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Occupational risk factors in inflammatory bowel disease

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Abstract. – OBJECTIVE: Crohn's disease and ulcerative colitis are the two main forms of inflammatory bowel disease (IBD). Although the aetiology of IBD is not completely understood, an interaction between genetic and environmental factors has been proposed. In this context, however, environmental epidemiology lacks a comprehensive evaluation of the possible role of occupational exposures in IBD development and progression. Therefore, aim of our review was to evaluate how certain occupational risk factors may affect IBD pathogenesis, clinical history and severity of disease manifestations.

MATERIALS AND METHODS: A critical revision of available literature concerning exposure to groups of potential workplace hazardous agents and IBD, as it appears in Medline and Web of knowledge, was performed.

RESULTS: The role of workplace exposures to chemical and biological agents, ionizing or non-ionizing radiations, shift-works, indoor, and sedentary works as well as job strain on IBD has been critically revised. However, the limited number of studies addressing these issues prevented us from extrapolating definite conclusions.

CONCLUSIONS: Our review pointed out some critical aspects concerning the relationship between occupational factors and IBD, in terms of causative pathways, hazardous exposure, susceptibility and consequences of IBD functional limitations on career choice and fitness for work that need future investigations. Overall, this seems a challenging public health issue, considering the strong IBD impact on patients' quality of life, work productivity and costs to society.

Moreover, this review may encourage concerted actions of health care specialists, occupational physicians, employers and IBD workers to plan preventive and protective measures for "healthier patterns of work" for IBD and to develop innovative perspectives for an integrated management of "IBD at work".

Key Words:

Inflammatory bowel disease, Crohn's disease, Ulcerative colitis, Occupational risk factors; Workplace hazardous agents, Biological and physical agents, Chemicals, Organizational aspects, Ability to work, Inflammatory bowel disease management.

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the two main forms of inflammatory bowel disease (IBD). CD is a relapsing systemic illness, mainly affecting the gastrointestinal tract, that frequently presents with abdominal pain, fever, and clinical signs of bowel obstruction or diarrhoea with passage of blood and/or mucus[1]. UC is characterized by a chronic inflammation restricted to the mucosal surface which starts in the rectum and generally extends proximally in a continuous manner through the entire colon. Bloody diarrhoea is the characteristic symptom of the disease[2]. The incidence and prevalence of IBD are increasing with time and in different regions around the world, indicating its emergence as a global disease[3]. The highest annual incidence per 100000 person-years for UC and CD was estimated in 24.3 and 12.7 in Europe, 19.2 and 20.2 in North America, respectively. Comparably, the highest reported prevalence values for IBD were in Europe (UC, 505 per 100000 persons; CD, 322 per 100000 persons) and North America (UC, 249 per 100000 persons; CD, 319 per 100000 persons). Although increasing, rates were lower in the southern hemisphere and eastern countries[4]. Age stratification showed a peak in IBD incidence rates in the second to fourth decade, with the highest incidence among 20-29 years old, while a second modest rise was reported in latter decades of life, 60-70 years[3,4].

The etiology of IBD has been extensively studied in the past few decades, although the disease pathogenesis is not yet fully understood[5]. It is widely considered that IBD occurs due to a disturbed innate and adaptive immune response towards a diminished diversity of commensal microbiota in genetically predisposed subjects triggered by environmental influences[6,7]. Environmental factors, in fact, are essential components of the pathogenesis of IBD and primarily respon-

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sible for its growing incidence around the globe. Epidemiological, clinical and experimental evidences support an association between IBD and a large number of seemingly unrelated environmental factors, which include smoking, diet, drugs, geographical and social status, stress, microbial agents, intestinal permeability and appendectomy[8,9].

Unfortunately, in the environmental epidemiology of IBD, a deep analysis of the possible role of potentially "longlife" occupational exposures in affecting the development, clinical history and severity of IBD manifestations, is still lacking. Only few earlier socio-economical studies, in fact, suggested that IBD tended to affect the higher social classes more frequently than the lower ones, as well as the white collar employees more than blue collars, with IBD patients more likely to be employed in professional, managerial, skilled labour positions[10-18]. Overall, this socioeconomic/occupational distribution may be explained by an increased workplace exposure to a distinct set of environmental triggers which could act as possible risk factors for the occurrence and exacerbation of IBD. The definition of such risk factors may, in fact, give an insight into the yet unknown etiology of the disease. At the same time, it is worth considering that IBD imposes patients practical restrictions to their working lives leading to choose certain job occupations, as well as requiring great efforts to maintain job and to daily face work-related risks and problems.

