



Original research

Relatives of Crohn's disease patients and breast cancer: An overlooked condition



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ABSTRACT

Recent data suggest that patients suffering from Crohn's disease (CD) may be at higher risk of developing extra-intestinal malignancies. This is attributed to inflammation and immunodepression due to medications. However, a genetic predisposition cannot be ruled out. In the present study we investigated the prevalence of breast cancer in first-degree female relatives of CD patients compared with relatives of patients without evidence of gastrointestinal diseases. A total of 1302 female first-degree relatives of CD patients and 1294 relatives of controls were included. We found that CD was an independent risk factor for breast cancer development (OR = 2.76, 95% CI = 1.2–6.2; $p = 0.017$), and this is particularly evident in mothers (3.6% vs 1%, $p = 0.009$ – OR = 3.7, 95% CI 1.4–10). Among CD group, smoking habit of CD patients was associated with increased risk of cancer compared with relatives of non-smokers (7.7% vs 2.9%, $p = 0.01$ – OR = 2.8 95% CI 1.2–6.6). Intriguingly, stage at diagnosis was significantly higher in CD relatives ($p = 0.04$). Our findings suggest that first-degree female relatives of CD patients are at higher risk of developing breast cancer but receive diagnosis at more advanced stages, therefore advocating the need of more active screening protocol in this population.

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1. Introduction

Crohn's disease (CD) is an inflammatory bowel disease characterized by chronic and relapsing inflammation. Recent studies suggested that the risk of colorectal cancer in CD patients is lower than previously thought, but these patients may have an excess risk of extra-intestinal malignancies [1]. Cancer development in inflammatory bowel diseases is different from sporadic cancer and is strictly related with inflammation and disease duration [1]. The increase in survival justifies the higher rates of patients which are being diagnosed in the elderly [2,3], who presumably have long-standing, overlooked disease. Inflammatory bowel diseases are also common in the childhood [4], and these patients are fated to have long-lasting diseases. These observations suggest the importance of early diagnosis and screening; however, less attention is paid to relatives of patients diagnosed with CD. It has been

suggested that first-degree relatives of CD patients may be at higher risk of breast cancer [5].

Assuming that CD is an immune disease, and that immunological disorders may be inherited and shared with other diseases, in the present study we aimed to investigate the prevalence of breast cancer in relatives of our CD patients compared with controls, seeking for potential influence of CD.

2. Material and methods

In this case–control study, we prospectively collected clinical data on consecutive CD patients admitted at our IBD referral Centre. The prevalence of breast cancer in first-degree female relatives was investigated. A control group of parents of age-adjusted patients with no evidence of gastro-intestinal diseases living in the same geographic area was established.

Results were stratified according to age at diagnosis and disease behaviour.

Five hundred and three outpatients (55% males, median age 36.2, range 3–87 years) with established diagnosis of CD referred at

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the Unit of Gastroenterology or at the Unit of Surgery of our Centre were prospectively enrolled. Patients were not enrolled if they were diagnosed with cancer. Five hundred control patients (52% males, median age 37.3, range 3–91 years) served as controls.

First-degree female relatives of included subjects were investigated for breast malignancies, by means of a questionnaire submitted to patients. When needed, the general practitioners of the relatives were contacted for additional information. A total of 1302 female first-degree relatives of CD patients and 1294 relatives of controls were included in final analysis.

Clinical data of CD patients were collected and used for comparisons. Clinical and imaging data were matched with surgical details, in order to compare the definitive stage of breast cancer between groups.

2.1. Statistical analysis

Statistical analyses were performed by means of SPSS statistical package (17 – SPSS Inc., Chicago, IL, USA). Continuous data are reported as median with range or mean \pm SD. Univariate comparisons between were performed with χ^2 test. The relative risk was calculated and reported as Odds ratio (OR) with 95% confidence interval (95% CI). Continuous variables were compared by means of Student's *t* test. A value of $p < 0.05$ was considered as statistically significant. The impact of potential confounding known risk factors for breast cancer was assessed by a logistic regression including CD.

3. Results

CD relatives group included 501 mothers, 541 sisters, and 260 daughters; 500 mothers, 539 sisters, and 255 daughters were enrolled in control group.

We found 22 breast cancers (1.72%) in relatives of CD patients and 8 (0.61%) in those of controls (OR = 2.76, 95% CI = 1.2–6.2; $p = 0.017$). Median ages at diagnosis of cancer did not differ between groups (53 vs 50, $p > 0.99$).

Cancer occurred in 18 mothers (81.8%) and 4 sisters (18.2%) of CD relatives, compared with 5 mothers (62.5%) and 3 sisters (37.5%) of controls ($p = 0.34$). Mothers of CD patients were at higher risk of developing breast cancer than those of controls (3.6% vs 1%, $p = 0.009$ – OR = 3.7, 95% CI 1.4–10).

