. By periodical follow-up endoscopy after *H. pylori* eradication therapy, most gastric cancer can be detected at an early stage, resulting in a quite favorable prognosis and a sharp decrease of gastric cancer-related deaths. Potentially, it might be possible to eliminate gastric cancer-related deaths from Japan around the middle of this century.

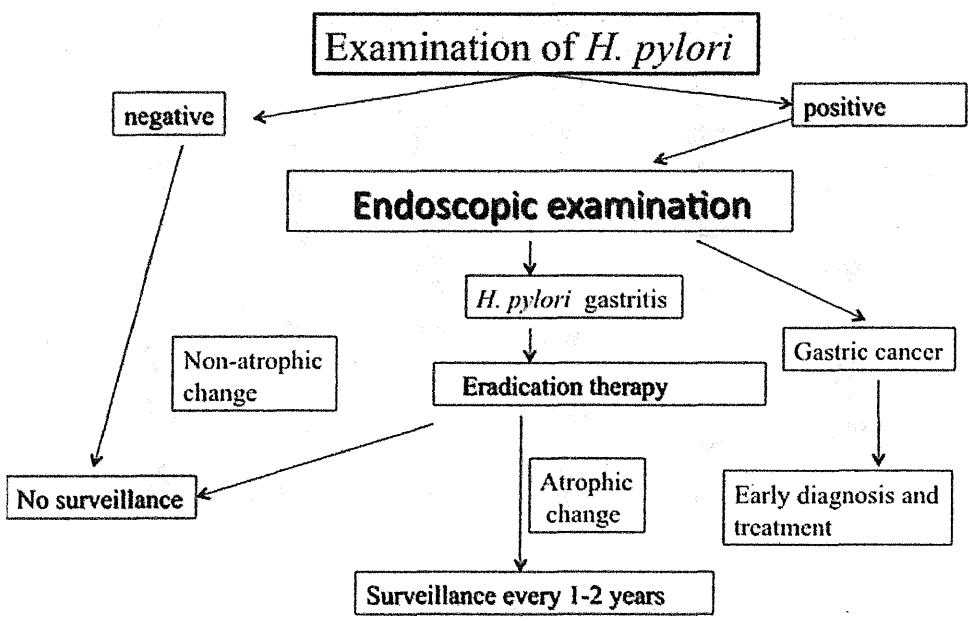

Figure 4. An approach for elimination of gastric cancer deaths after 50 years in Japan.

The principle of "innocent until proven guilty" is accepted in the legal field. Conversely in the field of infectious diseases, the principle of "guilty until proven innocent" applies. Therefore, proactive preventive measures are used for cancers that are suspected to be caused by infection so that the incidence of the target infection is dramatically decreased, thereby resulting in a reduction of cancer-related deaths. The effect of primary prevention based on the causes of cancer is more reliable and durable than secondary measures including screenings, and it also helps to reduce medical costs.

The possible success with elimination of gastric cancer in Japan should lead other countries with a high incidence of gastric cancer such as East Asia and Latin America to consider using a similar strategy, which might then lead to extermination of gastric cancer worldwide.

Conclusion

A gastric cancer elimination project that combines *H. pylori* eradication therapy and surveillance of high-risk patients is both appropriate and feasible for Japan, where excellent methods of diagnosis and endoscopic treatment for early gastric cancer are already available. In this country, the baby-boom generation is now passing 60 years and reaching the cancer-prone age, and therefore, an increase of medical costs related to gastric cancer is impending. Application for medical insurance in patients with *H. pylori*-related chronic gastritis due to the Basic Plan to Promote Cancer Control Programs might be a first step to eliminate gastric cancer deaths in Japan.

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Diagnostic accuracy of urine-based kits for detection of *Helicobacter pylori* antibody in children

Short title: Diagnostic accuracy of urine antibody kits for *H. pylori* in children.