Therefore, the present review aims to give a comprehensive evaluation of the possible relationship between exposure to specific occupational risk factors and IBD. This may provide valuable insights into the role of certain job factors and the mechanisms that contribute to the occurrence and progression of IBD in order to define issues for future epidemiologic research. It may be extremely important also from a public health perspective, considering the increasing global burden of IBD and its strong and lifelong impact on the patient's quality of life and work productivity as well as on health care resources.

Lastly, this review may give a stimulus to develop innovative perspectives for a global/integrated IBD management, providing also health care specialists, occupational physicians and employers additional information to plan and adopt adequate preventive measures to protect IBD workers, and to give them efficient support to face occupational risks to which they may be more susceptible.

Materials and Methods

Aim of this review was to overcome the quite fragmented knowledge concerning the socio-economical stratification of CD and UC patients toward a more accurate comprehension of the IBD occupational distribution according to the "type of environment" in which they work[19]. We conducted a systematic search of articles, published in Medline and ISI Web of knowledge up to December 2014, regarding occupational risk factors potentially related to the development and progression of IBD.

Although we carried out a preliminary Medline search for the terms "inflammatory bowel disease" and "occupational risk factors", only 26 references were retrieved. Out of these, only 9 were considered suitable for our scope by title and abstract screening. Therefore, we extended our research including the following keywords as free terms in the electronic search: "inflammatory bowel disease", "Crohn's disease", "Ulcerative colitis", which were individually combined with the operator "AND" with the terms related to the major subject of "exposure to workplace hazardous agents", such as "occupation* OR work* OR workplace OR job exposure", "chemicals", "metals", "biological agents", "bacteria", "physical factors", "physical workload OR activity", "magnetic field", "ionizing radiation exposure", "ultraviolet exposure", "shift-work", "night-work", "work related stress", "job strain".

In this formative phase of knowledge, the search strategy was intended to be broad in order to maximize the capture of citations of peer-reviewed English publications including reviews, articles, letters and commentaries relevant to extrapolate useful data to understand the role of occupational risk factors for IBD epidemiology. All fulltexts of the papers considered valuable for the aim of our review were obtained and a critical evaluation performed. Citation pool of relevant publications identified in the literature search was further supplemented through the manual assessment of the reference list accompanying published papers for other potentially eligible articles.

Results

Potential workplace hazardous agents identified have been grouped in common risk factors categories in order to clearly define the complex

interplay between occupational risk factors and IBD manifestations, in particular workplace scenarios as well as the relationship between IBD morbidity and ability to face specific risk factors.

Chemical Risk Factors

The possible causative role of chemical exposure in IBD development has been suggested by a series of occupations associated with an increased risk of disease. Instrument makers, electricians, persons in health-related occupations, and hairdressers were reported to have an higher prevalence of IBD by Sonnenberg[20]. Li et al[21] found men employed as drivers, textile, glass, ceramic and tile workers, chemical process, smelters and metal foundry workers to be at increased risk of hospitalization for CD and UC in an economically active Swedish population. Comparable results were reported for women employed as mechanics, printers, iron and metalware, wood and related workers[21]. According to the Authors[21], these occupations were characterized by a variable degree of chemical exposure. Unfortunately, only job title was used to assess the association between occupation and proximity to specific agents, therefore, it was not feasible to identify the kinds of agents that may be involved in the casual pathways.

For many years, exposure to xenobiotic like metals have been suggested to induce an immune response in different diseases including autoimmune diseases[22]. Aluminum (Al) was firstly suggested as an environmental exposure factor possibly involved in the pathogenesis and/or maintaining of CD[23]. Exposures to Al dusts and fumes are among occupational hazards of workers in the Al refining and metal industry, printing and publishing, and automotive dealerships and services. Al immune effects share domains with the immune pathology of CD such as the activation of antigen presenting cells, the induction of a T-helper (Th-1) inflammatory response exerted by luminal bacteria or dietary compound adsorbed to the metal, the enhancement of pro-inflammatory, apoptotic and oxidative stress molecule expression, the transmural granuloma formation as well as the induction of colitis in a CD animal model[22-24]. It is possible that barrier permeability abnormalities, due to epithelial tight junction disruption and restitution arrest, gross mucosal lesions, or defective functioning of Peyer's patches or M (Microfold cells) epithelium, described in CD, may operate in concert to increase the toxicity of nano-microparticles containing Al, thus, inducing or aggravating the disease[25,26]. Pearl et al[27] put forward the hypothesis that, due to bacterial-metal interaction, Al and other metals can play a role in CD induction. The Al uptake by certain microbial organisms, in particular mycobacterial species, may alter the pathogenicity of these organisms and exacerbate the host's responses to them inducing a prominent granulomatous immune response, therefore, giving rise to the pathologic features of CD.

