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SPECIAL TOPIC

Invited review

Clinical and epidemiological data on IBD. Colorectal cancer and Helicobacter Pylori infection in Portugal

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INTRODUCTION

Epidemiological studies aim, besides determination of incidence and prevalence, to find associations between specific environmental or genetic features and the development of a disease.[1]

We are going to deal with three different subjects, each one raising serious problems.

IBD is a disease whose incidence and prevalence is raising in Portugal and is interesting to point out, that even in such a small country, differences of incidence have been found between northern and southern regions.

Colon cancer is a serious problem and again is increasing in Portugal.[2]

It is the 2nd cause of death by neoplasia, being only surpassed by lung cancer.

Helicobacter pylori became nowadays a problem of public health.

The conference on H. pylori in USA in 1994 raised several very important points:

- The relation *H. pylori* – ulcer; the relation between *H pylori* and non ulcer dispepsia and the relation *H pylori* gastric cancer[3] will be dealt sequentially and available Portuguese data will be shown.

Key Words: Inflammatory bowel disease, ulcerative colitis, Crohn´s disease, colorectal cancer, HNPCC, FAP, screening, adenocarcinoma, Helicobacter pylori prevalence, duodenal ulcer, gastric ulcer, gastric cancer.

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I. Inflammatory bowel disease (IBD)

Several IBD related studies have been performed in Portugal so far.

An upward trend in incidence was observed in a retrospective hospital study performed in the North of Portugal. The same trend was observed in an epidemiological study carried out in northern Portugal from 1975 to 1988.[5]

However only between 1991-93 a prospective population – based study was designed among twenty European centres aimed at obtaining reliable epidemological IBD data.

This multicentre study was included in the European Collaborative Study on Inflammatory Bowel Disease - a concerted action project of the Commission of the European Communities.

Results and Comments

In Portugal two areas were selected one in the North – district of Braga[6] with 265.096 inhabitants - and one in the South including the districts of Almada, Seixal and Sesimbra with 294.538 inhabitants.[7]

In both areas most of the population lived in urban areas. During the two years of study, 61 news cases were diagnosed, 31 Ulcerative colitis (UC), 26 Crohn's disease (CD) and 4 indeterminate colitis (IC).

Table1. The mean incidence for UC and CD per year varied according to the area. In the North UC had a mean incidence of $4.3/10^5$ per year while the southern areas had a mean incidence of $1.4/10^5$. On the other hand, CD

Table 1. Number of IBD patients in Portugal

	Total	UC	CD	IC
North	39	23	15	1
South	22	8	11	3
Total	61	31	26	4

had a mean incidence of $2.8/10^5$ per year in the North, while in the South CD had an incidence of $1.86/10^5$ incidence per year.

Table 2. There seems to exist a North /South gradient which could be explained by a different ethnic background. Populations in the North of Portugal are of Celtic origin while in the South there is a strong North African ancestry. The clinical pattern was on the whole benign, particularly in the ulcerative colitis, which was relatively distal and mild. Most Crohn's disease patients had ileal involvment at the time of diagnosis. In rural areas a lower incidence of both UC and CD was observed. These regional variations may be associated with differences in nutritional habits between urban and rural populations. The increase in incidence of IBD in Portugal over the past decade can be related to socio-economic factors, including new dietary habits.

II. Colorectal Cancer (CRC)

Specific epidemiological studies on colorectal cancer in Portugal are scarce .

The National Cancer Registry for 1988 shows that colorectal cancer represents 13%of the overall mortality for cancer in Portugal.[2] It is one of the highest incidence in the world in similar to what happens in the United States of America.[8]

In the last two decades there was an increase in incidence of 80% (between 1980 and 1998). In 2001, 2.754 deaths for CRC were reported in Portugal. These findings strongly support a wide screening policy. In Portugal a national campaign for screening and prevention of CRC is being conducted. Screening aims at the detection of asymptomatic adenomas or carcinomas allowing an early curative therapy.

Surveillance is also being improved in order to follow those patients treated for adenomas or previous CRC.

Table 2. Total incidence of IBD

	UC	CD
North	$4.3/10^5$	$2.8/10^5$
South	$1.4/10^5$	$1.9/10^5$

Besides age, a positive family history is the most common risk factor.

Some studies were conducted in Portugal in some specific conditions.

1. Hereditary non polynosis colorectal cancer (HNPCC)

HNPCC is a cancer susceptibility syndrome linked to inherited defects in human mismatch repair (MMR) genes.[9]

HNPCC is responsible for 1-5% of all new CRC cases and is probably the most frequent hereditary cancer syndrome.[10]

M. Cravo et al[11] conducted a study on forty one subjects from 10 Portuguese families with a personal or familiar history of colorectal cancer, selected from a previous study.[12]

Different missense and splice site mutations in $hMSH_2$ and $hMLH_1$ mismatch repair genes were studied in order to find out if they could be interpreted as disease causing mutations or just as rare polymorphism.

