

MALIGNANCIES IN PATIENTS WITH CHRONIC

INFLAMMATORY BOWEL DISEASE:

EURICA (European IBD and cancer study)

A EUROPEAN INTERNET STUDY

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1. Introduction

The development of gastrointestinal and certain extraintestinal malignancies is a well known phenomenon in patients with long-standing inflammatory bowel disease (IBD). This enhanced risk probably applies to both ulcerative colitis (UC) and Crohn's disease (CD),

although the majority of clinical data relates to ulcerative colitis. Established risk factors for the development of dysplasia and/or cancer include duration of the disease and extent of the inflammation in the colon. The presence of coexistent chronic cholestatic liver disease is probably also a significant risk factor. Other factors such as the presence of stenosis, the intake of certain immunomodulating drugs, the presence of small bowel disease and certain surgical interventions have been suggested as additional risk factors but remain questionable, predominantly because of a lack of sufficiently large study groups.

Surveillance programs based on repeated colonoscopies to detect early dysplastic or neoplastic lesions have been unsuccessful with regard to improving survival, so far. If it were possible to establish a better defined risk profile, surveillance procedures could be restricted to 'high risk patients', and the yield of these programs would probably increase significantly.

2. Goal of the study

To establish a well-defined risk profile for the development of dysplasia and cancer in a large population of IBD patients from all over Europe. Not only will we confirm 'accepted' risk factors such as duration and extent of disease, but we will also examine questionable and yet unexplored risk factors. The originality of the study consists in the size of the patients population, which will allow firmer conclusions than what has been reported so far, and the 'Internet' method, consisting of data collection through a dedicated website.

3. *Type of study and sample size*

3.1. Matched case-control study.

Cases are patients with inflammatory bowel disease who developed malignancy AFTER January 1st, 1998 (end of study to be determined later)

Controls are patients with inflammatory bowel disease who have NO known malignancy

and matched with cases for:

- sex
- age (+/- 3 years)
- type of disease: Crohn's, UC or indeterminate colitis
- duration of IBD (+/- 2 years)
- location of disease

(NO RESECTIONS of organs at risk allowed, e.g. a patients with a malignancy in the cecum must not be matched with a patient in whom the cecum has been resected)

3.2. Sample size: between 500 and 1,000 cases and the same number of controls

Give these numbers, 1 control per case will suffice

3.3. Matching: The matching process should ideally be performed via an IBD-patient registry. Central pathology labs are often best equipped for this type of procedure, although clinical registries can be used as well. The controls should be treated in the same country as the cases, and preferably in the same center.

4. Inclusion criteria for cases

4.1. Firm diagnosis of ulcerative colitis, Crohn's disease or indeterminate colitis with *pathologic* confirmation and documentation of extent by means of endoscopy and/or radiology

4.2. Firm diagnosis of at least one of the following malignancies diagnosed after 1/1/98:

Adenocarcinoma of the oesophagus

Spinocellular carcinoma of the oesophagus

Adenocarcinoma of the stomach

Lymphoma of the stomach

Adenocarcinoma of the jejunum

Lymphoma of the jejunum

Adenocarcinoma of the ileum

Lymphoma of the ileum

Adenocarcinoma of the colon

Lymphoma of the colon

Adenocarcinoma of the rectum

Anal cell carcinoma

Cholangiocarcinoma

Hepatocellular carcinoma

Adenocarcinoma of the pancreas

Lymphoma in any other location

Other GI malignancy

4.3. Sufficient documentation of the staging of the malignancy at diagnosis

5. Inclusion criteria for controls

5.1. Firm diagnosis of ulcerative colitis, Crohn's disease or indeterminate colitis with *pathologic* confirmation and documentation of extent by means of endoscopy and/or radiology

5.2. Meeting the 'matching criteria' as described in 3.1.

6. Methods

All the data of both cases and controls will be entered on a dedicated website on the internet.

Only a complete case linked to an appropriate control can be entered.

If certain key data are missing, the set of case and control can not be sent to the central registry (will be refused by the program).

Once the data is sent, no further correction is possibly except through telephone contact with the central office.

An investigator will be able to review data, however ONLY of the data sent by the regional group to which he/she belongs.

Each regional study group will receive his own password.

Each group will also have a central responsible investigator, via whom all contacts with the central office will take place.

7. Statistics

Methods for analysis of matched pairs in a case-controls study will be used. Crude data will be analyzed using McNemar's test. Conditional logistic regression will be used to control for possible confounding effects and to examine for interactions. Ninety-five per cent confidence intervals that exclude unity are statistically significant ($p < 0.05$).

8. Medical secrecy

The names of the patients will not be entered in the registry. Given the size of the population, however, we ask for three digits of both first and last name. All the information remains the property of the 'European association of regional IBD study groups', located in Rome. Any publication of data will need to be approved by all regional responsables.

9. Sponsoring

The belgian IBD research club, to which two of the principal investigators (G D'H and MP) belong, has agreed to sponsor this study by paying the development of a dedicated internet site

and further data analysis. Dr Ekblom will be in charge of statistical supervision. There will be no fee for entering case-control data, since we hope that the originality of the study and the

acknowledgement of all participants in the final paper will encourage investigators to take part.

10. Informed consent

If written informed consent would be required for this type of study in any of the participating countries, we encourage the responsible investigator to write it in agreement with local requirements. Based on our information, written consent is unnecessary in most countries.

11. Publication rights

After collection and analysis of all the data, we will organize a meeting to which all participating investigators will be invited, to discuss the way in which the results should be presented. The principal authors will be the principal investigators of the study, and in addition all regional groups are invited to select one author. The ranking of the authors will be determined based on the number of case/control pairs enrolled by the entire group to which the author belongs. All participating investigators who are not 'authors' will be acknowledged in the appendix.

12. REFERENCES

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