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Decreasing prevalence of helicobacter antibodies in Finland, with reference to the decreasing incidence of gastric cancer

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SUMMARY

Time trends and geographical variation of *Helicobacter pylori* antibodies in Finland were investigated by enzyme immunoassay in 20- to 34-year-old randomly selected females from six localities during 1969–73 ($n = 375$), and 15- to 45-year-old females representing nine communities and four geographical areas in 1983 ($n = 882$) and 1995 ($n = 842$). In the six communities investigated at three different time points, the overall prevalence declined from 38 to 12%, with an emphasis on the latter 12 years. The regionally varying rate of decrease in helicobacter prevalence changed the pre-existing geographical variation, leaving northern Finland with the highest rate. A 10%-units higher local helicobacter prevalence seemed to predict a 23% (95% CI 3–44%) higher gastric cancer incidence 20 years later. The overall decline in helicobacter seropositivity is consistent with earlier reports from Finland and other developed countries, and supports the cohort theory as an explanation for the age-related increase in *H. pylori* seroprevalence.

INTRODUCTION

Helicobacter pylori-induced chronic gastritis is a life-long infection [1] and a major risk factor for peptic ulcer disease [2] and gastric cancer [3]. It is a widely distributed disease which, through its severe complications, is associated with considerable morbidity and mortality [4]. The prevalence of *H. pylori* antibodies increases with age in both developed and developing countries [1]. In Western and Northern Europe this age-related increase in helicobacter seropositivity appears to reflect a cohort effect due to an acquisition of infection in childhood [5, 6] rather than a constant infection rate over time as suggested in data from Canada [7]. The decreasing incidence of *H. pylori* in children leads to a declining seropositivity rate in successive birth-cohorts. This decline is especially seen in developed countries, and has been associated with economic development and improved hygiene.

Being associated with each other, distal gastric cancer and helicobacter infection show certain similar features in their worldwide occurrence and epidemiology. These common features include time trends as

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well as geographical variation [8] but, in contrast to gastric cancer, the infection with *H. pylori* is independent of gender [9, 10].

The decreasing seroprevalence of *H. pylori* infection in a developed country has recently been demonstrated in the Finnish town of Vammala [6]; during the 21-year period from 1973 to 1994, the age-adjusted prevalence of helicobacter antibodies decreased by 25%-units in an adult population aged 15–74 years. In females the drop was 19%-units (from 52·5 to 33·4%), with the emphasis on younger age groups of 15–54 years. At the same time, the nationwide incidence rate (adjusted for age of the world standard population) of gastric cancer in Finnish females decreased from 15·1 per 100000 person-years in 1973 to 8·0 per 100000 person-years in 1994 [11]. The decrease during the entire period of cancer data available is about sixfold: from 39·5 in 1953 to 6·7 in 1997 [11, 12].

The variation in *H. pylori* prevalence between developed and developing countries and different ethnic groups has been well established [1]. Geographical differences in helicobacter seroprevalence within one country have, however, seldom been investigated. Finland as a North-European country with substantial geographical dimensions (338145 km^2, maximum length 1157 km) and an ethnically uniform population (5·117 million in 1995), offers an excellent opportunity for such regional comparisons. The aim of the present study was therefore to evaluate time trends as well as geographical variation in *H. pylori* infection within a developed country, Finland. A remark will be made on the geographical association of *H. pylori* prevalence and incidence of gastric cancer.

SUBJECTS AND METHODS

Study population

In Finnish maternity clinics, blood samples are routinely collected from all pregnant females in order to screen for congenital infections. In this study, we investigated all maternity clinic samples ($n = 1724$) taken in nine different localities in 1983 ($n = 882$) and in 1995 ($n = 842$). The communities studied represent northern (Kemijärvi, Kittilä), eastern (Joensuu, Kiihtelysvaara, Tohmajärvi), southern (Jaala, Kuusankoski) and western (Vammala, Uusikaupunki) Finland. The median age of the mothers was 27 years in 1983, and 29 years in 1995 (range 15–45 years), and the corresponding birth dates were 1956 (range 1939–67 in 1983) and 1966 (range 1950–79 in 1995).

