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SPECIAL TOPIC

*Invited review*

# Clinical and Epidemiological Data on Inflammatory Bowel Disease, Colorectal Cancer and *Helicobacter Pylori* infection in Turkey

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## SUMMARY

**Turkey is a bridge between east and west and a midway for many emigrations. Although there is no big ethnical groups in this country,there is a great variation in culture, living conditions, dietary habits, environment, access to medical care. These factors topped by different socioeconomical conditions and genetic background lead to different epidemiology of certain diseases throughout the country. Improving hygienic conditions and socioeconomical level made the seroprevalence of Helicobacter pylori infection to decrease from 78.5% to 66.4 over the past ten years. Similar to the western epidemiological data Hp tends to affect less the young age group as compared to adults. On the other hand increasing resistance to antimicrobials used to eradicate the bacterium will obviate the need for more powerful and effective regimens in the near future. Inflammatory bowel diseases are frequently encountered in Turkey Its incidence is less than North and West Europe but close to Middle East. (4.4/100.000 for UC and 2.2/100.000 for CD). The disease affects both sexes to the same degree. Distal Colitis in UC and ileocolitis in CD are more frequent than other localizations. Amebiasis occurs in about 1/3 of cases in UC and 10 % of cases with CD. This parasite is observed as a concomitant infestation with IBD or as a trigger for flare up in both conditions. Colorectal cancer is the second most common GI malignancy after gastric cancer in Turkey. The distribution of colorectal cancer shows variations from west to east.Whilst esophageal and gastric cancers are more prevalent in the east, colon cancer is relatively more common in western parts of Anatolia. Males and females seem to be affected to the same degree and the 5th and 6th decades are the more frequent ages of involvement. Although some studies reported a trend towards right sided involvement in colon cancer, rectum and sigmoid are still the sites of predilection for colon cancer. Many environmental and genetic factors play a role in the development of colon cancer but the existing small studies discussing the contribution of some etiological factors such as dietary habits, vitamin and mineral deficiencies, environment etc. have to be validated in larger,controlled trials. The common denominator of all three conditions is their strong link with some socioeconomical parameters, the threat of environmental factors, their changing incidence over the past decades and their malignant or potential malignant character which affects their prognosis. Whether it be infectious or non infectious the best would be to bring together all the existing information and to unite forces in such a direction that these disorders could be prevented or completely eradicated from the region.**


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## INTRODUCTION

Turkey is one of the most populated Mediterranean countries with its 65 millions of inhabitants and a relatively mixte type of population.

The implementation of more appropriate hygienic measures and organized campaigns against common infectious diseases have succefully deleted some nightmare diseases of the past from the scene and reduced the inci-

dence of some others. Frequent immigrations to metropoles and relstively bigger cities to seek a job or find new opportunities to live; natural disasters or change in employment hinder the achievement of reliable epidemiological studies and modify the profile and clinical outcome of diseases of unknown origin.

In this brief article an outline of the epidemiological pattern of Inflammatory Bowel Disease (IBD), colon cancer and helicobacter pylori (Hp) in Turkey will be presented.

## A. EPIDEMIOLOGY AND CLINICAL DATA INFLAMMATORY BOWEL DISEASE IN TURKEY

The incidence of IBD and the disease course is quite varible in the Mediterranean countries. There is ample data about its frequency in some countries but very few in some others. Ulcerative colitis (UC) seems to occur more frequently in Italy (6.8 per $10^5$ inhabitants), Jerusalem ($6.3/10^5$ inhabitants) and Greece (8.9 per $10^5$ inhabitants) as compared to Spain ($2/10^5$ inhabitants), Portugal ($1.6/10^5$ inhabitants) and Northern France ($3.2/10^5$ inhabitants), whilst the incidence of Crohn's disease (CD) is higher in France as compared to Italy, Greece and Spain.

The existing data about the incidence and clinical characteristics of both disorders in Turkey is still insufficient. The aim of the present study is explore the epidemiological and clinical characteristics of inflammatory bowel disease in Turkey, a Mediterranean country of strategic importance as being located between Europe and Middle East.

