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Evaluating Lymphoma Risk in Inflammatory Bowel Disease

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1. Introduction

The risk of lymphoma in inflammatory bowel disease (IBD) has been a topic of great interest for many years. In 1928, the first published series of colorectal malignancies in ulcerative colitis (UC) patients included a case of lymphosarcoma, the name given to an early classification of lymphoma (Bargen, 1928). Since then a huge number of case reports, case series, cohort studies, population-based studies and meta-analyses have been presented on the topic but the matter remains controversial with conflicting results based on poor quality evidence. Most recently, a type of non-Hodgkin's lymphoma (NHL) known as hepatosplenic T-cell lymphoma (HSTCL) has understandably drawn much attention despite its rarity. HSTCL has an invariably fatal outcome despite reports of early response to treatment, it almost exclusively affects young men with Crohn's disease (CD) and seems to be linked to commonly used drugs for the management of IBD, the thiopurines and tumour necrosis factor (TNF) antagonists (Kotlyar et al., 2011). A further source of concern stems from a trend by IBD physicians to use these drugs earlier in the course of disease and also in combination because recent studies suggest that these strategies may improve outcomes (Colombel et al., 2010, D'Haens, 2009).

Proving causality has been difficult because it is difficult to separate the multiple factors involved in lymphomagenesis using the evidence that is available (see Figure 1). It has long been suspected that the chronic inflammation seen in IBD itself may be the cause of lymphoma in this setting but there has been growing concern that it is in fact the drugs used in the treatment of IBD which confers this risk. One could also speculate that it is the combination of both these factors which results in the development of lymphoma.

The case of lymphosarcoma identified by Bargen in 1928 was in an era when immunomodulators were not available for the treatment of IBD suggesting that the disease itself may predispose to lymphoma development. There are other reports of lymphoma in drug-naïve IBD patients (Aydogan et al., 2010). There does appear to be an increased risk of lymphoma in other chronic inflammatory and autoimmune conditions as well including rheumatoid arthritis (RA), primary Sjögren's syndrome, systemic lupus erythematosus (SLE) and Hashimoto's thyroiditis (Smedby et al., 2006). There is some evidence that increased severity of the disease may increase the risk of lymphoma in these conditions (Baecklund et al., 2006, Theander et al., 2006, Lofstrom et al., 2007).

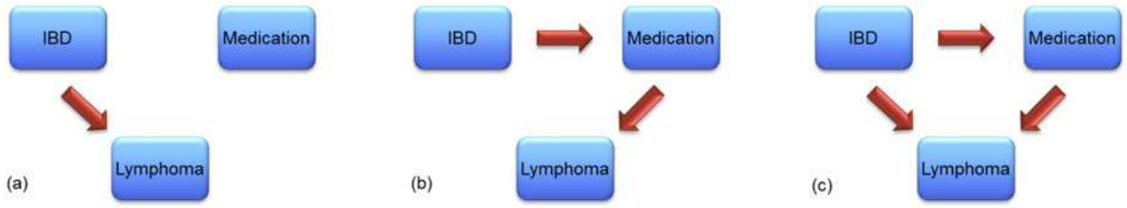

Fig. 1. Assessing the causality of lymphoma in IBD. IBD itself may be the cause of lymphoma (a), or lymphoma may be due to the medication used to treat it (b) or lymphoma may be due to a combination of the disease and the treatment (c).

Both primary and acquired immunodeficiency states have been associated with lymphoma which is important because many of the drugs used for the treatment of IBD have immunosuppressive effects. There is an increased risk of lymphoma with Human Immunodeficiency Virus (HIV) infection and in post-transplant patients treated with immunosuppressives (Serraino et al., 1992, Grulich et al., 2007b). The role of Epstein-Barr virus (EBV) is well established in lymphomagenesis in post-transplant patients and this also appears to be important in IBD patients (Dayharsh et al., 2002).

IBD is associated with significant morbidity and a small mortality (Rubin et al., 2004, Ghosh and Mitchell, 2007). It is important that IBD physicians are able to help patients weigh up the risk of lymphoma with the benefits of drugs used to treat IBD. A number of attempts have been made to quantify this risk. One of the largest population-based studies utilised a primary care database from the United Kingdom but did not find a statistically significant increased background risk of lymphoma in IBD patients (Lewis et al., 2001). A cohort study from Dublin found an alarmingly higher rate of lymphoma in their IBD patients with up to a 59-fold increase (Farrell et al., 2000). Kandiel et al performed a meta-analysis of 6 studies to evaluate the risk of lymphoma in IBD patients treated with thiopurines and found a 4-fold increased risk of lymphoma in these patients (Kandiel et al., 2005).