To extend the scope of the study further, we also investigated sera originally collected in a large Finnish health examination study carried out during 1966–73 [13]. This 'Finnish Mobile Clinic Health Examination Survey' was conducted by the Social Insurance Institution and performed in a number of rural, semiurban and industrial communities in various parts of Finland [13]. Total populations or random samples from 30 communities (including six of the localities investigated in the present study) were represented by over 48000 adults ($\geqslant$ 15 years of age); frozen serum samples were available from 82·5% of the study population. For the present study, we received a total of 375 sera from 20- to 34-year-old females, and the six communities involved were Joensuu, Kemijärvi, Kuusankoski, Tohmajärvi, Uusikaupunki and Vammala. The median age of the women studied was 27 years, and the median birth date was 1944 (range 1935–53). By studying the samples from the maternity clinics and the 'Finnish Mobile Clinic Health Examination Survey', we were able to determine the helicobacter seroprevalence in 20- to 34-year-old women throughout Finland over three successive decades.

Laboratory analyses

IgG antibodies against *H. pylori* were determined by an enzyme immunoassay (Pyloriset EIA-G, Orion Diagnostica, Espoo, Finland) according to the manufacturer's instructions [14]. Serum samples were diluted to 1/201 and four prediluted calibrator sera were pipetted into microtitre wells coated with specific *H. pylori* antigens. After incubation at room temperature for 60 min, the wells were washed. Alkaline phosphatase conjugate, a swine anti-human IgG, was pipetted into each well and the wells were covered with plastic tape. The plates were incubated at room temperature for 60 min and washed before a substrate solution was added. The enzyme reaction was stopped with 1 M NaOH after a 30 min incubation. Absorbance values at 405 nm were recorded with a Titertek Multiskan analyser (Eflab Oy, Helsinki, Finland) and converted to reciprocals of the endpoint titres. Titres of 300 or higher were considered positive for *H. pylori* IgG antibodies. With this recommended cut-off limit, a sensitivity of 99% and a specificity of 98% have been documented in a Finnish adult population for the test used [15].