### *Patients and Methods*

The epidemiological and clinical features of UC and CD were examined retrospectively in 20 centers from 6 regions and 10 major cities of Turkey (Marmara, Middle Anatolia Aegean, East Anatolia, East-South Anatolia and Mediterranean) by reviewing the charts of patients with IBD who had applied to IBD Referral centers and their affiliated centers between the years 1995-1997.

Population data were extracted from from the 1995 census,from the bulletin of Government Institute of Statistics and reports of Municipalities. Recent immigrants to the region (residents for less than a year) were excluded from the study.

The following parameters were carefully searched in the charts and patients were contacted by phone calls when sufficient information was lacking: Age, sex, place of birth, habitation place (rural vs urban) occupation, education (elementary school vs higher education), smoking and alcohol consumption, dietary habits, use of oral contraceptives or NSAID, family history of IBD, age of IBD, extension (proctitis, left sided colitis, extensive or pancolitis) and the presence of concomitant amebic infestation. Student t test and $\chi^2$ test was used for comparison of various groups.

### *Results*

There were a total of 1107 patients from 20 centers distributed over 6 regions of Turkey. 854 of the patients had the diagnosis of UC and 234 CD and 19 had undeterminate colitis as confirmed by colonoscopy or surgery and biopsy.

402 (47%) of the UC patients were female and 452 (53%) were male ($p< 0.004$). The mean age was 42.1. The incidence of ulcerative (UC) colitis was found to be 4.4 per $10^5$ population Positive family history was obtained from 13 (2%) of the UC patients. Eighty five % of the patients were settled in urban areas whereas 15% were living in rural areas ( $p< 0.0001$). 78 % of the patients were graduated from elementary school, 22% of them were graduated from University ($p<0.0001$). Smoking history was positive in 211 (25%) and use of moderate amounts of alcohol was positive in 44 (4%). 22 (3%) of the patients were taking NSAID and 13 patients (2%) were taking oral contraceptive pills. The localizations in UC were as follows; 340 (40%) had distal, 275 ( 33%) left sided, 43 (5%) extensive and 185 patients (22%) had pancolitis. 189 (22%) of the patients suffered from concomitant E. Histolytica infection.

In CD patients group (n= 234 ), 124 patients (52%) were female, 97 (48%) were male ($p> 0.05$) and the mean age was 35.3. The incidence of Crohn's disease was found to be 2.2 per $10^5$ population Family history for IBD was positive in 7 (3%) of the patients. Two hundred and three (89%) of the patients were living in urban areas and 26 (11%) were living in rural areas. ($p< 0.001$). 75 % of the CD patients were graduated from elementary school and 25% were graduated from University ($p<0.001$). İleocolitis was diagnosed in 113 (51%), ileitis in 56 (25%), colitis in 47 (21%) and other localizations in 21 (3%) of the CD patients. 83 (32%) of the patients were smoker and 10 (4%) were taking alcohol. Four (2%) of the CD patients had a history of NSAID use and 4 (2%) had a history of oral contraceptive pill use. 24 out of 234 patients (10%9) were found to harbour E. Histolytica infection.

### *Discussion*

This preliminary study showed us that the incidence of UC is 4.4/100 000 and that of CD is 2.2/100 000 in Turkey. The survey was carried out in 21 centers in 6 regions and of Turkey comprising the majority of referral centers including the University and State hospitals.

There are practically very few ethnic groups in our country the majority living in metropoles. Most of the population which is around 65 000 000 according to the last census in 2000 is located in 3 big cities Istanbul, Ankara and Izmir.

Epidemiological studies for such diseases as inflammatory bowel diseases showing great variabilities according to environmental, genetic factors and socioeconomical state are very difficult to achieve. Immigration, sanitary conditions, facilities in reaching medical care, educational and socioeconomic state may all affect the incidence and prevalence of the disease. Moreover the lack of a nationwide reliable registration system and databank in our country further obcures the accuracy of the epidemiological studies carried in this subject.