A single case report of an electrician with recurrent exacerbations of UC associated with industrial mercury vapour exposure suggested the role of this metal in UC reactivation[28]. Symptoms began within 24 hours after he performed maintenance services upon mercury filled electrical blocks in an electroplating plant for one full-workday. The timing of the recurrent reactivations, suggested that occupational over-exposure to mercury vapour may lead to a disease relapse hypothetically due to an increased adsorption of ingested mercury through the UC abnormal mucosa. Unfortunately, the lack of subsequent confirming data does not allow to support a causative role of this kind of chemical in UC re-activation.

The perfluorooctanoic acid (PFOA), a substance widely employed in the manufacture of a variety of consumer products, such as Gore-tex and Teflon[29] and able to affect the immune responses in *in vivo* experiments[30,31] has been investigated as an influencing factor in IBD incidence[32]. A PFOA exposed Mid Ohio Valley community population living and working in contaminated water districts and a cohort of exposed workers employed at the DuPont chemical plant between 1948 and 2002 have been studied[33]. Median PFOA serum levels for community residents was estimated in 24 ng/ml while it was 113 ng/ml for workers. UC, but not CD, showed a significant positive association with cumulative PFOA exposure with adjusted rate ratios (RR) ranging from 1.76 to 2.86 for all three upper quartiles versus the lowest quartile (RR:1.00) of estimated cumulative exposure. Plausible mechanisms linking PFOA and UC, extrapolated by experimental findings, may include shifts in the balance of tissue macrophages towards an anti-inflammatory phenotype and/or a Th-2-like response to specific antigens suggesting a general increase in host susceptibility to infections[34].

Biological Risk Factors

Infectious agents are thought to be involved in the pathogenesis and clinical course of IBD ei-

ther through the colonization of the inflamed mucosa of IBD patients as secondary invaders or innocent bystanders, or via the direct induction of the disease[35]. Since the first description of the similarities between CD and Johne's disease (JD) in cattle[36], it has been argued that *Mycobacterium avium* subspecies *Paratuberculosis* (MAP), which causes JD, might also act as a causal factor in CD[37]. As a confirmation, the conclusion of a recent meta-analysis seemed to indicate an association between MAP and CD[38]. However, the establishment of this association is controversial, since critics of the mycobacterial theory argue that MAP is a secondary invader rather than a causal factor[39].

To further explore the hypothesis that occupational exposure to MAP, through MAP-infected cattle or dairy products, increases risk for CD, a cross-sectional study was conducted to obtain information on the occurrence of CD in U.S. dairy and beef cattle producers (n. 702) and veterinarians (n. 774)[40]. Fifty nine, 71% and 42% of veterinarians, dairy and beef producers, respectively, reported contact with cattle with confirmed cases of JD. There were 3 CD cases in producers and 4 in veterinarians. Importantly, no association was found between exposure to JD and the occurrence of CD, therefore, no association was demonstrated between CD and MAP. Comparably, a study carried out on dairy farmers from United Kingdom detected a CD prevalence in these workers not different from that in the general population and failed to find an association between exposure to clinical cases of JD and the development of CD or UC[41]. However, the small number of IBD cases limits the power of these studies to detect important differences[40,41].

It has been suggested that hypersensitivity to baker's yeast, *Saccharomyces cerevisiae*, or related antigens may play a role in CD, as these patients demonstrated IgA and IgG titres to this yeast significantly higher than controls[42-44]. Strains of this organism are used in baking and brewing and are found in a wide variety of foodstuffs, and could explain the ubiquitous occurrence of CD. Evidence for the involvement of baker's yeast in CD has been reported by Sonnenberg[20,45] investigating the occupational distribution of CD prevalence and mortality[46]. As regards this latter issue, analyses of occupational mortality from CD in England and Wales[45] have shown a proportional mortality ratio (between observed and expected value) close to 3.5 times greater for bakers than the one for managers in retail (who had the second highest ratio of all professions). These findings were further supported by the social security statistics from West Germany showing that, among all professions in men, bakers had the highest odds ratio for CD[20].

Finally, with respect to biological risk for healthcare workers, a first study carried out on British nurses with IBD, failed to identify the regular assistance to IBD patients as a biological risk factor for the development of the disease, although they manifested IBD at an earlier age compared to the members of the community[47]. Subsequent studies reported conflicting results for IBD risk in health care professions which resulted at increased risk in Sonnenberg[20] while at decreased risk in Li et al[21]. Therefore, the definition of biological risk factors for inflammatory gastrointestinal disorders needs to be deeply defined.

