

SPECIAL TOPIC

Invited review

Clinical and epidemiological data on colorectal cancer, inflammatory bowel disease and *Helicobacter Pylori* in Greece

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COLORECTAL CANCER

Colorectal cancer is one of the most common cancers and a leading cause of death from cancer. It is particularly common in the Western world and accounts for hundreds of thousands of deaths each year. The vast majority of colorectal cancer cases is sporadic and arises from pre-existing colorectal adenomas. Unfortunately, prospective epidemiological on the annual incidence and prevalence as well as on morbidity and mortality rates from colorectal cancer in Greece are not available.

However, indirect evidence can be derived from mortality rates for the Greek population.¹ It appears that life expectancy between 1980 and 1997 for Greek men increased from 72.2 to 75.3 years and for Greek women from 76.6 to 80.6 years. Between 1990 and 1998 a decrease in total mortality rates for both sexes by 17.5% was noted. However, the ratio of deaths in people living in urban and rural areas has not changed. The leading causes of death in the Greek population during this period were heart and circulatory diseases, malignancies and accidents. Regarding malignant neoplasms a progressive increase was seen between 1990 (159 deaths/100.000/year) and 1993 (163/100.000/y) and a more or less steady rate thereafter. Thus, contrary to what is recorded in Western countries, there is a rising incidence of deaths from malignancies in Greece. The annual death toll from gastrointestinal diseases has risen from 17.9/100.000 population in 1990 to 21.2/100.000 in 1992 and

but declined to 17.7/100.000 population in 1996. Overall, deaths from GI diseases were accounted for by 2% for deaths from all causes in 1997. Unfortunately the National Statistics Agency has not released a detailed chart with the specific causes of death from gastrointestinal diseases. However, malignant neoplasms of the gastrointestinal tract were the main cause of death from all malignancies. In 1996, 29% of deaths from malignant causes were due to gastrointestinal malignancies, which were responsible for 46-48 deaths/100.000/year between 1990 and 1996. Given the low incidence of gastric cancer in Greece we can reasonably assume that colorectal cancer is the leading cause of death from GI malignancies. When these figures are broken for decades of life, it appears that for the age group 15 to 69 years mortality rates from lung cancer are slightly higher than from GI malignancies. However, GI malignancies are responsible for the majority of deaths from cancer in people over 70 years. The highest mortality rates from gastrointestinal malignancies were recorded in Macedonia.

More hard core data regarding deaths from colorectal cancer comes from a post mortem study of Paspatis et al in Crete.² This study included post mortem findings from 320 males and 182 females mean age at death 65 years (range 16-93). Colorectal adenomas were found in 73 (14.5%) but only 17 adenomas were advanced, i.e. larger than 1 cm. The prevalence of adenomas increased with age. Adenomas were distributed in the recto-sigmoid area in 43 (38%), the descending colon in 25 (22%), the transverse colon in 21 (8.5%) and the right colon in 24 (21.2%). The prevalence of adenomas in the Crete study was one of the lowest in post mortem studies performed in the Western world, compared with a 21.7% in Spain, 33.3 to 37.1 in Norway, 33% in UK, etc. This is

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not a surprise because Crete is an area with a low prevalence of colorectal as well as gastric cancer. It is probably associated with the effect of environmental and/or genetic factors operating on the Cretan population collectively for many decades. Therefore, this excellent and laborious study is only in part informative for the general population in Greece.

Other data come from our Clinic at Evangelismos Hospital in Athens.^{3,4} In accordance to surveillance programs for prevention of colorectal cancer we have been encouraging 1st degree relatives (FDR) of patients with colorectal adenomas or cancer to undergo screening colonoscopies. Although the recruitment rate is still low (approximately 20%) we have estimated the relative risk for harboring a colorectal adenoma to be 3.6 in a FDR of a patient with an advanced colorectal adenoma (diameter >1cm) and 3.0 in a FDR of a patient with colorectal cancer. More specifically, 110 FDR of patients aged 55 years (range 32-82) underwent colonoscopy and 32 of these (29%) were found to harbor a colorectal adenoma ($P < 0.0001$ over controls without family history). Furthermore, 125 FDR of patients with colorectal cancer aged 54 years (range 35-75) were endoscoped to the caecum, and 39 (31%) of these carried a colorectal adenoma ($P < 0.0001$ over controls). This has expended our previous observations on a smaller proportion of FDR. The location of the adenomas was not different from that in the autopsy study of Paspatis et al² and corresponds to the left-sided distribution of the colorectal cancer in Greece.