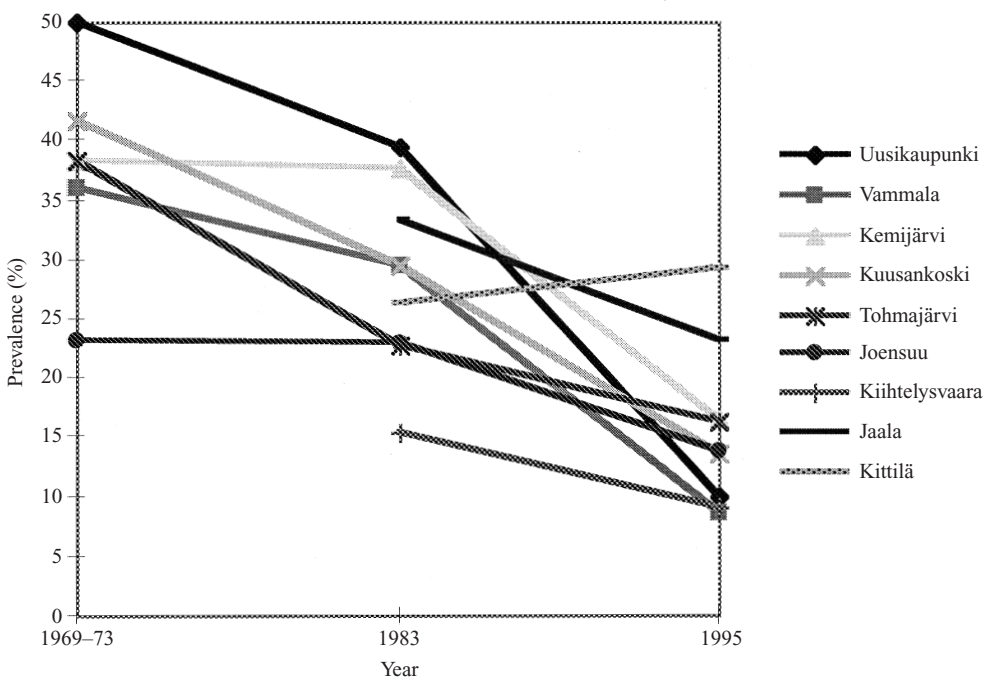

Fig. 1. Prevalence of *H. pylori* antibodies in various Finnish communities in 1969–73, 1983 and 1995. Sera collected from 20- to 34-year-old women.

Cancer data

Municipality-specific SIR values (standardized incidence ratio) of gastric cancer in 1987–95 were obtained from the Finnish Cancer Registry, a national institute that has collected and produced information on the occurrence of cancer in Finland since 1953. The SIR was defined as observed/expected number of gastric cancer cases, expected number being based on national sex-, age-, and calendar year-specific incidence rates.

Statistical methods

Statistical significance of the differences between proportions was calculated by the χ^2 test and by the Cochran–Armitage trend test (StatXact 4.01, Cytel Software Corporation, 1998), when appropriate. Significance of the association between *H. pylori* prevalence and SIR-values of gastric cancer was tested by the Poisson regression model (Egret for Windows 2.0, Cytel Software Corporation, 1999). The log-linear model (BMDP 7.0, Statistical Solutions, 1993) was used to test the significance of interactions between prevalence of helicobacter antibodies and time point (decades), adjusting for age and locality. All second-order interactions were included in the model.

RESULTS

H. pylori seroprevalence by time

The prevalence of *H. pylori* antibodies decreased with time in eight out of the nine communities studied (Fig. 1). In the six 'mobile clinic' communities studied over three successive decades, a statistically significant interaction between *H. pylori* seroprevalence and the year concerned was demonstrated ($P < 0{\cdot}0001$). The drop in overall prevalence between 1969–73 and 1995 was 26%-units, from 38 to 12% ($P < 0{\cdot}0001$, trend test) (Table 1), and the difference was especially marked (from 31 to 12%) between 1983 and 1995. This decreasing trend was confirmed when the results of all nine maternity clinics and communities studied were combined; during the 12-year period between 1983 and 1995, the total *H. pylori* seroprevalence in 20- to 34-year-old women declined from 30 to 13% ($P = 0{\cdot}0001$, χ^2 test) (Table 2). When all age groups (range 15–45 years) were included in the comparison, the decrease in *H. pylori* prevalence was 14%-units (from 29% in 1983 to 15% in 1995, $P = 0{\cdot}0001$, χ^2 test).

Geographical variation

Although the prevalence of *H. pylori* antibodies decreased with time in all but one locality, the

Table 1. *Prevalence rates of* H. pylori *antibodies in six Finnish communities in 1969–73, 1983, and 1995. Sera collected from 20- to 34-year-old women*

		H. pylori positive						
		1969–73		1983		1995		
Area	Locality	%	95% CI	%	95% CI	%	95% CI	Trend test *P* value
North	Kemijärvi	38·3	(26·1, 51·8)	37·5	(27·4, 48·5)	16·4	(8·2, 28·1)	0·0109
West	Uusikaupunki	50·0	(36·8, 63·2)	39·5	(30·9, 48·1)	9·9	(5·1, 17·0)	< 0·0001
West	Vammala	36·0	(25·2, 47·9)	29·5	(23·4, 35·7)	8·6	(5·0, 13·5)	< 0·0001
East	Joensuu	23·3	(13·4, 36·0)	23·0	(14·6, 33·2)	13·7	(7·5, 22·3)	0·1222
East	Tohmajärvi	38·3	(26·1, 51·8)	22·9	(13·7, 34·4)	16·2	(6·2, 32·0)	0·0143
South	Kuusankoski	41·7	(29·1, 55·1)	29·4	(20·0, 40·3)	13·6	(7·6, 19·6)	< 0·0001
All		37·9	(33·0, 42·8)	30·9	(27·4, 34·4)	11·9	(9·3, 14·4)	< 0·0001