Physical Risk Factors

Limited attention has been paid to the possible association between exposure to physical agents in the workplace, such as ionizing and non-ionizing radiation, and IBD also in complicated forms. As concerns the potential effects of radiation exposure on IBD, there is no a strong literature concerning the potential synergy between radiation and UC in developing colon cancer which is a recognised risk for IBD patients[48]. Several factors have been associated with an increased risk of colorectal cancer in IBD patients with duration and extensive disease, a family history of sporadic colorectal cancer, uncontrolled inflammation, shortened colon, and multiple pseudopolyps as the most important[1,2,49]. In this context, only one paper, from an occupational health perspective, stated that an x-ray technician affected by UC should not be at increased risk of any type of cancer if all the proper preventive and protective procedures are followed, if modern x-ray equipment is used to prevent the dispersion of the x-rays and if appropriate shielding apron is worn to protect the entire colon. Certainly, a continuous, close medical follow-up is strongly recommended[50]. However, it is a complex issue considering also that the standard management of IBD patients actually includes performing repeated imaging tests using ionizing radiation which may have a cumulative effect on the patients and increase their own risk of malignancy in the long term[51,52].

Concerning electro-magnetic fields, a single occupational case report described the onset of thyroiditis and IBD following a prolonged and intense exposure to 50 Hz magnetic fields[53]. The patient was a manager, employed in a shopping centre for 7 years exposed to a chronic daily over-exposure of magnetic field due to her office location immediately above the 50 Hz substation for the centre and three busbars carrying high current. The magnetic field from the substation was found to be 1000-1400 mG at 0.5 m above the floor where her chair was placed, and up to 3400 mG at floor level with an Australian public exposure limit of 1000 mG[54]. The Author suggested that the chronic daily overexposures could have stimulated the smooth muscle or myenteric plexus of her gastrointestinal tract contributing to the development of IBD. Tuncel et al[55] have shown that a chronic exposure to 5 mT (50 000 mG) of 50 Hz electromagnetic fields can affect cytoplasmic E-cadherin expression and weaken cell adhesion mechanisms in a rat colon tumour model. This may have caused a 'leaky' bowel mucosa, permitting the entrance of foreign antigens, which may be a pathogenic pathway in IBD inducing also an immune cross-reaction to the thyroid[53]. Conversely to the "pro-inflammatory" effects reported by Hocking[53], a pulsating electromagnetic field (50 Hz with a flux density of 45 mT for three hours/day with 24 h intervals) induced a significant reduction in cell viability, a decrease in interferon-γ production as well as an increase in interleukin (IL)-10 release in peripheral blood mononuclear cells isolated from non-treated CD patients compared to unexposed controls, supporting a potential role of the electromagnetic field therapy in IBD treatment[56].

Interestingly, certain job characteristics such as exposure to open air might be protective against developing IBD. This is because individuals who work outdoor receive more sun exposure, thus more ultraviolet exposure, with a greater synthesis of vitamin D. This may explain why farmers and agricultural production of livestock resulted among the occupations and industries, respectively, with the lower proportional IBD mortality ratio, as retrieved from computized 1991-1996 data files of the US National Center for Health Statistics. Conversely, IBD mortality was increased, although in a not significant manner, in occupations associated with indoor work, i.e. sales persons, secretaries and administrative personnel[18]. However, a correct interpretation of these data requires to consider that the occupations recorded at the time of death frequently reflected only the period of last or longest employment, with other employments going unnoticed. Moreover, IBD mortality may seem artificially low among occupations that attracted expecially healthy persons, inducing a potential selection bias in the data evaluation[18].

However, the beneficial effects of sun exposure on IBD were confirmed by North-South gradients in CD rates described in Europe and in North-America: they reveal how environments with southern exposures, which receive more sunlight and translate into spending more time outdoors, are associated with a lower prevalence of disease[19,57-59]. As concerns the relationship between UV exposure and IBD severity, lower ultraviolet exposure was also associated with greater rates of hospitalization, prolonged hospitalization and the need for bowel surgery[60]. As UV exposure is a strong determinant of vitamin D status, the observed effects of UV exposure on IBD hospitalization and severity may be mediated by vitamin D[61]. In fact, *in vitro* and *in vivo* data have demonstrated vitamin D to possess immunomodulatory properties through several mechanisms such as diminished inflammatory response to antigenic stimulation, down-regulation of the expression of pro-inflammatory cytokines in favour of anti-inflammatory proteins and the shift from a Th-1, Th-17 profile to Th-2 and regulatory T cells[61].