A number of more recent studies have been presented in the literature including large cohort studies from the United States (US) and Spain (Chiorean et al., 2010, Van Domselaar et al., 2010) as well as large population-based studies from the UK and the Netherlands (Armstrong et al., 2010, Vos et al., 2010). Most notably, the French CESAME study published in 2009 with almost 50,000 patient-years of follow up, set out to quantify the risk of lymphoma and made attempts to distinguish the background risk of lymphoma due to IBD itself from the risk conferred by its treatment (Beaugerie et al., 2009a).

This chapter aims to provide an up to date systematic review of the available literature regarding the risk of lymphoma in inflammatory bowel disease. Meta-analysis techniques have been used to pool data from multiple studies.

2. Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic, idiopathic, remitting and relapsing disorder of the gastrointestinal tract. It comprises of two main disease types, ulcerative colitis (UC) and Crohn's disease (CD), which have many similar but also certain distinct pathological and clinical characteristics.

2.1 Epidemiology

IBD affects 400 per 100,000 population in the United Kingdom but there is considerable variation worldwide with the highest prevalence in developed countries (Rubin et al., 2000). It most commonly presents in teenage or young adult life but it can affect any age and there is an approximate equal sex distribution.

2.2 Aetiology

The aetiology is unknown but evidence suggests an immune dysfunction which is triggered by an environmental factor in a genetically susceptible individual (Cho, 2008) leading to chronic inflammation and injury to the gastrointestinal tract. Many of the susceptibility genes identified in recent studies have been shown to have important roles in immune regulation but there is increasing evidence that these genes pertain to the innate immune system and are involved in the sensing or intracellular processing of bacteria (Packey and Sartor, 2008). Potential microbial triggers which have been studied include a form of enteroadherent *Escherichia coli* and *Mycobacterium paratuberculosis,* but more recent investigation suggests that a disturbance of normal enteric microflora may play a role in aetiology (Sartor, 2008). Additionally, a number of other potential environmental factors have also been studied including diet, smoking, appendiceal inflammation, certain drugs and stress but causality has remained difficult to establish (Bernstein, 2010). The particular combination of susceptible genes and environmental triggers probably varies between individuals with IBD and leads to different patterns and severity of disease.

Ulcerative colitis causes a continuous mucosal inflammation of the colorectum, whereas Crohn's disease can affect any part of the GI tract, characteristically with skip lesions and transmural inflammation. Additionally, chronic inflammation in Crohn's disease can lead to fistulising and stricturing disease behaviours (Satsangi et al., 2006).

2.3 Treatment

A curative treatment for inflammatory bowel disease is yet to be identified. Strategies for the management of IBD involve treatment of flares and maintenance of remission. Although a wide range of therapies including enteral nutrition (Zachos et al., 2007), antibiotics (Lal and Steinhart, 2006) and complementary medicines (Langmead and Rampton, 2006) are used in IBD, the mainstay of treatment has been with anti-inflammatory and immunomodulatory drugs. Corticosteroids, 5-aminosalicylates (5ASA), azathioprine (AZA), mercaptopurine (6MP), methotrexate (MTX) and cyclosporin A (CSA) have been the most commonly used drugs. In an attempt to reduce steroid exposure and maintain remission, immunomodulatory therapy is being used earlier, for prolonged periods and in combination. The concern is of an increased risk of side effects with this approach. Estimates suggest that up to 30% of patients may not respond to this treatment and may require more aggressive strategies. The increased understanding of the pathogenesis of IBD, has led to investigation in to a number of therapies targeted towards the abnormal cytokine expression seen in patients with IBD. Of these, only the monoclonal antibodies against tumour necrosis factor are currently in clinical use but other targets have been identified and are undergoing laboratory and clinical study. Infliximab (IXB) and adalimumab (ADA) are the two anti-tumour necrosis factor (anti-TNF) drugs available in the United Kingdom and a number of

studies have proven their efficacy (Hanauer et al., 2006, Hanauer et al., 2002, Jarnerot et al., 2005). A third, pegylated anti-TNF drug, certolizumab has also been studied and appears to have equivalent clinical efficacy (Sandborn et al., 2007a). Despite medical therapy, up to 50-70% of patients with CD will undergo surgery within 5 years of diagnosis and UC patients have a 20-30% lifetime risk of colectomy (Cosnes et al., 2005).