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Abstract:

Background. Rapid urine-HpAb is reported to be a reliable test of *H. pylori* infection in adults, but there is no data on the application of the test in children. ***Objective.*** To evaluate the accuracy of a urine-based ELISA (urine-HpELISA) and immunochromatography (rapid urine-HpAb) kit for anti-*H. pylori* IgG antibody in children, we compared its sensitivity and specificity in reference to the ^{13}C-urea-breath test (UBT) and *H. pylori* stool antigen test (HpSA). ***Materials and methods.*** 101 Japanese children without significant upper-abdominal symptoms were included (mean age, 7.1 years; range 2 to 15 years). Their sensitivity and specificity were evaluated in reference to the ^{13}C-urea breath test (UBT) and *H. pylori* stool antigen test (HpSA). ***Results.*** 37 children were judged *H. pylori*-positive and 64 negative by UBT and HpSA. No discrepancy in the results was observed between UBT and HpSA. Urine-HpELISA showed 91.9% sensitivity and 96.9% specificity with an accuracy of 95.0%. Rapid urine-HpAb showed 78.4% sensitivity and 100% specificity with an accuracy of 92.1%. Seven false-negative results for rapid urine-HpAb were from children aged under 10 years, and their antibody titers of urine-HpELISA were lower than true-positives. ***Conclusions.*** For the diagnosis of *H. pylori* infection in Japanese children, the both tests may be non-invasive, inexpensive, reliable and easy-to-perform methods giving satisfactory accuracy, although the sensitivity of the rapid urine-HpAb kit was inferior to that of the urine-HpELISA kit, especially in children aged under 10 years showing relatively low titer of *H. pylori* antibody.

Key Words: *Helicobacter pylori*, Urine antibody, HpSA, UBT, children

Abbreviations: ELISA, Enzyme-linked immunosorbent assay: urine-HpELISA, Urine-based enzyme-linked immunosorbent assay for anti-*H. pylori* immunoglobulin G

antibody; UBT, ^{13}C-urea breath test; HpSA, *H. pylori* stool antigen test; CI, Cut-off index of urine-HpELISA: rapid urine-HpAb, Rapid urinary IgG antibodies to *H. pylori*

Introduction

Helicobacter pylori is a common pathogen causing chronic gastritis, and gastric and duodenal ulcers in adults [1-3] and children [4]. Many simple, non-invasive, inexpensive but accurate tests are available for the initial diagnosis and epidemiological evaluation of *H. pylori* infection. Serological tests for detection of *H. pylori*-specific IgG antibodies by enzyme-linked immunosorbent assay (ELISA) have been developed and perform well in adults, with sensitivity and specificity values reported to be higher than 90% [5]. However, their usefulness in children remains controversial [6-8]. In our previous study, we reported that urine-HpELISA (URINELISA, Otsuka Pharmaceuticals Co, Ltd, Tokyo, Japan) was a reliable method for diagnosis of *H. pylori* infection in Japanese children [9]. The rapid urine antibody detection test (rapid urine-HpAb) detects the same antigen as urine-HpELISA, and is faster non-invasive and convenient. It has been proved to be reliable with excellent sensitivity and specificity in adults [10-12], but has yet to be evaluated in children. In this study, we evaluate the sensitivity and specificity of the rapid urine-HpAb test in reference to HpSA and UBT.

Subjects and methods

Study population

This study included 101 Japanese children living in Wakayama Prefecture (mean age, 7.1±3.3; range 2-15). We had previously performed an epidemiological study at Wakayama Rosai Hospital on 484 children by HpSA, and found 31 positives [13]. In the present study, we re-invited 37 children, 31 known positives and 6 known negatives to participate. We also invited 64 children whose *H. pylori* status had not been examined. None of the children had significant upper-abdominal symptoms, a history of *H. pylori* eradication or renal disorders. They had not received any antibiotic or other significant medical treatment in the previous four weeks that might have affected the

results. Informed consent was obtained from all parents. All the children provided a urine sample at the day of UBT and a fecal sample within seven days of UBT. The research protocol was reviewed and approved by the Ethics Committee of the institution.

Methods

^{13}C-UBT: Children were fasted at least 4 hours before UBT and breath samples were collected before and 20 min after ingestion of ^{13}C-urea. Dosage of ^{13}C-urea was altered according to age; 50mg for children under 6 years of age, 75mg between 7 to 12 years, and 100mg over 13 years. An infrared spectrometer (UBiT- IR300, Otsuka Electronics Co, Hirakata, Japan) was used in this study and an increase of more than 3.5% was considered positive [14].