Physical Workload

Shifting workforce proportion to sedentary occupations and technology developments in traditionally physically demanding occupations have resulted in low physical workloads for many workers. Insufficient physical stress is known to result in reduced bone density, muscular strength and endurance, impaired neuromuscular coordination and cardiovascular fitness and deterioration in mood and psychological state[62].

As regards the effects of physical activity on IBD, Sonnenberg[20], using occupation as a proxy, described an inverse correlation between occupations involving exercise and risk of CD and UC, supporting the thesis that having to exercise seems to be a protective working condition. In fact, the occurrence of IBD was low among workers in building and construction, unskilled labourers, machinists and transport men as well as in housekeepers, cleaning and maintenance workers. Comparably, IBD mortality was low among blue collar workers and high among white

collar ones, which demonstrates the protective influences associated with physically demanding occupations[63]. Particularly, a lower mortality rate was reported in occupations associated with manual work, i.e. among farming occupations, manufacturing occupations, and manual labourers, while a greater rate was described in sedentary works such as among sales persons, secretaries, managerial occupations and teachers[18,63].

As an ulterior confirmation, a sedentary job has been suggested as a plausible risk factor for IBD given that abdominal transit time may increase in persons with sedentary jobs, therefore allowing more time for immunologic reactions to dietary and bacterial antigens to take place in the intestine[64]. An epidemiology study on soldiers with UC in American Army[65] showed that there was a significantly greater occurrence of the disease among white officers than among white enlisted men. Evaluated on the basis of occupation within the military service, a significant preponderance was found among men who had previously been engaged in trade, and a minor representation among men who had previously been involved in agriculture. Furthermore, data from the population-based study by Bernstein et al[16] found that individuals with IBD were twice as likely to have sedentary jobs. This was in line with previous findings by Boggild et al[64] who found that female office workers had a greater risk of hospital admission for IBD and with those by Li et al[21] who reported a significantly increased risk of hospitalization for CD and UC in drivers.

The potential protective role of physical activity in CD development, as well as the existence of an inverse association between CD and physical exercise, has also been supported by the results of two large prospective cohort studies on US female nurses[66]. Compared with women in the lowest fifth of overall physical activity, the age adjusted risk of CD decreased with increasing level of exercise. Active women with at least 27 metabolic equivalent task (MET) hours per week of physical activity, or the equivalent of more than nine hours per week of walking at an average pace, had a 44% reduction in risk of developing CD compared with sedentary women with <3 MET hours per week. Physical activity was not associated with risk of UC. Consistently, Ng et al[67], examining environmental risk factors prior to the development of IBD in a population-based cohort in Asia-Pacific, found that daily exercise, when compared with less frequent one, was protective for CD. Although the exact mechanism for this association is not clear, physical activity may induce autophagy and regulate innate immunity to reduce chronic inflammation[68].

As previously mentioned, caution should be paid in interpreting the higher IBD prevalence in sedentary-low physical demanding occupations, because they may show an unduly high prevalence of disease not due to their hazardous influence but to their less demanding working conditions attracting chronically affected IBD workers[18]. Such potential bias may impress an artificial protection from IBD among more active occupations while attributing an aggressive influence to more sedentary ones and, therefore, requires to be carefully evaluated in prospective epidemiological studies.

Organizational Risk Factors

Expansion of service sector, growing impact of information technology, flexibility of employment arrangements have induced profound changes in the nature of employment and work, with consequent health adverse work time arrangements affecting large part of the workforce[69]. Therefore, it seems extremely important to understand how work organizational characteristics in modern economies can affect the health of working people, with a specific attention on those chronically affected by disabling illness.

Increased evidence has supported disrupted sleep in shift workers as a risk factor for a number of gastrointestinal disorders[70]. As regards IBD, Sonnenberg[20] suggested that extended and irregular shift work could be a risk for contracting IBD as demonstrated by the most noticeable increases in odds ratio determined in electricians, technical assistants, bakers and female hairdressers. These occupations seem to exemplify the working environments characterized by artificial lights, extended and irregular shifts, and infringement of the normal diurnal rhythm. Conversely, Boggild et al[64] in two register-based cohort studies on Danes IBD patients, failed to demonstrate a relationship between non- daytime jobs and hospitalization for IBD. Neither groups with predominately night and morning work, late evening work, and 24-hour services, nor groups with other forms of irregular working hours had an elevated risk of hospitalization. More recently, Swanson et al[71] reported that they clinically noted a strong association between worsening of the disease course in two UC patients, one policeman and one female nurse, and one CD patient, a

fire-woman, who started shift work and in two patients with CD and multiple periods of jet lag and an improvement when they returned to a normal schedule.