Colorectal cancer may arise on the background of chronic ulcerative colitis or Crohn's colitis. It has been shown that the risk for developing cancer in patients with Crohn's colitis is almost identical to that reported for patients with UC of similar disease extent. In our own experience, none of the patients attending the IBD clinic in the last 12 years has developed colorectal cancer.⁵ On the contrary, we have diagnosed 10 cases of colorectal cancer, 8 in patients with chronic UC and two in patients with Crohn's colitis. The distribution of these cancers was not different from that of the sporadic cancer, that is most of them developed in the left side of the colon. None of the cancer patients attended any IBD clinic regularly or received continuously the appropriate treatment. This simply means that the development of colorectal cancer in IBD is directly related not only to time with or extent of disease but in addition to lack of appropriate treatment which by maintaining remission of disease will down-regulate inflammatory events leading onto dysplasia and cancer. In the long-term study of Trianta-

fillidis et al,⁶ six patients with colorectal cancer were diagnosed in a population of 413 patients followed for 16 years. No information is given on how strictly those patients were receiving their treatment and what course their disease was following until cancer was diagnosed.

INFLAMMATORY BOWEL DISEASES

On the evidence of existing publications before the decade of the '90ies it had been anticipated that Inflammatory Bowel Diseases (IBD) and especially Crohn's disease (CD) is much less common in Greece and other Southern European countries (or areas) than in the European North. However, at least for Greece this impression was based on scattered, inappropriately designed and, therefore, inconclusive epidemiological studies. The lack of firm data was due to the underdevelopment of the country as a whole and the Health system in particular. Furthermore, Gastroenterology was not an established medical subspecialty and was practiced by a few brilliant people in a few hospitals in Athens and Thessaloniki. Thus, the source of epidemiological data on the IBD was usually the notes of the patients who had been admitted for medical or surgical treatment in these hospitals.

In the beginning of the '90ies two Academic Centers, one in Heraklion, Crete (Prof. Manousos) and the other in Ioannina, Epirous (Prof Tsianos), participated in a prospective collaborative IBD epidemiological study conducted by Dr Shivananda in Maastricht under EC supervision and funding. Many other centers in Northern and Southern Europe were also participated. This study aimed at evaluating the prevalence and incidence of IBD in certain European areas, unraveling any changes in the epidemiology of UC and CD, testing the hypothesis for the existence of a North-to-South gradient, etc. The areas in which these studies were conducted were not selected randomly. On the contrary, they were well defined and fulfilled the necessary prerequisites for the ideal epidemiological study. Epirus is a rural area amongst the poorest in Europe where the living conditions and the traditional life style had been preserved for centuries. It is only during the last 50 years that dramatic changes in the distribution of the population have taken place with people leaving small mountain villages and settling in cities. On the other hand, Crete as an island has preserved until recently the traditional values of life, amongst those the famous Mediterranean diet. However, in the last 50 years thanks to tourism the island had an influx of population from the continental Greece as well as European countries. As a result the life style of the average

people has been insidiously but constantly changing. The two epidemiological studies targeted these changes for a period of 5 years and reported interesting results.

In Heraklion, Crete, the epidemiologically defined area covered 2641 Km² with a population of 263.670. Two regional hospitals, 5 health centers and 109 family practitioners participated in this prospective, population-based study. The mean annual incidence of Crohn's disease for the years 1990-94 was 3.0/100.000 inhabitants.⁷ However, a steady rise in the incidence was noted from 1.9/100.000 in the year 1990 to 3.8/100.000 in the year 1994. The higher incidence was found for people with age range 25-34 years, smokers, inhabitants of urban areas, of higher education level and males (the male to female ratio was 2:1). Thus, not only CD was common in Heraklion, but its incidence was at the rise during the observation period and approaching slowly but steadily that of Northern European countries. For UC, 117 patients (75 males, 42 females) were diagnosed between 1990 and 1994. The mean annual incidence for UC was 8.9/100.000 inhabitants and the male to female ratio was 1.8:1.⁸ Half of these patients were ex-smokers and a third of these had never smoked. Approximately 10% of the patients had a positive family history for IBD. Thus, in striking contrast to CD the annual incidence of UC in Heraklion was rather constant and as high as in Northern European countries. There was no evidence that the course of IBD was strikingly different in the registered population than in other European countries.

