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Risk of gastric cancer in *Helicobacter pylori* infection in a 15-year follow-up

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ABSTRACT

Objective: We investigated the risk of gastric cancer among men with *Helicobacter pylori* (*H. pylori*) infection or atrophic gastritis (AG) in a 15-year follow-up.

Materials and methods: Study population consists of 12,016 men aged 50–65 years at the beginning of the follow-up in 1994–1996. Serum levels of pepsinogen I (SPGI) and antibodies (IgG) to *H. pylori* (HpAb) were assayed from serums collected in 1994–1996. Incidence of gastric cancer in the study population was assessed in follow-up from 1994 to 2011 by data from the nationwide cancer registry. Based on SPGI and HpAb values, standardized incidence ratios (SIRs) of gastric cancer were calculated in three subgroups, that is, in those with a healthy stomach, those with *H. pylori* infection but without AG and those with AG. Risk ratios (RR) of gastric cancer were calculated using SIR of subgroups.

Results: During 15 years, seven gastric cancers appeared per 79,928 person years among men with healthy stomachs, 50 cancers per 92,533 person years in men with *H. pylori* infection but without AG, and 8 per 8658 person years in men with AG. Risk ratio (RR) of stomach cancer in men with *H. pylori* infection was 5.8 (95%CI: 2.7–15.3) compared to men with healthy stomachs, and 9.1 (95%CI: 2.9–30.0) in men with AG. There were no differences in cancer risk between cardia and distal stomach.

Conclusions: Risk of gastric cancer is low in men with healthy stomachs. It is significantly increased in those with *H. pylori* infection and more in those with AG.

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Introduction

Atrophic gastritis (AG) and acid-free stomach, which is either autoimmune or a consequence of *Helicobacter pylori (H. pylori)* infection, are risk conditions for stomach cancer, for the cancer of an intestinal type in particular.[1–8] Less is known about the magnitude of cancer risks in subjects with healthy stomach mucosa or in those with only nonatrophic *H. pylori* infection, although the *H. pylori* infection was classified as a class 1 carcinogen by WHO/IARC already in 1994.[1]

The *H. pylori* infection causes chronic gastritis that is initially nonatrophic, but it may later develop into various forms and stages of atrophic gastritis and may end up as an acid-free stomach.[6–9] Like AG, the nonatrophic form of *H. pylori* gastritis is likely a precancerous condition, particularly for gastric cancer of the diffuse type.[1,3,10]

In the present study, we investigated the long-term risk of gastric cancer in a large population-based sample of men with or without *H. pylori* infection or AG. The study population consisted of 12,016 men representing the general male population from two Finnish cities and was collected from men who participated in a serum pepsinogen I (SPGI) screening study in 1994–1996. Thereafter, the men were followed for 15 years, and gastric cancers in the study population during follow-up were identified from the nationwide cancer registry. The status of gastric mucosa in all 12,016 men was assessed with biomarker tests for SPGI and antibodies (IgG) to *H. pylori* (HpAb) from serum samples collected in 1994–1996. Based on the biomarker assays, we could classify the study population into three subgroups; that is, those with a healthy and normal gastric mucosa, those with pure *H. pylori* infection (chronic nonatrophic gastritis) and those with moderate or severe atrophic gastritis.

The main objective of this study was to estimate the risk of gastric cancer due to only *H. pylori* infection; that is, in chronic gastritis that is caused by *H. pylori* but not yet progressed to the atrophic stage. The other objectives were to estimate the risk of gastric cancer in men with healthy stomach mucosa, and to look at whether the *H. pylori* related risk of gastric cancer varies between cancers in gastric cardia and distal stomach.

Methods

Study population and the study cohorts

Initially, 16,872 men (50–65 years old) from two Finnish cities were identified from the population registry and were invited

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Table 1. Follow-up data for total study population and three subgroups, and on referral actions carried out in men from 1994–1996 to 2011.