2.4 Cancer risk in IBD

The increased risk of colonic adenocarcinoma in patients with ulcerative colitis and Crohn's colitis is well documented (Rutter et al., 2006, Jess et al., 2006). One study has suggested a protective role for thiopurines in this context (Beaugerie et al., 2009b) though these patients were not corrected for co-administration of 5ASA preparations which may also have a protective role in this setting.

There also appears to be an increased risk of certain non-colorectal malignancies amongst IBD patients. In the same cohort of patients from the CESAME study, prospective data suggested a 20-fold increased risk of small bowel adenocarcinoma and suggestion of an increased risk of skin and cervical malignancy (Beaugerie et al., 2009c). In a database of over 27,000 UC patients from Sweden, the standardised incidence ratio (SIR) for all cancers was 1.46 with increased risk of malignancy of the liver, small bowel (carcinoid), prostate and breast (Hemminki et al., 2008). In a recent review of malignancies associated with thiopurine therapy, Smith et al concluded that these drugs did not increase the risk of cervical dysplasia, colonic cancer or solid organ tumours in IBD patients (Smith et al., 2010). A retrospective cohort study of over 50,000 IBD patients from the US suggested an increased risk of non-melanomatous skin cancer and that this risk was highest in patients treated with thiopurines (Odds Ratio 4.27) and biological therapies (Odds Ratio 2.18) (Long et al., 2010).

Many of these studies have also shown an increased risk of lymphoma and this will be discussed further in this chapter.

3. Lymphoma

Lymphoma is a broad term used to describe a variety of neoplasms due to proliferation of lymphoid cells. Traditionally, lymphoid neoplasms that presented with bone marrow and blood involvement were referred to by the term *leukaemia* and those that presented with a mass would be called a *lymphoma*. However, it is now appreciated that any *lymphoma* can present with or evolve in to a leukaemic picture and occasionally, *leukaemia* can present with a mass lesion.

3.1 Classification of lymphoma

The earliest classifications of lymphoma were based entirely on the morphological features of the neoplastic cells involved. Historically, lymphomas represented by large cells were known as *reticulosarcomas* and those by small cells were *lymphosarcomas* (Diebold, 2001). Later, lymphomas began to be distinguished according to their origin from B or T lymphocytes. With the development of immunophenotyping and cytogenetics, as well as an appreciation of differences in prognosis and patient stratification, more complex classification systems have developed. The World Health Organisation (WHO)

Classification of Tumours of Haemopoietic and Lymphoid Tissues, updated in 2008 (see Table 1), is now widely accepted (Swerdlow et al., 2008) and categorises lymphoid neoplasms in to those derived from:

- B cell progenitors - bone marrow derived
- T cell progenitors - thymus derived
- Mature T lymphocytes - cytotoxic or killer T cells, helper T cells or T regulatory cells
- Mature B lymphocytes - B cells or plasma cells

Non-Hodgkin's Lymphoma	
Precursor B-cell lymphomas	**Precursor T-cell and NK-cell lymphomas**
Precursor B-cell lymphoblastic lymphoma	Precursor T-cell lymphoblastic lymphoma
	Blastic NK-cell lymphoma
Mature B-cell lymphomas	
	Mature T-cell and NK-cell lymphomas
Small lymphocytic lymphoma	
Lymphoplasmacytic lymphoma	T-cell prolymphocytic leukaemia
Splenic marginal zone lymphoma	T-cell large granular lymphocytic leukaemia
Hairy cell leukaemia	Aggressive NK-cell leukaemia
Plasma cell neoplasms	Adult T-cell lymphoma/leukaemia
Extranodal marginal zone B-cell MALT lymphoma	Extranodal NK-/T-cell lymphoma, nasal type
Nodal marginal zone B-cell lymphoma	Enteropathy-type T-cell lymphoma
Follicular lymphoma (grades 1, 2, 3a and 3b)	Hepatosplenic T-cell lymphoma
Diffuse follicle centre lymphoma	Subcutaneous panniculitis-like T-cell lymphoma
Mantle cell lymphoma	Mycosis fungoides
Diffuse large B-cell lymphoma	Peripheral T-cell lymphoma unspecified
Mediastinal (thymic) large B-cell lymphoma	Angioimmunoblastic T-cell lymphoma
Intravascular large B-cell lymphoma	Anaplastic large cell lymphoma
Primary effusion lymphoma	
Burkitt lymphoma	
B-cell proliferations of uncertain malignant potential	
Lymphomatoid granulomatosis	
Post-transplant lymphoproliferative disorder	

Hodgkin's Lymphoma
Classical Hodgkin's lymphoma
Nodular sclerosis classical HL
Mixed cellularity classical HL
Lymphocyte rich classical HL
Lymphocyte depleted classical HL
Nodular lymphocyte predominant HL

Table 1. WHO Classification of Non-Hodgkin's and Hodgkin's Lymphoma (Swerdlow et al, 2008). (MALT – mucosa-associated lymphoid tissue; HL – Hodgkin's Lymphoma; NK – Natural Killer).