Stool antigen test: Stool samples were stored at -20°C until use. An enzyme immunoassay kit (Premier Platinum HpSA, Meridian Diagnostics Inc., Cincinnati, Ohio) utilizing a polyclonal anti-*H. pylori* rabbit antibody adsorbed to microwells was used to detect *H. pylori* antigen in stool according to the manufacturer's instructions. Values greater than or equal to 0.120, between 0.100 and 0.119, and less than 0.100 were considered positive, equivocal, and negative, respectively.

Urine-HpELISA (URINELISA): Single-void urine samples were obtained and stored at 2°C to 8°C until use. Urinary IgG antibodies to *H. pylori* were determined using a urine-HpELISA kit (URINELISA, Otsuka Pharmaceuticals Co, Ltd, Tokyo, Japan) that utilizes a *vacA* and *cagA*-positive *H. pylori* strain isolated from a Japanese gastritis patient as the antigen source [15]. Ninety-six-well microtiter plates coated with *H. pylori* antigen were used according to the manufacturer's instructions. Absorbance at 450 nm was measured and calculations were as follows: Cut-off index (CI) reflects the ratio of absorbance of sample tested / cutoff value. Cut-off values were calculated as the

mean absorbance of 2 positive controls / 8.5 + mean absorbance of 3 negative controls. CI values greater than or equal to 1.0 was judged positive, and those less than 1.0 were judged negative.

Rapid urine-HpAb (RAPIRUN): Rapid urinary IgG antibodies to *H. pylori* were determined using immunochromatography (RAPIRUN, Otsuka Pharmaceuticals Co, Ltd, Tokyo, Japan) using the same antigen as in URINELISA. This test is judged to be positive if red lines appear in both the control and test zone, and to be negative if a red line is observed only in the control zone. Without a visible red line in the control zone, the test is considered to be invalid.

Proteinuria test: Since proteinuria may give a false-positive reaction in the urine-based ELISA [16], BM test® (Roche Diagnostics Co, Germany) was also performed on urine-HpELISA-positive samples.

Determination of *H. pylori* infection: *H. pylori* infection status was determined by positive results in both UBT and stool antigen test.

Results

Measurement of UBT and HpSA

Of 101 children, 37 were positive (mean age, 7.1±3.4; range 2-15) and 64 were negative (mean age, 7.1±3.3; range 2-14), as judged by UBT and HpSA (Table 1). Statistically difference was not detected between positive and negative subjects on age. There were no equivocal results in the HpSA, and no discrepancy was observed between the two tests.

Rapid urine-HpAb and urine-HpELISA

Twenty-nine out of 37 *H. pylori*-positive children by UBT and HpSA were positive with rapid urine-HpAb and one was invalid, while all 64 *H. pylori*-negative children were negative (Table 1). Thus the rapid urine-HpAb showed 78.4% sensitivity (29/37)

and 100% specificity (64/64) with an accuracy of 92.1% compared to UBT and HpSA (Table 2). In comparison, Urine-HpELISA showed 91.9% sensitivity (34/37) and 96.9% specificity (62/64) with an accuracy of 95.0% (Table 2).

To evaluate whether age or antibody titers affected the results of the rapid urine-HpAb, CI of the urine-HpELISA was plotted against age (Fig. 1). There was no significant correlation between the CI values and the age in *H. pylori*-positive subjects (Fig. 1A). CIs of urine-HpELISA of the true positive subjects with negative rapid urine-HpAb ranged from 0.35 to 3.3.

Sixty-two out of 64 true negative subjects showed CI values less than the cut-off value for urine-HpELISA, but all 64 subjects showed negative rapid urine-HpAb (Fig. 1B). It can also be noted that 6 out of 7 false negative urine-HpAb results showed CI values of <3.3 suggesting a strong relationship between antibody titer and sensitivity.

Sensitivity and specificity of the two tests according to age groups were compared (Table 3). In the under 10 age group, sensitivity of the rapid urine-HpAb was lower than that of urine-HpELISA (75.0 vs. 89.3%) and specificity was equivalent. In the over 10 age group, sensitivity and specificity of both tests were adequate. No proteinuria was detected in *H. pylori*- positive subjects.