Subgroup	Biomarker test SPG1 μg/L	HpAb (IgG)	Persons Number	Person Years	Actions and tests Carried out in each group
Healthy	25+	<30	5232	79,928	SPG1 assayed in 1994–1996 HpAb status assayed in 2014 from serum samples taken in 1994–1996 No active clinical interventions in 1994–1996
H. pylori infection	25+	30+	6178	92,533	SPG1 assayed in 1996–1996 HpAb status assayed in 2014 from serum samples taken in 1994–1996 No active clinical interventions in 1994–1996
Atrophic gastritis	<25	any	606	8658	SPG1 assayed in 1994–1996 HpAb status assayed in 2014 from serum samples taken in 1994–1996 All referred in 1994–1996 to consultation, treatment, endoscopies and surveillance in local hospitals or health care centers
Whole sample	any	any	12,016	181,118	All 16,872 men born 1929–1949 in two cities were invited to the SPG1 test in 1994–1996 12,016 men could be tested for SPG1 and HpAb (IgG) status from same serum samples taken in 1994–1996 SPG1 was assayed in 1994–1996 and HpAb status in 2014 Follow-up of the study cohort from 1994 to 2011 by Finnish Cancer Registry

to give a blood sample for the SPGI test, half in the autumn of 1994 and half in the autumn of 1996 [11] (Table 1). Altogether, 12,016 men (71%) participated and form the study population in the present investigation. Among participants, the serum levels of pepsinogen I (SPGI) and *H. pylori* antibodies (IgG) (HpAb) were assayed from blood samples collected in 1994–1996 to determine the presence or absence of an ongoing *H. pylori* infection (chronic gastritis) and the presence or absence of a moderate or severe stage of atrophic gastritis in the stomach. The HpAb assays were done in 2012–2013 from the same serum samples from which the SPGI tests were done already in 1994–1996.

Blood sampling and tests for SPGI and H. pylori *antibodies*

Fasting sera were collected in aprotinin (Trasylol, Bayer Germany; 200 KIE/mL) containing Venoject tubes and stored at −70 °C until analyzed. SPGI was analyzed in 1994–1996 using the specific enzyme-linked immunosorbent assay (ELISA) tests provided by Biohit Healthcare Plc, Helsinki, Finland. The assay has been calibrated to correspond to results obtained by radioimmunoassay (RIA) used by Samloff [12] using 238 serum samples with serum pepsinogen concentrations between 1.5 and 120 μg/L. The sensitivity and specificity of the SPGI test for advanced (moderate or severe) atrophic gastritis are 92% and 90% at a cutoff level of 30 μg/L, respectively, according to the manufactureŕs kit instructions for use. In clinical practice and in endoscopy and biopsy histology controlled trials, the SPGI cutoff level of 25 μg/L has been demonstrated to be a reliable criterion in exclusion, inclusion or delineation of cases regarding the presence or absence of advanced (moderate or severe) atrophic corpus gastritis.[13–15] Therefore, the level of 25 μg/L was also selected as a cutoff criterion for SPGI in the present study. In addition, this cutoff corresponds with the SPGI levels of assays initially specified by Samloff.[12]

The HpAb assay was done in 2012–2013 by the ELISA test provided by Biohit Healthcare Plc, Helsinki, Finland, and was performed according to the instructions of the manufacturer. The sensitivity and specificity of the test to detect the ongoing *H. pylori* infection are 93% and 96%, respectively, according to an independent analysis and report of AFSSAPS (Agence Francaise de Securite Sanitaire des Produits de Sante) on commercial *H. pylori* ELISA test kits in 2008.

The serum levels of SPGI and HpAb were used as criteria in the classification of the study population into three subcohorts (subgroups). The SPGI levels of 25 μg/L or more (25+) were considered to exclude the cases with advanced (moderate or severe) atrophic gastritis in the stomach, irrespective of the cause of atrophic gastritis (autoimmunity or *H. pylori* origin).[14–16] The HpAb levels 30 EIU or more (30+) were considered to indicate an ongoing *H. pylori* infection (gastritis).[17]

Classification into three subgroups was as follows (Table 1):

Healthy. Men with normal and healthy stomach mucosa: SPGI 25 μg/L or higher (SPGI 25+) and HpAb lower than 30 EIU (HpAb <30).