Although conflicting results emerged from these studies and further occupational research seems necessary, the biological plausibility that disturbed sleep may be a modifiable behavioural risk factor for IBD has been suggested by a series of other studies[72-74]. CD patients with disturbed sleep while in clinical remission had nearly double the likelihood of disease flare at 6 months compared with those with unimpaired sleep[75]. Moreover, the totality of clinically active IBD patients studied by Ali et al[76] revealed abnormal sleep patterns. In animal models, acute or chronic sleep deprivation increased susceptibility to dextran sodium sulphate-induced colitis, a widely used mouse model of IBD[77,78].

Altered sleep and sleep deprivation can negatively affect gastrointestinal function, but has also the potential to cause immune activation of natural killer cells and monocytes and the release of inflammatory cytokines such as tumor necrosis factor (TNF)-α and IL-6, thus, impacting disease course in gastrointestinal inflammatory disorders like IBD[9,71,79]. Inflammatory processes can in turn affect sleep pattern, with inflammatory mediators such as TNF-α found to suppress clock gene expression which are involved in regulating intestinal permeability and thus create a vicious cycle and positive-feedback loop to maintain and perpetuate inflammation[71,80]. Moreover, melatonin, which is important in the regulation of circadian rhythms has been demonstrated to be a powerful antioxidant and free radical scavenger and has also been found to decrease levels of TNF-α. The disregulation of melatonin cycling production may act triggering these important pathways in IBD. These preliminary studies give a rationale to proceed with future investigations examining the effects the disruption of sleep/circadian homeostasis due to shift works may have on disease course of IBD[81].

With the advent of economic globalization, stressful psychosocial work environments have become even more important in terms of adverse health effects[69]. IBD patients readily identify stress as causing or triggering their disease[82,83]. There is consistent evidence, in fact, that psychological factors may play a role both in the pathophysiology and manifestations of IBD as well as on the manner patients deal with their disease[82,84,85]. The physiological response to stress involves a cascade of reactions through the so called brain-gut axis. It starts from the hypothalamus, proceeds via the stimulation of the sympathetic and parasympathetic nervous systems, and communicates with the gut's own rich nerve supply that controls gut motility and endocrine and exocrine functions in the gastrointestinal tract[83,85,86].

However, it is difficult to establish a definite causal relationship between stressful life events and IBD considering also that once it develops, the unpredictability, uncertainty and chronic course of the disease itself can cause in turn a wide range of personal, interpersonal and professional concerns requiring a complex, stressful adaptive process[83]. Moreover, activation of a stress response is highly dependent on the appraisal of the circumstance as stressful which is influenced by individual difference factors such as coping strategies, life experience and personal resources[82].

Even more difficult is to understand the role of work related stress in the disease development and progression. In the early 1960s, Bonnevie[10] reported that a greater percentage of UC civil servants and wage earners belonged to the senior salaried grade and to the skilled labor group, respectively, compared to the entire population of the Copenhagen city district. These results could be also interpreted according to the hypothesis that occupational psychic strains, i.e. social striving and competition to get on, in the civil servants and salaried grades group, had the effect to more frequently unmask diagnostically evident UC, from a slightly inactive, subclinical form, than in persons found in less ambitious socioeconomic strata.

More recently, as a part of the Manitoba IBD cohort study, Rogala et al[87] reported no significant differences in the level of work-related stress in IBD partecipants compared to a community sample as control. Bernstein et al[82] found that IBD patients were more likely to have a major stressful event occurring in the period before the relapse compared to inactive patients. This event was more commonly in the family/domestic or less frequently in the personal health-related stress categories.

Importantly, Heikkila et al[88] conducted a meta-analysis to investigate the association between work-related stress and incidence of CD and UC according to individual-level data obtained from 11 European studies with over 95000 partecipants. Findings suggested that job strain, defined

as high demands and low control at work, was not a major risk factor for CD and UC. The Authors pointed out that these findings did not take away the cross-sectional evidence that IBD patients often experience stress, or that stress can trigger symptoms and exacerbations in these diseases. However, they underlined that the trigger-effect was evident in studies in which the time from the stressful event or experience to the onset of symptoms or diagnosis of IBD was relatively short. As an occupational example, increases in stress, anxiety, and depression as well as pro-inflammatory immune activations and alterations in intestinal permeability, all factors predisposing to IBD, were determined after a short period (6 weeks), high-intensity combat training course in Asian male soldiers[89]. The several years of follow-up in Heikkila et al[88] may be essential for disentangling the possible impact of job strain on the disease process. Importantly, these findings may not be generalised to other indicators of work-related stress or sources of stress outside work. Further large, prospective, population-based studies seem necessary to clarify whether other operationalisations of work-related stress or stress in other areas of life have a role in the aetiology of IBD.