Discussion

Diagnostic accuracy of the rapid urine-HpAb kit and the urine-HpELISA kit was evaluated in children and the both kits gave satisfactory results, although the sensitivity of the rapid urine-HpAb test was inferior to the urine-HpELISA kit, especially in children aged under 10 years.

It can be a weak point of the current study that subjects with stool antigen test results were included, which could be a bias. If the subjects had been invited according to urine *H. pylori* antibody status, it would have distorted the results. As at the time of

invitation, information of urine *H. pylori* antibody status was lacking, in other words blind, little bias by the selection of the subjects is expected. No discrepancy was there between results of UBT and HpSA. The results are thought to be reliable as gold standard for sensitivity and specificity.

Various epidemiologic studies have revealed a significant relationship between gastric cancer and *H. pylori* infection in the Japanese population [17-18]. It is also reported that *H. pylori* infection is associated with the development of both intestinal-type and diffuse-type gastric cancer [19]. In these studies, gastric cancer was shown to develop only in patients carrying *H. pylori*, which confirms that infection is a main cause of gastric cancer in Japan.

It is also proven that eradication of *H. pylori* infection reduces the occurrence of gastric cancer [20-21]. In a high-risk region of China, a prospective, randomized, placebo-controlled, population-based primary prevention study showed that the incidence of gastric cancer was similar between participants receiving *H. pylori* eradication therapy and those receiving placebo during a period of 7.5 years [22]. However, in the subgroup without precancerous lesions, eradication of *H. pylori* significantly decreased the development of gastric cancer. According to these findings, *H. pylori* eradication in the Japanese population will reduce the development of gastric cancer, and therapy before the development of atrophic gastritis is desirable. This makes the age of eradication for prevention of gastric cancer and the most effective screening test for *H. pylori* infection in children and young adults an important issue.

Urine antibody testing is a simple, low-cost and rapid process with minimal patient discomfort and seems ideal for screening of *H. pylori*. However, the accuracy of antibody tests for *H. pylori* in childhood has previously been considered controversial due to their low sensitivity. We have shown in a previous report that the sensitivity of a

serum-HpELISA kit, HM-CAP, was only 51.4% (18/35) for children below 10 years compared to HpSA [8]. However, an EIA test using serum samples based on Japanese strain-derived antigens, JHM-CAP, had significantly better performance than HM-CAP, which is based on U.S. strain-derived antigens, in a study population of Japanese asymptomatic young children [23]. Similarly, we reported that a urine-HpELISA using *H. pylori* antigens derived from a Japanese strain had 94.4% sensitivity and 96.9% specificity with an accuracy of 96.0% in children [9]. This shows that performance in children is highly dependent on the locality of the *H. pylori* strains used in the ELISA system.

Akamatsu *et al.* performed screening tests for *H. pylori* infection in a study population of 1,224 high school students using the rapid urine-HpAb and found 64 positive subjects [24]. Thirty of these 64 *H. pylori* urine antibody-positive students had an upper gastrointestinal endoscopy in the author's institution and 24 (80%) were diagnosed *H. pylori* positive by histology and culture. Among remaining 6 rapid urine-HpAb positive subjects, two subjects were endoscopically diagnosed as severe atrophic gastritis with serum anti-*H. pylori* positive, indicating 13.3% (4/30 subjects) of false positive in the rapid urine-HpAb test. In this study, as there are no reports on the reliability of a rapid urine-HpAb test in children, we evaluated a rapid urine-HpAb test in children and found that the sensitivity of the rapid urine-HpAb test was lower than urine-HpELISA. While urine-HpELISA was judged according to OD values, rapid urine-HpAb is detected by visualizing a positive reaction band. In 12 *H. pylori* positive urine samples showing a CI value of less than 3.3 by urine-HpELISA, six had negative rapid urine-HpAb results, showing that low antibody titers of the specimens tend to result in a false negative. The difference in diagnostic accuracy between the rapid urine-HpAb and the urine-HpELISA tests was observed only in subjects aged under 10