***H. pylori* infection**. Men with only *H. pylori* infection (gastritis) without moderate or severe atrophic gastritis (AG), and without an acid free stomach: SPGI 25 μg/L or higher (SPGI 25+) and HpAb 30 EIU or more (HpAb 30+).

Atrophic gastritis. Men with moderate or severe atrophic gastritis in the gastric corpus or fundus (SPGI <25 μg/L), irrespective of the presence or absence of an ongoing *H. pylori* infection. The atrophic gastritis can be either autoimmune (HpAb negative) or of *H. pylori* origin (HpAb positive).

Follow-up and recording of the cancer incidence data in 1994–2011

Information about cancer cases during the follow-up from 1994 to 2011 was received in 2012 from the Finnish Cancer Registry (FCR). Due to mandatory reporting of all cancer diagnoses in Finland, the FCR has a national coverage of over 99% of all new cancer cases in Finland.[16] The follow-up began on 1 December 1994 for the first half of the men and on 1 November 1996 for the second half of the men (one month after finishing SPGI screening) and ended on 31 December 2011).

The cancer registry includes data on all invasive cases of cancer. It does not include data on cases classified as noninvasive (preneoplastic lesions, dysplasia or intramucosal neoplasia). Information from the FCR provided data on the subsite of cancer in the stomach. Therefore, the analyses could be performed separately for cases in which the cancer was located in the distal stomach (pylorus, antrum, angulus, corpus or fundus) or in the gastric cardia.

In calculating the standardized incidence ratios (SIRs), the age-standardized incidence of cancer in the total male population of Finland (expected rates) were compared with the observed incidence rates of cancer in the subcohorts. The expected number of cancers for each age group (5-year age categories) and 4-year calendar period were estimated by multiplying the number of person years in the category accumulated in the subcohorts with the respective incidence rate in the total male population at the same age in Finland. The standardized incidence rates were calculated according normal procedures of age standardization.[17] The 95% confidence intervals (CI) were calculated on the basis of standard error of SIR [15] and these were estimated assuming a Poisson distribution for the number of observed cancers. The p values of the differences between SIRs were calculated on the basis of confidence intervals.[18,19]

The authors had official permission for collection of the data and for carrying out the present investigation by linking the laboratory test results with the information from FCR (Dnro THL/1349/5.05.00/2009).

Results

Altogether, 65 gastric cancer cases appeared in 15 years in the present study population. Of these, only seven (11%) occurred in men with a healthy stomach (without *H. pylori* infection or AG) mucosa at the time of drawing the blood sample (1994–1996).

Table 2 presents the observed and expected cumulative incidence of gastric cancer in three subgroups during the 15-year follow-up period. Results on the incidence of cancer separately in the distal stomach and gastric cardia are provided. In addition, Table 2 presents the SIRs of gastric cancer and the SIR of total cancer (all malignant diseases) in each subgroup and in the whole-study cohort.

We found the SIR for gastric cancer among men with healthy stomachs to be significantly lower than the corresponding SIR among men with *H. pylori* infection (SIR 0.21, 95% CI: 0.04–0.60) and lower than among the whole study cohort (Table 3).

Table 3 provides information on incidences of gastric cancer and on SIRs according to different lengths of follow-up time during the 15-year study period. A similarly low SIR of gastric cancer was evident among men with healthy stomachs over the whole 15 years of follow-up. Among men with *H. pylori* infection (gastritis), the incidence of gastric cancer tended to increase with the length of follow-up time. The SIR of gastric cancer was significantly ($p < 0.05$) increased among men in the *H. pylori* infection group, followed up to 10 years or more.

The risk ratio (RR) of gastric cancer between those with *H. pylori* infection and men with healthy stomachs was 5.8. The RR between those with AG compared to those with *H. pylori* infection was 1.6 (0.6–3.3), and 9.1 (2.9–30.0) as compared to men with healthy gastric mucosa. The risk ratios were quite constant regardless of the sub-site of gastric cancer (Table 4).