Hodgkin's lymphoma (formerly known as Hodgkin's disease) arises from B-cells of germinal or post-germinal centres of peripheral lymph nodes. It is pathologically and clinically distinct from other lymphoid neoplasia and generally has a good prognosis. Hodgkin's lymphoma has a distinguishing cellular composition on biopsy of lymphomatous tissues with abundant inflammatory cells and only a minority of neoplastic cells, known as Reed-Sternberg cells. Reed-Sternberg cells are large, binucleated or multinucleated containing multiple eosinophilic nucleoli and have prominent cytoplasm. Hodgkin's lymphoma (HL) is classified in to *nodular lymphocyte predominant HL* and *classical HL*, which is further subdivided in to *nodular sclerosis*, *mixed cellularity*, *lymphocyte-rich* and *lymphocyte-depleted* types (see Table 1).

The term Non-Hodgkin's lymphoma encompasses all other types of lymphoma. Although the WHO classification does not distinguish NHL on the basis of disease activity, it has classically been divided in to two subtypes:

- High-grade NHL develops quickly and aggressively.
- Low-grade or indolent NHL develops slowly and there may be no symptoms for many years.

3.2 Non-Hodgkin's lymphoma

NHL can occur in children and adults but over two-thirds are diagnosed in people aged over 60 years. There is a male preponderance with a ratio of up to 1.5 in older age groups. NHL is the fifth most common cancer in the UK with over 10,000 people diagnosed with the condition in 2007 and an age-standardised rate of 14.2 per 100,000 population (Cancer-Research-UK, 2011) (see Figure 2A). In the United States, the Surveillance Epidemiology & End Results (SEER) registry provides an age-standardised rate of 19.6 per 100,000 between 2003 and 2007 (Altekruse et al., 2010). The incidence of NHL seems to be rising in the UK