The tendency to rise in the incidence and prevalence of both disorders – notably of Crohn's disease- in Turkey comes probably also from the improvements in diagnostic facilities and medical awareness of the condition.

Major drawbacks of this small study can be summarized as follows:

- IBD is frequently encountered in Turkey. Its incidence is less than North and West Europe but close to Middle East.
- Positive family history can be obtained to the same degree in both groups
- Distal Colitis in UC and ileocolitis in CD are more frequent than other localizations
- Smoking is more frequently encountered in CD as compared to UC. Smoking is said to protect against UC and worsen CD
- Stress,diet and use of drugs which were reported to affect IBD course, had minimal impact on the outcome of the disease
- A considerable number of patients (22% in UC and 10.9 in CD %) had concomitant amebiasis. Since most of the studies were based on stool examination by microscopy, more sensitive tests such as ELISA and/or pcr are necessary to get firm conclusions
- Urbanization in conjunction with a modification in dietary habits is an important contributing factor to the occurrence and course of both disorders.

Updates on the incidence and prevalence of both UC and CD are awaited.

## B. EPIDEMIOLOGY AND CLINICAL DATA ON HELICOBACTER PYLORI IN TURKEY

Helicobacter Pylori is a very common pathogen affecting more than ¾ of the healthy population in Turkey. Since its re-discovery by Warren and Marshall in 1983 this spiral bacteria of worldwide reputation, recognized as the cause of chronic active gastritis, peptic ulcer, Malt lymphoma and gastric adenocarcinoma has gendered an explosion of research and publication in our country and elsewhere.

Initial studies carried out on the epidemiology of Hp have revealed a 85% of seropositivity among adult healthy volunteers by serology. Studies conducted so far have shown a high seropositivity rate among young childen and adults in Turkey. Table 1, 2 and 3 show Hp seropositivity in various groups

**Table 1.** Hp seroprevalence in Turkey in various age groups

| Age | (n) | Hp+ AntiIgG (+) |
|---|---|---|
| 0-2 | 68 | 14,7 |
| 3-6 | 64 | 20,3 |
| 7-11 | 99 | 72,7 |
| 12-17 | 81 | 64,4 |
| 16-24 | 69 | 76,8 |
| 25-55 | 19 | 84,2 |

Özden A, et al. Here is the Hp There is the Ulcer, 2000

Helicobacter Pylori is spread by oro-oral or oro-fecal route and common living in close communities facilitate the transmission of the infection. İntrafamilial spread is common and schoolchildren are mostly affected.

Iatrogenic transmission via endoscopes, tubes or infected specimens is also possible. Person to person transmission seems to be the most probable way provided that the bacterium has ben isolated from dental plaques, oral specimens, mouth ulcers, oral cavity or saliva. Though it seems unlikely that food contains Hp, low temperature in aliments may allow longer survival. A survey done in endoscopy unit among nurses and hospital staff in Tur-

key did not show a statistically significant difference in Hp seropositivity between nurses, hospital staff and age and sex matched controls (Endoscopy staff, 86.4%, ICU nurses 72.2%, Administrative staff 63.7% healthy volunteers 63.7% and p>0.05).

The availability of Urea Breath test (UBT) has rendered the epidemiological studies not only more accurate but also easily applicable especially in Children. A recent survey with UBT in various groups all over Turkey has evidenced a wide variation in the occurence of Hp positivity.

**Table 2.** Hp positivity by UBT in the year 2000

| City | Hp(+)% | City | Hp(+)% |
|---|---|---|---|
| Amasya | 62,4 | Ankara | 75,9 |
| Antalya | 81,3 | Izmit | 75,6 |
| Mersin | 75,5 | Erzurum | 66,7 |
| Samsun | 71,3 | Eskişehir | 67,8 |
| Istanbul | 69,6 | Bolu | 68,6 |
| Tekirdag | 65 | Manisa | 65,6 |
| Gaziantep | 75 | Izmir | 63,5 |
| Adana | 80,3 | Bursa | 70,7 |
| Diyarbakir | 73,1 | Edirne | 71,1 |
| Aydin | 60 | Total | 70,3 |