Table 2. Cancer registry based observed and expected incidence and SIR of gastric cancer in three subgroups and in whole study population during the follow-up from 1994–1996 to 2011.

Subgroup, cancer type and site	SPG1 μg/L	HpAb (IgG)	Obs.	Exp.	SIR	95%SD
Healthy	25+	<30				
Gastric cancer						
Distal stomach			5	25	0.20	0.01–0.39
Cardia			2	7	0.29	0.01–0.73
Stomach, all sites			7	32	0.22[a]	0.04–0.40
Total cancer, any site			1403	1341	1.05	0.97–1.16
H. pylori infection	25+	30+				
Gastric cancer						
Distal stomach			37	31	1.19	0.62–1.76
Cardia			13	8	1.63	0.19–3.06
Stomach, all sites			50	39	1.28	0.75–1.82
Total cancer, any site			1692	1642	1.03	0.96–1.13
Atrophic gastritis	<25	any				
Gastric cancer						
Distal stomach			6	3	2.00	0.01–4.77
Cardia			2	1	2.00	0.01–6.80
Stomach, all sites			8	4	2.00	0.01–4.40
Total cancer, any site			167	165	1.01	0.79–1.32
Whole sample	any	any				
Gastric cancer						
Distal stomach			48	60	0.80	0.50–1.10
Cardia			17	15	1.13	0.35–1.92
Stomach, all sites			65	75	0.87	0.58–1.15
Total cancer, any site			3262	3146	1.04	0.99–1.10

[a]$p = 0.009$.

Table 3. Cancer registry based observed and expected incidence and SIR of gastric cancer in three subgroups in different time periods of follow-up from 1994–1996 to 2011.

Subgroup, cancer type and site	SPG1 μg/L	HpAb (IgG)	Obs.	Exp.	SIR	95%SD
Healthy	25+	<30				
Gastric cancer						
Follow-up 0–2 years			1	3	0.33	0.01–1.62
Follow-up 2–9 years			3	14	0.21[a]	0.04–0.62
Follow-up 10 + years			3	14	0.21[a]	0.04–0.62
H. pylori infection	25+	30+				
Gastric cancer						
Follow-up 0–2 years			4	4	1.00	0.25–2.32
Follow-up 2–9 years			17	17	1.00	0.57–1.55
Follow-up 10 + years			29	17	1.71	0.68–2.72
Atrophic gastritis	<25	any				
Gastric cancer						
Follow-up 0–2 years			2	0.5	4.00	0.50–14.83
Follow-up 2–9 years			2	2	1.00	0.13–3.97
Follow-up 10 + years			4	2	2.37	0.65–6.06
Whole sample	any	any				
Gastric cancer						
Follow-up 0–2 years			7	8	0.88	0.32–1.73
Follow-up 2–9 years			22	33	0.67	0.41–1.00
Follow-up 10 + years			36	34	1.06	0.75–1.48
Total cancer						
Follow-up 0–2 years			215	214	1.00	0.87–1.14
Follow-up 2–9 years			1384	1325	1.04	0.99–1.08
Follow-up 10 + years			1663	1608	1.03	0.99–1.07

[a]$p = 0.025$.

Table 4. The risk ratios (RR) and CI95% of risk ratios of gastric cancer between the subgroups by site of cancer from 1994–1996 to 2011.