Table 2. *Prevalence rates of* H. pylori *antibodies in various parts of Finland in 1983 and 1995; all nine communities studied included in comparison. Sera collected from 20- to 34-year-old women*

	1983		1995		1983–95 Change	
Area	HP* positive/all	(%)	HP positive/all	(%)	(%-units)	95% CI
North	43/125	34·4	22/102	21·6	−12·8	(−24·4, −1·3)
West	111/334	33·2	27/298	9·1	−24·2	(−30·2, −18·2)
East	40/183	21·9	20/143	14·0	−7·9	(−16·1, 3·9)
South	26/88	29·5	20/138	14·5	−15·1	(−26·2, −3·9)
All	220/730	30·1	89/681	13·1	−17·1	(−21·2, −12·9)

* HP, *H. pylori*.

magnitude of this drop varied from one locality, and one region, to another (Fig. 1, Table 2). Thus, in the eastern community of Joensuu, the change in the initially low prevalence was relatively small, less than 10%-units, in comparison to other 'mobile clinic' localities with higher initial prevalences (Table 1). When all nine localities studied in 1983 and 1995 were included in comparison, the lowest initial seroprevalence (22 *vs.* 33% for the rest of the Finland, $P = 0{\cdot}0048$ χ^2 test) and smallest decrease (8%-units *vs.* 24%-units in western communities) were demonstrated in eastern Finland (Table 2). The lowest prevalence rates in 1995 were detected in the western communities of Vammala and Uusikaupunki, the differences between the western and (high prevalence) northern communities (12·5%-units) being statistically significant ($P = 0{\cdot}0009$; χ^2 test) (Table 2). The observed changes in 'inter-regional' relationships persisted when all age groups (15- to 45-year-olds) were included in the comparison (data not shown).

In the six 'mobile clinic' communities studied, the SIR values of gastric cancer in women during 1987–95 varied between 0·7 and 1·5. The association between helicobacter antibodies in 1969–73 and subsequent SIR values (in 1987–95) was statistically significant ($P = 0{\cdot}0274$, Wald's test), the rate ratio of 1·0229 per%-unit change in *H. pylori* prevalence obtained by the Poisson regression model. This indicates that, between communities, a 10%-units higher prevalence of *H. pylori* antibodies was equal to a 23% (95% CI 3–44%) higher risk of gastric cancer.

DISCUSSION

Our findings demonstrate that the prevalence of *H. pylori* antibodies in 20- to 34-year-old Finnish females has dramatically decreased during the last 22–26 years. In the 'mobile clinic' communities studied, the overall prevalence of *H. pylori* in 1995 was only one-third of that observed in 1969–73. This decrease over successive decades seems to have accelerated during the last 12 years, being approximately 61% between 1983 and 1995 in comparison with 18% between 1969–73 and 1983. The magnitude of the drop varied,

however, form one area to another, being highest in western (73% between 1983 and 1995) and lowest in eastern (36% between 1983 and 1995) Finland.

The observed time trend is consistent with earlier reports from Finland [6] and other developed countries [5, 16, 17]. In the Finnish town of Vammala, the reported decrease in (total) age-adjusted *H. pylori* prevalence in 15- to 74-year-old adults was 44% between 1973 and 1994 (from 56 to 31%) [6]. In Dutch children [17] and 70-year-old Swedish persons [16], the corresponding figures were 52% (from 21 to 10%, between 1978 and 1993) and 33% (from 78 to 52%, between 1971–2 and 1992), respectively.