Ozden A, et al, Turkish J Gastroenterol 2000 (abstract)

Some big cities such as Antalya, Adana and Ankara had higher prevalence than others. This fact can be explained the presence of a more cosmopolitan population living in metropoles and the high immigration rate among inhabitants

Another study carried out in 347 schoolchildren and kindergarten kids by Urea Breath Test reported a frequency of 49.5% with a steadily increasing incidence of Hp with age. Values for children < 4 years, 4-6.5 years, 7-10 years, 11-12 years were 18.2%, 41%, 48-63% and 71.4% respectively. The variables affecting Hp positivity were found as low socioeconomic level, small domicile multiple children,absence of breast feeding and heating with a stove.

Recent studies however have put in evidence a fall in the prevalence of Hp especially in young age groups (notably at the age of seven and ten years). This fact is more a pattern of western type of infection, the seropositivity rising at older ages (Table 3).

According to these studies, the reason for the decrease in Hp seroprevalence was stated as improvement of hygienic conditions,awareness of the problem by the families, less childbirth better living conditions,the availability of running water at home, better nutrition,longer interval between childbirths, increase use of antimicrobials etc.

**Table 3.** Decline in Hp seroprevalence over ten years time

| Age | 1990 | 2000 | p |
|---|---|---|---|
| 7 | 76,5 | 50 | <0,05 |
| 8 | 70 | 85 | >0,05 |
| 9 | 73 | 60,9 | >0,05 |
| 10 | 89 | 63 | <0,01 |
| 11 | 84 | 67,4 | >0,05 |
| 12 | 100 | 80 | >0,05 |
| 13 | 100 | 58,8 | >0,05 |
| 14 | 75,7 | 57,1 | >0,05 |

Ozden A, et al. Turkish J Gastroenterol, 2000

The use of more sensitive assays in detecting Hp prevalence may be another explanation for this shift towards lower frequency.

The epidemiological pattern of Hp has distinctly shown us long time ago that Hp prevalence was lower in infants and children in developed countries in contrast to the profile in developing countries. Hp is most prevalent in adults in developed countries.

The changing epidemiological pattern observed in Turkey over the last 10 years is a marker of improvement in sanitary conditions and the evolution in healthcare system.

## C. EPIDEMIOLOGY AND CLINICAL DATA ON COLON CANCER IN TURKEY

Colon cancer is second most common GI malignancy after gastric cancer in Turkey. Although it is well known that genetic factors have an important impact on the development of colon cancer, change in dietary habits,urbanization and social life may have an influence on the development of this widespread malignancy.

According to the Statistics of the Governement of Health the incidence of colorectal carcinoma in Turkey is $5.9/10^5$ in 1995. The number of patients admitted for treatment in oncology clinics are represented on Table 4. The frequency of colorectal cancer among all types of cancer in Turkey was reported as 6.7 in females and 5.2 in males. The distribution of the colorectal cancer cases

**Table 4.** Frequency of colon cancer according to age and year,

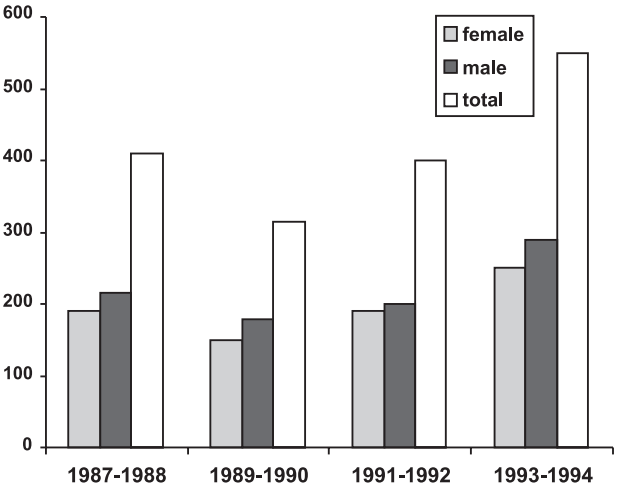
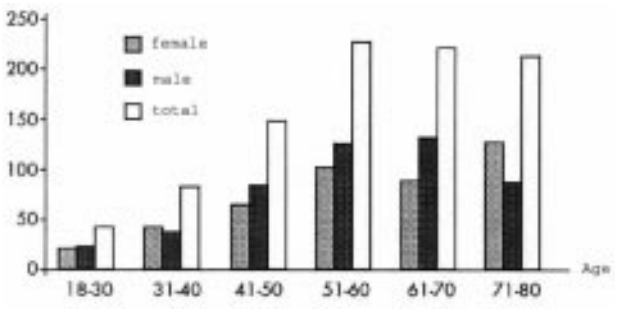