Site of cancer	Between *H. pylori* and healthy mucosa	Between atrophic gastritis (AG) and *H. pylori* infection	Between atrophic gastritis (AG) and healthy mucosa
Distal stomach	6.0 (2.3–19. 0) $p = 0.001$	1.7 (0.6–4.0) $p = 0.276$	10.0 (2.5–41.0) $p = 0.001$
Cardia	5.7 (1.3–52.0) $p = 0.064$	1.2 (0.1–5.4) $p = 0.867$	7.0 (0.5–97.0) $p = 0.148$
Stomach, all sites	5.8 (2.7–15.3) $p = 0.000$	1.6 (0.6–3.3) $p = 0.283$	9.1 (2.9–30.0) $p = 0.000$

Discussion

Altogether, 65 gastric cancers developed in the whole study population of 12,016 men during the 15-year follow-up period, of which only 7 (11%) cancers developed in men with healthy stomach mucosa (5232 men). The SIR of gastric cancer in the subgroup of men with healthy stomachs was nearly 80% lower than expected, and the RR of SIRs was approximately six times higher in those with *H. pylori* infection compared to men with a healthy stomach. Thus, the people with healthy stomach mucosa are clearly those who have the lowest risk of gastric cancer known so far.

The present observation also demonstrates that an *H. pylori* infection alone (nonatrophic *H. pylori* gastritis) is by itself a clear risk condition for gastric cancer as was suggested by the IARC/WHO statement in 1994.[1] The observation indicates that the simple infection markedly increases the cancer risk when compared to a healthy stomach. Supporting the conclusions of *H. pylori* infection as a risk condition for gastric cancer, the SIR of gastric cancer among men with *H. pylori* infection tended to rise during follow-up. Practically, a half (29 of 50) of gastric cancers in the *H. pylori* subgroup appeared during the last 5-year period (10+ years).

We authors consider the estimates of SIRs and RRs of gastric cancer in the present subgroups of 'Healthy stomach mucosa' or '*H. pylori* infection without AG' to be reliable and epidemiologically valid. The delineation of men into subgroups was based on biomarker tests that are highly reliable in reflecting the health of stomach mucosa and enable noninvasive tests of large populations of asymptomatic people with a simple method.[17–20] Furthermore, the gastric cancers identified during the follow-up period were based on cancer cases recorded by nationwide cancer registry with coverage of over 99% of all cancer cases in Finland.[16] In addition, the subgroups followed up in the present investigation were derived from the study population that represents the general population of males who were 50–65 years old at the beginning of the follow-up and were living in two cities in southern Finland in 1994–1996.[11]

All men in the subgroups of healthy gastric mucosa or *H. pylori* infection without AG had normal levels of SPGI in 1994–1996. No referral to treatment, clinical surveillance or other actions were carried out by the investigators fpr anyone, and all men were passively followed up by the cancer registry during the 15-year follow-up period from 1994 to 2011.[11] In addition, the delineation of the men to those with healthy stomach mucosa and to those with nonatrophic *H pylori* gastritis was done with the HpAb test (from serum samples collected in 1994–1996) only at the end of the follow-up period. However, unknown confounders may still exist that may contribute to estimates of cancer risks in the study subgroups. For example, differences in smoking, dietary habits, alcohol consumption, socioeconomic status or eradication of *H. pylori* during the 15-year follow-up among thousands of men in each subgroup, could not be controlled for in the present investigation. However, these possible biases, even though certainly existing, can hardly explain the differences observed in the gastric cancer risk between men with healthy gastric mucosa and those with *H. pylori* infection.

On the other hand, the observed SIRs and RRs of gastric cancer are likely severely biased in the present study in the subgroup of men with AG; that is, in the group of 606 men who had moderate or severe atrophic gastritis in gastric corpus and fundus by the SPGI test in 1994–1996. All these men had a low (<30 µg/L) serum level of pepsinogen I (SPGI) and were, therefore, considered to have a hypochlorhydric or even achlorhydric stomach in 1994–1996; that is, a severely sick and atrophic stomach mucosa considered to be a premalignant condition that needs special attention.[1–5] Therefore, all these men were actively referred in 1994–1996 for medical consultation, treatment and clinical surveillance in specialized hospitals or health care centers.[11]

Possible endoscopic, surgical, therapeutic or preventive interventions carried out among the 606 men with AG may decrease the incidence of gastric cancer in the 15-year follow-up.[11] Therefore, the observed incidences and SIRs of gastric cancer in this subgroup of men are likely underestimations of the real cancer risk. The authors were not able to explore the procedures that were done to these 606 men with AG during the 15-year follow-up period. In spite of this, the RR of gastric cancer was approximately 9 in the subgroup of men with AG as compared to men with healthy stomach mucosa.