Discussion

To the best of our knowledge, this review represents the first attempt to provide a comprehensive evaluation of the possible role of specific occupational risk factors in the development and relapse of IBD. This seems an intriguing topic which goes to fill a gap in the scientific literature concerning environmental epidemiology of this disorder. Moreover, the increasing global burden of IBD, its effects on patients' quality of life and ability to work, the impacts on the health care resources and on the overall economic system due also to the indirect costs of the disease based on work loss and productivity reduction, clearly make this issue a public health concern[15,17,87,90-92].

Importantly, IBD can affect patients in their early adulthood, an age when most people make critical decisions regarding both their education and career which in turn may affect the course of their illness. IBD continues throughout the entire life of patients, with a history characterized by remissions and relapses, often requiring hospitalizations and surgery, necessitating work absences and disability. In this context, work may be a relevant functioning area affected by IBD that requires both patient's efforts to participate in the labor force as well as adequate programs of risk/health management in workplaces. Moreover, with the aging of the active working population, and considering the second smaller IBD peak of incidence in subjects between 50 and 70 years, occupational physicians may find themselves to manage aged IBD employees to pursue their expertise while facing occupational risks and functional limitations.

Unfortunately, only a limited number of studies addressed the relationship between potential dangerous occupational exposures and IBD, often with conflicting and quite fragmented results that do not allow to extrapolate strong evidence and definite conclusions. In fact, although some studies have found increased risk for CD and UC among people in certain occupational categories[18,20,21,64], few have reported association between specific occupations and the incidence of IBD. Therefore, uncertainty remains about direction of causality. This means that it is not yet clearly defined if certain jobs pose risks for the development of IBD or whether patients with IBD choose particular occupations because of the practical restrictions their illness presents[19].

It is plausible that particular jobs can expose workers to harmful agents, but most of the reviewed studies did not provide qualitative and quantitative information in this regard as well as details regarding job tasks performed by IBD workers, thus preventing the identification of specific occupational triggers for IBD induction and relapse**.** Therefore, future cohort and case-control studies should be focused to this aim, particularly addressing the relationship between workplace and job task features and disease clinical phenotypes, activity and comorbidities. Great stimulus in this direction may be provided by early findings obtained from the general epidemiological research, which may be extrapolated to and specifically investigated in occupational settings.

In this context, the environmental monitoring, i.e. the periodic measurement of the level or concentration of a chemical, physical or biological risk factor in the workplace, as an indirect measure of human exposure, should be routinely performed to check the appropriateness of collective and personal protective measures adopted to avoid levels of exposure exceeding permissible or recommended limits. Biological monitoring of chemical or biochemical markers may be also an

important instrument to assess the individual real dose of exposure of IBD workers. An altered mucosal permeability, in fact, may induce an overexposure to some xenobiotics, i.e. through an easier gastrointestinal adsorption of substances resulting from the mucociliary clearance of inhaled particles, in case of accidental events or when proper standards of personal and industrial hygiene are not met. This overexposure may in turn cause more severe health effects.

Furthermore, due to the potential interplay between genetic, personal habits, i.e dietary and smoking habits, general environment and workplace factors in affecting IBD, a global health surveillance of patients in their workplace environment should firstly include an accurate collection of anamnestic data. These may be comprehensive of information concerning physiological and medical history, lifestyle and disease course and features. Occupational history should be gathered including performed jobs and duration of employment as well as patient perceptions of risks, difficulties and limitations at work, together with accommodations thought necessary for a more comfortable job. Moreover, as epidemiological evidence becomes more substantial, as in the case of sleep impairment and disease relapse, the assessment of certain organizational aspects of jobs, i.e. shift-works, should become routinely assessed in IBD care[75]. Physical examination, also looking for extra-intestinal disabling manifestations[93,94] and laboratory studies including the evaluation of early biomarkers of disease activity, appear essential to identify early signs of relapse as well as to define those risk factors for which IBD patients may be more susceptible.

The identification of susceptibility to certain job risk factors seems essential to ascertain IBD fitness for work. However, current evidence is not so strong as to conclude that some agents are or are not dangerous for IBD or that certain jobs can be continued or not. In this context, future epidemiological research should firstly clarify if the greater prevalence of IBD in certain occupations is effectively related to their intrinsic characteristics, i.e. if inactive working life can negatively affect IBD, or whether it depends on the selection bias due to the forced choice of less physical demanding activities due to IBD related functional limitations and fatigue[95]. Particularly, concerning the protective role of physical activity on IBD, the statement "more physical workload can be better" may be argued[62]. However, a careful evaluation of the possible adverse health effects induced by excessively stressing conditions of posture, biomechanical strain, force, lack of recovery and combinations of these exposures, as components of physical workload, should be performed to define a correct management of IBD on work.