**Table 5.** Distribution of colorectal cancer according to age and sex




according to years and sex is shown in Table 4 and 5.

According to a survey carried out in Turkey 1n 15 different hospitals (University and State) by reviewing the data for the years 1999 and 2000, 1476 cases with GI cancer were detected. The frequency of colon cancer was 27.8%.This percentage was significantly lower than gastric cancer (51.8 % of all cases) but higher than esophageal cancer (19.2%) in this region of the mediterranean basin. The frequency rates for these cancers in Eastern European Countries are shown in Table 6.

Another survey carried out in southeastern Anatolia comprising 2798 cases of malignant GI tumours revealed that at least 1/3 (33.3%)of these malignancies were indeed colorectal cancer.

Finally a recent analysis reported recently in an International meeting in Istanbul based on GI cancer records of 5 medical centers over the last 10 years is represented on Table 7.

Memik et al, according to their long term follow up of patients from the East Anatolian part of Turkey observed that esophageal cancer occurred more frequently than gastric and colorectal cancer in this region of Turkey and they linked this high incidence of upper GI cancers to dietary habits, malnutrition, widespread use of a smoked bread called "tandır", vitamin and rare elements deficiencies and unknown factors related to this region.

In conclusion, the present epidemiological data shows an approximately equal prevalence of gastric and colon cancer in Turkey The trend is towards upper GI cancers in the eastern parts of Anatolia, whilst colorectal cancer

**Table 7.** Distribution of GI cancers in East and West of Turkey (10 years data)

| Region | Location | | |
|---|---|---|---|
| | Esophagus | Gastric | Colorectal |
| Bursa (Marmara) | 15.0% | 43.3% | 41.5% |
| İzmir (Aegean) | 9.4% | 41.8% | 48.7% |
| Balıkesir (Marmara) | 15.9% | 56.5% | 27.4% |
| Erzurum (East) | 37.2% | 49.4% | 28.5% |
| Van (East) | 23.6% | 72.7% | 3.5% |

**Table 6.** The frequency of GI cancers in Eastern Mediterranean Countries (*Courtesy of Yurdaydin et al*)

| | Albenia | Bosnia Herzegovina | Bulgaria | Greece | Fyrom | Serbia | Turkey |
|---|---|---|---|---|---|---|---|
| EC | 5.8 | 4.8 | 6.1 | 3.7 | 1 | 4.8 | 19.2* |
| GC | 79.7 | 48.6 | 30.3** | 29** | 26.1** | 48.6 | 51.8 |
| CRC | 14.5# | 43.3 | 62.8 | 60.3 | 71.2 | 43.3 | 27.8# |
| SIC | 0 | 3.2 | 1.7 | 5.3 | 1.7 | 3.2 | 1.2 |

EC. Esophageal cancer, GC. Gastric Cancer; CRC, Colorectal Cancer; SIC, Small Intestinal Cancer

** p< 0.05 vs all other countries, ** p< 0.05 vs A, BH, S and TR, # p<0.05 vs BH, B, GR , M and S*

is more prevalent in the west. Males and females seem to be affected to the same degree and the 5th and 6th decades are the more frequent ages of involvement.

Although some studies suggest that dietary habits, processing of some foodstuff, environment (?), genetic factors, vitamin and mineral deficiencies may play a role in the distribution of gastrointestinal cancers and notably colorectal cancers in Turkey these statements need to be validated in larger and well designed studies.

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