No differences were observed according to CD pattern and localization, while CD diagnosis before 40 years of age exerted a protective effect over breast cancer development ($p = 0.03$). Among CD group, smoking habit of CD patients was associated with increased risk of cancer compared with relatives of non-smokers (7.7% vs 2.9%, $p = 0.01$ – OR = 2.8 95% CI 1.2–6.6).

Stage at diagnosis was significantly higher in CD relatives when compared with controls (Stage I or cancer in situ: 4.5% vs 37.5%, $p = 0.04$).

All cases of breast cancer were included in a multivariate regression analysis, which showed that a first-degree relative with CD was the only independent risk factor for breast cancer in this population.

4. Discussion

With this case–control study we were able to demonstrate an increased risk of breast cancer in first-degree relatives of patients suffering from CD, irrespective of disease localization and behaviour, compared with controls. The former were more often diagnosed with advanced cancer stage.

Previous studies suggested an association between CD and extra-intestinal malignancies (1). Riegler et al. (5) found that CD relatives show a trend toward increased prevalence of cancers, even

if the observation did not reach statistical significance. It was also found that advanced age at diagnosis may be associated with higher risk for cancer in first-degree relatives [5]. The effect was attributed by the older age of the subject as well as of the relatives. This observation was confirmed in the present series investigating breast cancer. This finding should not be underestimated, given the higher number of patients who are diagnosed with inflammatory bowel diseases in the elderly [2,3] due to the improved disease knowledge and to longer life expectancy. Moreover, optimal care is pivotal also in this population, as age does not represent a limitation for advanced procedure and treatment with curative intent [2,3,6,7].

When considering colorectal cancer, the pathway leading to cancer are different between CD and sporadic carcinoma [1]. CD patients often receives many drugs for prolonged time during their lives, which are active on the immune system [8,9], and these have also been suggested by some authors to predispose to cancer, but data are conflicting in the literature [1]. CD itself may play a role in developing extra-intestinal malignancies, but the high rates of such cancers in first-degree relatives may suggest that CD could share some genetic alterations with those underlying malignancies. Breast cancer in these population was alarmingly high when compared with controls. Mothers of CD patients had almost four times the risk of developing breast cancer than controls. By including all patients in a multivariate analysis, we were able to exclude confounding factors, confirming that only CD affecting a relative was the independent risk factor for breast cancer. This finding has an obvious practical implication, which is further highlighted by considering that relatives of CD patients diagnosed with breast cancer were eight times more likely receiving diagnosis at more advanced stages ($p = 0.04$). This impairs prognosis but also reduces the possibility of a conservative surgical approach, and advocates the need of diagnosing earlier breast cancer in these subjects.

A common genetic susceptibility to inflammatory bowel diseases and breast cancer has been hypothesized by some Japanese authors, and related to interleukin-1 (IL-1) polymorphism [10]. ILs play a central role in inflammatory bowel diseases as well as inflammatory cytokines and mediators, although the clinical picture may be silent [11]. Recent molecular evidences showed that these factors are also involved in breast malignancies, and a shift of the treatment toward a more tailored, immune-pathological approach is being observed in the recent years [12]. This is not surprising, as modification in the same gene (*MLH1*) has been associated with susceptibility to inflammatory bowel diseases and HNPCC, a syndrome predisposing to extra-intestinal malignancies [13,14]. These data make the fascinating hypothesis of a common genetic aetiology between CD and breast cancer more consistent.

Cigarette smoking is a known risk factor for developing CD and is associated with higher rates of relapse after treatment. Active smoking is a risk factor for many malignancies. Aiming to identify familial factors which may play a role in breast cancer development of CD relatives, we only took into account smoking habit of CD patients, and found that passive smoking was associated with almost three fold higher risk of developing breast cancer in this subgroup compared with non-smoker counterparts. This is consistent with recent evidences in Chinese women [15], and adds another reason for encouraging smoking discontinuation in CD patients.

Relatives of patients suffering from inflammatory bowel diseases are often neglected. However, these should be considered diseases involving the entire family group, and it has been recently reported that disease activity and patients quality of life is reflected by that of their first-degree relatives, such as parents [4]. This suggest the importance of actively involving relatives in the

treatment of CD patients. Similarly, given the increased risk of developing malignancies presumably due to a genetic predisposition, relatives should also receive an active screening protocol.

Our findings highlight the higher risk of developing breast cancer in first-degree female relatives of CD patients. When compared with controls, these tended to have more advanced disease at diagnosis. This may impair radicality of treatment, and advocates the need for obtaining earlier the diagnosis in these patients. It seems prudent to recommend close and active screening for breast cancer in relatives of CD patients.

Conflict of interest/Financial support

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Ethical approval

None.

Author contribution

Gianluca Pellino: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Guido Sciaudone: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Marta Patturelli: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

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Gabriele Riegler: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Francesco Selvaggi: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

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