Furthermore, in a retrospective study performed in a semi-rural area in North West Greece extended between 1981 and 1991, Tsianos et al have registered 61 patients with UC (estimated annual incidence of 4.0 cases/100.0000 inhabitants) but only five patients with CD.⁹ Although the incidence of UC was rising it was still amongst the lowest reported in a western European country. However, the particular characteristics (namely male to female ratio, urban residency, extent and course of disease, etc) were typical for a Western pattern of UC. Expansion of this data for the decade 1991 and 2001 is in preparation (Prof Tsianos, personal communication).

Excluding these two properly designed and executed trials no proper epidemiological study has been conducted in Greece. Despite the vast expansion of NHS and especially GI services and the financial thrive of our Society after the 1st EUGW event in Athens, in 1992, our Gastroenterology Society has been unable to plan and fund an appropriate National IBD epidemiological study. However, in mid '90ies the Hellenic Society of Gastroenterology funded a grant aiming at registering all new

cases of IBD for two consecutive years. This was a primitive research study based only on the completion of a questionnaire that was sent to all gastroenterologists and other members of the society. Provisions had been taken to avoid repetitive registration. However, with few exceptions the vast majority of the society's members did not respond and, therefore, this effort failed to achieve its goals.

An interesting study was reported two years ago from a single GI practice in Sparta, the capital of the prefecture of Laconia, with a population of approximately 100.000. Laconia is a predominant rural area and only in recent years the population has become urban. Dr Tamvacologos has been continuously registering all new and old IBD cases attending his practice for the last 9 years.¹⁰ A total of 190 cases of IBD, 165 UC, 15 CD and 10 indeterminate colitis were registered between 1990 and 1999. The estimated prevalence for UC was 12.88 new cases and for CD 1.33 per 100.000 population. There was a male predominance in the UC population (93 men versus 72 women) but with similar age distribution except for the 3rd to 4th decade of life when the male to female ratio was 2. The lesions affected the entire colon in 32% of the UC patients whereas left-sided colitis was seen in 26%, proctosigmoiditis in 22% and proctitis in 20%. Seven patients with CD had ileitis, 7 had colitis and one ileocolitis. The course of UC was relatively mild with only 5 patients developing steroid dependent disease necessitating treatment with azathioprine and another 5 patients undergoing colectomy with the formation of an ileoanal pouch. This data are extremely interesting because the incidence and the prevalence of UC approach that of Northern European countries. On the contrary, CD is still rare even if cases of CD may be still undiagnosed and therefore not yet registered. It also bears similarities to the data reported from the European collaborative study from Ioannina. More or less similar results regarding the epidemiology and clinical course of IBD were reported from another GI practice in the area of Tricala (Dr Tziortziotis). These single man-powered but remarkable trials despite inherent problems and drawbacks reveal that at least for UC Greece has probably reached the epidemiological plateau of other European countries. Furthermore, it emphasizes that the clinical course of this disease is mild and relatively "benign" in the community. However, data are scarce for CD.

Recently, Triantafillidis et al expanding previous observations reported cumulative hospital data for 413 patients with UC over a 16-year period.⁶ The disease was equally distributed between sexes with a higher incidence

in the 5th decade of life and a 2.7% family clustering of IBD cases. Patients were mostly residents of urban areas, well educated. The majority of the cases had left-side distribution of the lesions and colitis run with mild-to-moderate flares. However, the course of disease was relatively mild and surgery was performed in approximately 17% of the patients for aggressive and extensive disease especially associated with onset at a young age. Emergency operations in UC patients were significantly outnumbered by those performed on CD patients. The disease related mortality was relatively low and 3% of the patients developed colon or extraintestinal cancer. Furthermore, the same group has reported elderly patients with CD and UC may share similarities with elderly patients in other Western countries.^{11,12} However, they may also have striking differences in the mode of presentation and the clinical course of CD compared with younger patients, such as a delayed diagnosis, extraintestinal manifestations, anal and perianal disease, etc.