Economic development and improved hygiene are suggested explanations for the declining trend of *H. pylori* seroprevalence observed in developed countries. Since the critical period of obtaining infection is in childhood, the economic factors reflected in the observed prevalence rates would date years to decades earlier than the actual study years (1969–73, 1983, 1995) involved. In addition to low socioeconomic status [9, 18, 19], closely related risk factors associated with helicobacter infection include household crowding [19–22], large sibship size [23], sharing a bed in childhood [20, 22] and belonging to an ethnic group [18, 24]. On a community level these factors are, however, difficult to measure dependably, and such efforts were not included in this paper.

Even though the actual incidence of gastric cancer is higher in males than in females, the geographical variation is similar for both genders throughout Finland [12]. High-rate areas have traditionally been found in northern parts of Finland as well as in regions along the west coast and the southwestern archipelago [12]. Of these 'high-risk' areas, northern Finland has remained an area with a relatively high prevalence of *H. pylori* antibodies (22 *vs.* 12% for the rest of Finland in 1995; $P = 0{\cdot}0057$, χ^2 test), while the western communities (Vammala and Uusikaupunki) have experienced a dramatic decrease in *H. pylori* seroprevalence (from 42 to 9%, between 1969–73 and 1995). Thus, although a decline in helicobacter seroprevalence was evident throughout Finland, the rate of this change varied for different regions of the country. Reasons for these 'inter-regional' differences and their effects on future geographical variation of distal gastric carcinoma incidence are still unknown. In the six 'mobile clinic' communities studied, nevertheless, a statistically significant association between local *H. pylori* seroprevalence and subsequent (after a median latency of 20 years) gastric cancer incidence was demonstrated. To our knowledge this is the first attempt in an epidemiological study to overcome the problem of suspected latency period (from years to decades) between active helicobacter infection and development of gastric malignancy, the regional infection rates being previously compared with cancer rates in contemporaneous time periods. If the observation is confirmed in future studies, the suggested association of parallel decline of *H. pylori* infection and distal gastric cancer is strenghtened, thus indicating the importance of active measures to speed up the decline of helicobacter infections. Due to the fact that this is an ecological study, the association remains, however, indicative.

Being non-invasive, safe, relatively inexpensive and accurate, serology is the most widely adapted method for epidemiological studies on *H. pylori*. The test (Pyloriset) used in this study is highly sensitive [15], and has recently also been validated for children [14]. The composition of the study population varied from (1) random (female) samples in 1969–73 to (2) females from maternity clinics in 1983 and 1995. Virtually all women in Finland visit maternity clinics regularly during their pregnancies, and thus, the samples collected in maternity clinics may be considered fairly representative of females of reproductive age. Since the infection with helicobacter is regarded as independent of gender [9, 10], (in these age groups studied) the changes observed in the investigated populations are likely to reflect changes in the entire population. These assumptions are further supported by the similar prevalence rates observed in 20- to 34-year-old mothers (8·6% in 1995) and randomly selected female inhabitants in Vammala (9·1% in 1994) [6], as well as by the similar (crude) seroprevalence rates in randomly selected 15- to 44-year-old Vammala inhabitants (12·8% in 1994; both genders included) and mothers from the Vammala area (12·9% in 1995) [6]. Due to lacking background information, including place of birth and migration history, of subjects studied, the possible effect of migration on results obtained in different geographical areas could not be discounted.

In conclusion, the prevalence of *H. pylori* antibodies is rapidly decreasing in Finland. The overall decline in helicobacter seroprevalence demonstrated is in agreement with earlier reports from Finland and other developed countries, and supports the cohort theory as an explanation for increased seroprevalence with advancing age. The magnitude of the decrease varied, however, from one area (and one locality) to another

thus changing the pre-existing geographical variation, leaving northern Finland as the area with the highest prevalence rate. The local differences in *H. pylori* prevalence observed in 1969–73 seemed to predict subsequent gastric cancer incidences some 20 years later.

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