The importance of selecting factors that might play a role in pathogenesis has been the aim of a great number of investigators.

Cravo's work,[11] concludes that is important to be able to identify patients with HNPCC accurately for genetic counselling, screening and prevention as well as for predictive testing of unaffected family members. However in the study only 10% variants in the $hMLH_1$ and $hMSH_2$ met all criteria to be conclusively pathogenic.

Genetic diagnosis in HNPCC need to be carefully interpreted and should remain in specialised centres with geneticists and clinicians working in close collaboration.[11]

2. Familial adenomatous polyposis (FAP)

Familial adenomatous polyposis (FAP) is inherited as an autosomal dominant condition with almost complete penetrance but striking variation in expression.[13]

It is now clear that both genetic and environmental factors have to be studied in order to understand the pathogenesis of colorectal cancer[14] in this condition.

Although genetic alterations are required for the development of colorectal cancer it is suggested that high levels of reactive oxygen species (ROS) are involved in

the increased colonic cell proliferation induced by bile acids and reported in colonic cancerous tissue and in normal appearing rectal mucosa of these patients.[15]

A controlled study was conducted in 27 FAP patients (24 colectomized) from 12 Portuguese families diagnosed in the Portuguese Institute of Cancer.[16]

The Authors found that FAP patients had a statistically significant increase of oxidant products while at the same time ascorbate and tocopherol levels in peripheral blood cells were significantly reduced.[16] This finding, which agrees with other studies, supports the possible role of antioxidant metabolites in prevention or therapy at adenomatous polyps.

3. Other non-HNPCC non-FAP colorectal tumours

The clinical behaviour of colorectal carcinoma is highly variable without predictable makers of disease outcome. Histopathologic staging still remains the most valuable prognostic factor of neoplasia.[17]

The National Polyp Study demonstrated for the first time that endoscopic polipectomy reduces in the incidence of colorectal cancer from 76% to 90% .[18]

So the present policy in Portugal is a strong advise on prevention, doing a general screening for people over 50 years of age using a combination of fecal occult blood testing and sigmoidoscopy as advised by Winawer et al.[19]

Accordingly, a screening program with both occult blood testing and sigmoidoscopy was realized in the Portuguese Cancer Institute from 1994 to 1996. A thousand and two hundred asymptomatic individuals (age range 50 to 70 years old) were enrolled.

A prevalence of adenocarcinoma was found in 0.6% and high risk adenomas in 1.2%.

From the eight adenocarcinoma found (all in rectum and sigmoid) 6 were malignant polyps: 5 were treated by polypectomy and 1 did transanal ressection. The remaining two adenocarcinoms were operated on. As an alternative valid approach, a positive occult blood testing leads to a total colonoscopy; being the latter negative no screening is needed for the following 10 years. Portuguese guidelines are based on the guidelines stated by the USA Preventive Services Task Force.[20]

For the patients whom there are 1st degree relatives with colorectal cancer a surveillance policy performing colonoscopies every three years, according to the family risk.[2]

III. Helicobacter pylori infection

H. pylori infection is nowadays a problem of public health. In Portugal few studies were performed on epidemiology. The most important[21] one was conducted by (GEPHP) – Portuguese Study Group for H. pylori – and looked for the sero prevalence of *H pylori* antibodies in an heterogenous Portuguese population.

One thousand, a hundred sixty seven persons without known digestive tract pathology, from 20 Hospitals in 11 different Portuguese cities were studied.

The group was divided in sub group A (age 3-14 yr) 197 subjects and subgroup B (age 15-70) 970 subjects.

The sero-prevalence was 46.2% in group A and 82.8% in group B.

When we compare the sero prevalence with similar data from some developed countries (United States,[22] and Australia,[23] France[24] and Finland[25]) our values are very much higher than those of these countries. On the other hand our data are very similar to the data from developing countries mainly Algeria.[23,24]

The problem of gastric cancer and eventual association with H pylori is very accurate in Portugal, once we have a high incidence of gastric cancer. The estimated mortality rate for gastric cancer in Portugal was $29.7/10^5$ in males and $14.5/10^5$ in females.[26]

There are however some northern areas in Portugal (districts of Guarda and Viana do Castelo) where the mortality rate was $40.2/10^5$. Theses differences seem to be associated to an increased consumption of smoked food in those areas.[27]

A study was designed trying to sort out any correlation between gastric cancer and some different virulent H. pylori strains.

The study was performed in 319 patients,[28] all with endoscopy and gastric biopsy diagnosis. A straight correlation between vac AsI and cag A+ strains and duodenal ulcer, gastric ulcer or gastric cancer was established. However $vacA_{m1}$ was associated with gastric ulcer and gastric cancer but not with duodenal ulcer. Multiple H. pylori strains is a frequent finding in Portugal occurring mainly among duodenal ulcer patients. More epidemiological studies are in course and more updated results are to be expected in the near future.

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