In the present study, the RR of cancers in the gastric cardia was 5.4 in men with *H. pylori* seropositivity as compared to cardia cancers in subjects with healthy stomach mucosa. The SIR of cardia cancers was also quite similar (1.6 vs. 1.3) to that of distal gastric cancer in men with *H. pylori* seropositivity. Even though the number of cases is low, and even though the risk estimates are insignificant, the observations support the view that the *H. pylori* infection associates with cardia cancers similarly as with gastric cancers in the distal stomach.

The observations of *H. pylori* infection as an etiological factor for cancer of the gastric cardia have been contradictory. In contrast to the present observations, some studies indicate that cardia adenocarcinomas do not associate with *H. pylori* infection and that the pathogenesis of these cancers resembles the pathogenesis of lower esophageal adenocarcinomas in patients with gastroesophageal reflux disease (GERD).[20] Differences in pathogenesis of cardia and noncardia gastric carcinomas have been proposed.[21–25]

In the past, several prospective investigations with case–control design have been published on the risk of gastric cancer due to *H. pylori* infection. In a systematic review covering 10 studies before 1998, including approximately 800 gastric cancer cases, the analysis yielded a RR of 2.5 (95%CI: 1.9–3.4) for gastric cancer in *H. pylori*-seropositive people.[26] An European prospective case–control study of 233 gastric cancers and 910 controls, including the SPGI assay in addition to the *H. pylori* test, yielded a RR of 6.5 (95%CI: 3.3–12.6) for noncardia gastric cancer in subjects infected with a cytotoxic (CagA) *H. pylori* strain.[27] In a prospective Finnish study, the RR of gastric cancer was 3.1 (95%CI: 1.97–4.95) between *H. pylori* infected and non-infected persons.[28] The RR, based on case–control study designs, varied between 1.6 and 7.9 in three published papers from two extensive prospective nutritional intervention trials of over 29,000 males at age of 50–69 years in Linxian, China and Finland.[23–25]

Our estimate of the risk of gastric cancer due to *H. pylori* infection, 5.8 (95%CI: 2.7–15.3), is similar or somewhat higher than the published risks estimated in the above-mentioned prospective investigations. In contrast to the mentioned case–control investigations, the risk estimates for gastric cancer in the present study were received from all new cases of gastric cancer that appeared during the follow-up time in all subgroups of men without ongoing *H. pylori* infection or AG, and those with a verified ongoing *H. pylori* infection or AG at beginning of the follow-up.[11]

Differences in the magnitude of the observed risk of gastric cancer between the present and earlier published investigations may be due to differences in the study design, in the application of biomarker tests for defining *H. pylori* infection or AG, or in the criteria of the subjects who are classified as having healthy gastric mucosa or AG. All subjects with a negative *H. pylori* test do not have healthy gastric mucosa and therefore cannot be classified as healthy controls. *Helicobacter pylori* negative cases are, on the other hand, often considered healthy, even though their stomachs are, in fact, severely sick. In an earlier Finnish study among subjects with endoscopically verified atrophic gastritis, an ongoing *H. pylori* infection was found only in 82% of cases with the serological *H. pylori* test.[29] Thus, without controlling for SPGI, the *H. pylori* seronegative cases with AG are easily misclassified into the subgroup of people with normal and healthy gastric mucosa. On the other hand, the cases with *H. pylori*-seropositive AG and acid-free stomach may be erroneously classified as cases with a simple uncomplicated *H. pylori* infection.

We conclude that the present investigation emphasizes the following: of all gastric cancers that occurred during the 15-year follow-up among elderly men, only 11% appeared in men with healthy stomachs. The risk of stomach cancer is approximately six times higher among men with *H. pylori* infection than among men with healthy stomach mucosa, and the *H. pylori* infection raises the gastric cancer risk similarly in the gastric cardia and in other sites of the stomach.

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