Based on our hospital data, the ratio of registered new cases of UC to CD is dramatically changing and excluding referrals it approaches 1. Although this does not mirror the true life in the community since CD is more likely to be diagnosed in a hospital rather than in a private GI practice it points out the increasing incidence of CD in the society. In a cohort of 113 patients with newly diagnosed CD in our department (1990-1995) disease characteristics [mode and age of presentation, location, course (inflammatory, stenotic or fistulizing), response to treatment and rate of surgical intervention] were similar to those reported by other Western European centers (GJ Mantzaris, in preparation).

The aforementioned changing clinical course of CD is increasingly recognized. Most of the patients with this disease are now being affiliated to a referral hospital and attend specialized IBD clinics although they still have their family gastroenterologist.

Sphincter saving operations are now being performed in various centers in Greece on paediatric and adult patients. More than 300 subtotal colectomies and ileoanal anastomosis with the formation of J type pouch have been performed in our hospital and results are excellent according to international standards regarding pouch function, quality of life, and immediate or delayed complications, including pouchitis and pouch failure (S Baratsis, in preparation). Triantafillidis et al published interesting separate data for operated patients with Crohn's disease and ulcerative colitis.^{13,14}

In conclusion, although the incidence of UC seems

to be steady that of CD is rising in Greece. The clinical course of UC in the community still seems to be relatively mild with an acceptable morbidity and mortality and excellent long-term results for the majority of the colectomized patients. However, the clinical course of CD is increasingly becoming more aggressive. Most of these patients soon become steroid-dependent and are usually in need of immunosuppressants.

HELICOBACTER PYLORI

Although there are no hard data on the epidemiology of *H. pylori* infection at a national scale it is widespread feeling that the epidemiology of *H. pylori* infection is undergoing dramatic changes in Greece. Based on serological studies that were performed in healthy adults and children in the beginning of the '90ies and were repeated at the end of that decade it appears that the prevalence of *H. pylori* infection is decreasing.¹⁵⁻¹⁸ The most likely explanation is not different from what is reported for developing and developed countries. The economic development of this country has gradually and steadily resulted in a dramatic improvement of certain socioeconomic parameters and most importantly the living conditions. This, along with improvement of the level of education in the general population, information programs on the hygienic handling and widespread use of domestic appliances used for preparation and preservation of food and water, etc had an enormous impact on the epidemiology of *H. pylori* infection. Intrafamily transmission has been successfully shown in spouses of infected Greek individuals whereas almost all ascending 1st degree relatives of infected children are heavily colonized by *H. pylori*.^{19,20} Improvement of these parameters has been shown to prevent massive person-to-person and possibly environment-to-person transmission of the infection. As a result, significantly less Greek children and adolescents are now being infected during this crucial period of life. The pace of the socioeconomic and environmental changes is faster for urban than rural areas and this is actually mirrored by the increased incidence and prevalence of the infection as well as the slower rate at which the prevalence of the infection is declining in the rural population.

Because *H. pylori* infection follows the pattern of a cohort phenomenon dramatic changes are expected in the epidemiology of *H. pylori* associated diseases. In fact, all practicing gastroenterologists in urban areas and especially in referral centers face the declining of non-NSAID related duodenal ulcer disease and a steadily rising incidence of *H. pylori* negative/non-hiatal hernia as-

sociated reflux oesophagitis. Furthermore, it seems that the incidence of the *H. pylori* positive functional dyspepsia is declining. The prevalence of *H. pylori* infection is much higher in patients with functional dyspepsia aged over 50 than in the younger age group.