Medical treatment should be also considered for its role in modifying susceptibility to occupational exposures. Immunosuppressive actions of IBD drugs, such as azathioprine and mercaptopurine, as well as monoclonal antibodies are associated with an increased risk of potentially life-threathening infectious and malignant complications[96-101], thus probably making IBD workers more susceptible to the toxic action of biological as well as mutagenic or genotoxic chemical agents. Occupational epidemiological studies in this regard may be important to define the possibility for an IBD patient to remain long-term employed in particular professions. Consistently, research efforts in radiological protection should define the role that occupational exposure to ionizing radiations may play in enhancing risk for tumor development in IBD patients. This seems important, particularly for IBD workers with a more severe disease who undergo multiple x-ray diagnostic imaging procedures and require a more frequent use of immunosuppressive and/or biological drugs[102,103]. As an ulterior example, thiopurines photosensitize human skin to UVA radiation[1]. This sensitivity has been associated with an increased risk of non melanoma skin cancer in CD and requires protection against UVA and long-life dermatological surveillance[104]. Therefore, also the beneficial anti-inflammatory action exerted by UV radiation should be carefully contextualized in a case by case evaluation.

Overall, a deeper comprehension of the occupational factors involved in the causative IBD pathways and, in turn, of the effects that the disease may exert on patients' job quality and productivity may help to define the "healthy IBD patterns of work". These may include the identification of healthy levels of exposure, frequencies and durations, in respect of requirements and conditions in each specific occupation and company, with the due attention to the needs of the individual IBD employee. This may lead general practitioners, health care specialists, and occupational physicians to recognise modifiable workplace factors, to plan preventive and protective measures and to propose patients lifestyle and treatment actions to obtain a well-integrated and

successful disease management, while improving their well-being at work. In this context, the concerted action of all the prevention figures of the company, including employers, with the cooperation of the same IBD workers, according to an empowerment perspective, should be strongly encouraged[105,106].

Therefore, workers should be aware of their disorder, the possible consequences on work as well as of work-related problems and barriers and they should also be provided with information and training concerning the coping skills and social competences necessary to face them. Considering that what is more striking for IBD patients is the sense they have that they are not "keeping up" at work and have to reduce their activities[87], interventions aimed to give them adequate measures of control for job demand, together with the support from colleagues and managers and the appropriate organizational features, may be important to reduce job strain, perceived job discrimination and disability outcome. All these actions may help workers to retain their jobs and work pleasure, to increase feelings of self confidence or self efficacy in dealing with work-related problems, practical solutions and accommodations having in turn positive effects on their general health status.

Conclusions

Environmental factors are essential components in the pathogenesis of IBD. However, the potential role played by chronic occupational exposures in affecting the development and progression of CD and UC has not been clearly understood. Therefore, specific exposures to groups of potential workplace hazardous agents have been reviewed with the aim to define how certain jobs may pose risks for IBD and to describe possible underlined mechanisms of action. Unfortunately, a limited number of studies addressed this issue and uncertainty still remains regarding the affecting role of chemical and biological agents, the health effects of ionizing or non- ionizing radiation exposure, the possible consequences of shift-works, indoor, and sedentary works as well as job strain on IBD. However, critical points of discussion emerged which may give stimulus to future epidemiological research aimed to clarify the complex interplay between occupational risk factors and IBD course and, in turn, between IBD functional limitations and fitness for work.

In this scenario, occupational causative pathways for disease development and relapse, dangerous conditions of exposure, susceptibility to specific workplace risk factors according to IBD phenotype, comorbidities and treatment followed, as well as the consequences of the morbidity restrictions on career choice and expectations, ability to work, productivity and well-being should be carefully investigated. From a public health perspective this seems absolutely important considering the increasing global burden of IBD, especially in working-age adults, its consequences on patients' quality of life and ability to work as well as the impact on the health care resources. Although a certainly challenging issue, a more comprehensive knowledge may guide concerted actions of health care providers, occupational physicians, and employers together with IBD workers to plan preventive and protective measures for "healthy IBD patterns of work" and to develop innovative perspectives for an integrated management of IBD workers in differently hazardous occupational settings. All these actions may improve the quality of patients' working life, providing them coping skills, social competences and support to face job tasks and possible work related problems.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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