It is, however, very interesting that despite the decline in *H. pylori* infection acquisition the prevalence of *cagA*+ and *vacA*+ *H. pylori* strains isolated in the Greek population is still quite high¹⁹ and may predict underlying peptic ulcer disease.²¹ This interesting observation in a country with a low incidence of gastric cancer raises several challenging hypotheses, such as that the Mediterranean diet enriched with fresh fruits is protective against the development of atrophic gastritis despite the presence of *H. pylori*. This is further supported by the findings in the Eurogast study where the population of Crete had a very low prevalence of non-cardia gastric cancer in view of a high prevalence of *H. pylori* infection.²² Observations based on serological studies failed to link non-cardia gastric cancer and *H. pylori* infection.²³ However, this may not be quite true and could be due to a low sensitivity of the assays and a decreased serum titer of *H. pylori* antibodies in patients with gastric atrophy and, therefore, a scarce *H. pylori* population in the stomach. Subsequent studies have also given a wide range of conflicting results which may be influenced by selection bias, nonspecific site detection, inappropriate detection techniques, etc. Therefore, the rate of *H. pylori* detection in Greek patients with non-cardia gastric cancer is probably dependent on the methodology used in the studies. However, the higher rate of *H. pylori* infection is detected in intestinal type non-cardia gastric cancers.

Excluding gastric cancer, the pattern of *H. pylori* infection and the course of its associated diseases are not different in the Greek population compared with western European countries. Thus, the prevalence of *H. pylori* infection in peptic ulcer disease, functional gastritis, autoimmune gastritis, pernicious anaemia, coeliac disease, cystic fundic gland syndrome, Menetrier's disease, primary and secondary immune deficiency syndromes, cirrhosis, rheumatic diseases, are among the expected prevalence range.²⁴⁻³⁰ In addition, *cagA*+ *H. pylori* strains are most likely to be protective against the development of reflux oesophagitis and induce gastric atrophy and/or low grade MALT-B cell lymphomas. However, Greek patients with newly diagnosed Crohn's disease or ulcerative colitis had a significantly higher rate of *H. pylori* infection compared with their western Europeans counterparts which was of similar to age, gender and socioeconomic class matched historical controls.³¹

Disease associations with *H. pylori* infection are also pretty similar in the native Greek population to those reported in Western European countries. This applies to the prevalence of *H. pylori* infection in patients with diabetes mellitus, chronic renal failure, colon polyps, duodenogastric reflux, coronary artery disease, acne rosacea, children with recurrent abdominal pain, etc.^{32,33}

Regarding therapeutic issues Greece is amongst the European countries with the highest in vitro resistant strains to metronidazole.^{34,35} There have been very few reports for amoxicillin-resistance of *H. pylori* but resistance to clarithromycin is steadily rising (36, Mentis A, personal communication). Widespread abuse, misuse and inappropriate use of antibiotics is responsible for increasingly recognized resistant strains to *H. pylori* infection. It appears that the combination of a proton pump inhibitor with clarithromycin 500mg and amoxicillin 1g twice a day is the treatment of choice for the Greek population given the high resistance rates of *H. pylori* to metronidazole. The duration of treatment has not been extensively studied but there is inconclusive evidence that 10-day regimens may be superior to 7-day regimens.^{36,37} The immediate and long-term outcome of treatment may be influenced by various factors in the Greek population.^{38,39} Proton pump inhibitor-based quadruple therapies should be used as salvation therapies in patients who have failed to eradicate *H. pylori* infection on a triple therapy.⁴⁰⁻⁴² This regimen should be given for at least 10 and preferably 14-days. For infected children the therapeutic regimens in use are essentially similar to those for adults.

In conclusion, there is indirect evidence that *H. pylori* infection is a birth cohort phenomenon and, therefore, its incidence and prevalence are declining in Greece primarily as a result of the improved living and hygienic conditions in the last few decades.^{15-19,43} The prevalence of more virulent *H. pylori* strains is still high in the Greek population but this is not associated with an increased rate of gastric cancer. Why this happens is purely speculative. However, the interplay of environmental factors, such as the traditional rich in antioxidants diet, with genetic factors may arrest the cascade of events leading from inflammatory gastritis to gastric atrophy, intestinal metaplasia, dysplasia and cancer at a crucial evolutionary point before the development of gastric cancer. Greek gastroenterologists are increasingly facing the challenges of the post *H. pylori* era, i.e. a rising incidence of *H. pylori* negative or post eradication reflux oesophagitis, *H. pylori* negative functional dyspepsia and NSAID-associated gastropathy and peptic ulcer disease.

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