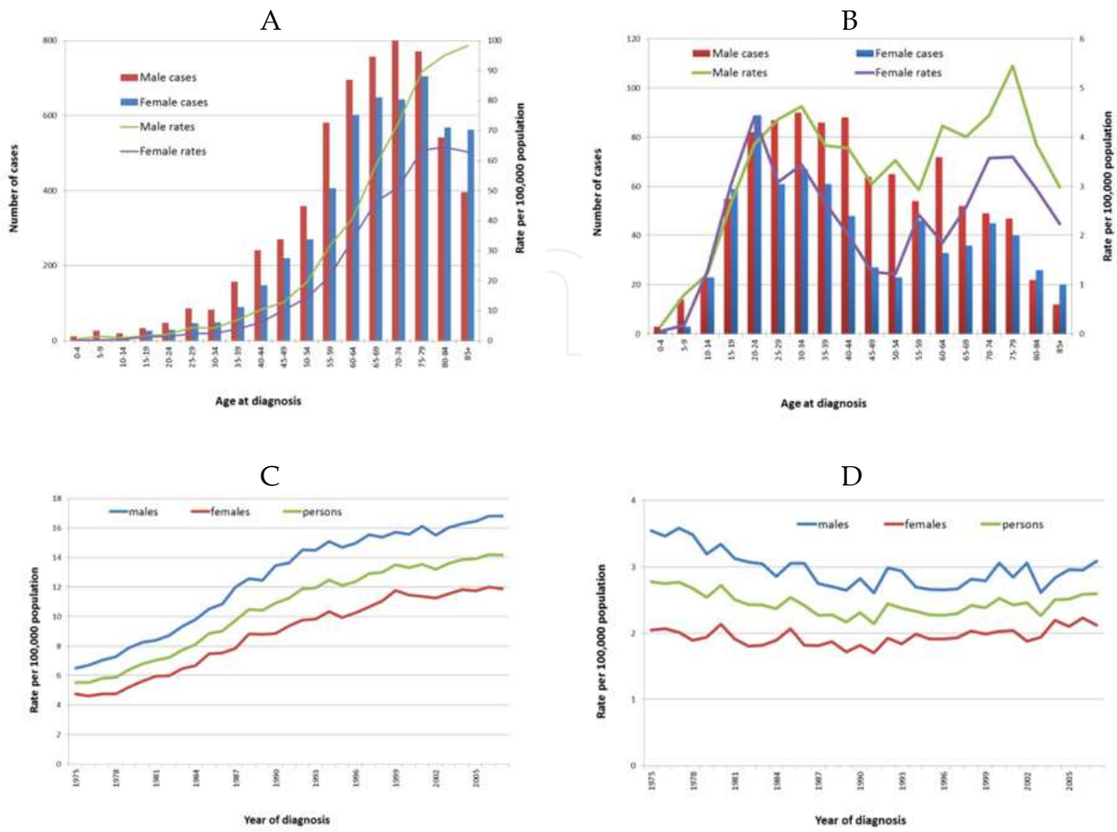

Fig. 2. Figures adapted from Cancer Research UK 2011. A: Incidence of non-Hodgkin's lymphoma by gender. B: Incidence of Hodgkin's lymphoma by gender. C: Age standardised incidence rates for non-Hodgkin's lymphoma. D: Age standardised incidence rates for Hodgkin's lymphoma.

with an increase of 35% during the 20 year interval between 1988 and 2007 (see Figure 2C). This trend seems to be reflected throughout the world. Mortality in the UK is estimated at 6.9 per 100,000 from NHL and with improvements in treatment, it is estimated that over half of patients now survive for at least 10 years following diagnosis. Up to 15% of all extra-nodal NHL presents in the GI tract (Newton et al., 1997).

A number of risk factors for the development of NHL have been studied:

- **Infectious agents** – It is thought that a proportion of the worldwide rise in incidence of NHL parallels, but is not completely explained by, the HIV epidemic. The risk of NHL in HIV and AIDS is well documented but only 3-5% of these patients will develop NHL (Serraino et al., 1992). Epstein-Barr virus has been linked to Burkitt's lymphoma and post-transplant lymphoma (Epstein et al., 1964). Other infections associated with an increased risk of NHL include *Helicobacter Pylori* (Xue et al., 2001), Hepatitis C (Dal Maso and Franceschi, 2006) and Human T-cell Lymphotropic Virus (HTLV-1) (Parkin, 2006).
- **Immunosuppression** – The use of immunosuppression following organ transplant has been shown to increase the risk of NHL and in a significant proportion of these, EBV

infection has been implicated (Kawashima et al., 1994). A recent meta-analysis suggests an 8-fold increased risk of NHL in post-transplant patients (Grulich et al., 2007b).

- **Autoimmune conditions** – Conditions such as autoimmune haemolytic anaemia, systemic lupus erythematosus and Sjögren's syndrome, where there is a longstanding stimulation of the immune system have been shown to carry an increased risk of NHL but the exact mechanisms remain poorly understood (Ekstrom Smedby et al., 2008). Coeliac disease is associated with T-cell lymphoma and less frequently, B-cell lymphoma (Chandesris et al., 2010, Oruc et al., 2010). This risk can be reduced by treatment with a gluten-free diet (Silano et al., 2008).
- **Genetic susceptibility** – The sibling or progeny of an affected individual has an approximate two-fold increased risk of developing NHL and there appears to be concordance in NHL subtype (Altieri et al., 2005).
- **Exposure to chemical carcinogens** – A number of studies and meta-analyses suggest an increased risk of NHL in individuals with occupational exposure to agricultural pesticides (Merhi et al., 2007), benzene (Steinmaus et al., 2008) and aromatic hydrocarbons (Miligi et al., 2006).
- **Diet and obesity** – Dietary factors and the risk of lymphoma are controversial. A recent study from Iowa found a 31% risk reduction for women with a higher intake of fruit and vegetables (Thompson et al., 2010). However, an earlier cohort study did not corroborate this finding (Zhang et al., 2000). NHL appears to be associated with obesity with one meta-analysis showing a relative risk of 1.4 for diffuse large B-cell NHL amongst individuals with a BMI ≥ 30 kg/m^2 (Larsson and Wolk, 2007).

3.3 Hodgkin's lymphoma

Hodgkin's lymphoma represents 15% of all lymphomas and accounts for only 0.6% of all cancers diagnosed in the United Kingdom (Cancer-Research-UK, 2011). The age standardised incidence in 2007 was 2.6 per 100,000 population in the UK and 2.8 per 100,000 in the USA (Altekruse et al., 2010) (see Figure 2B). In the UK, age-specific peaks in incidence occur in early adult life (for men at 30 to 34 years and women at 20 to 24 years old) and in later life (over 70 years). Unlike NHL, the incidence of Hodgkin's lymphoma seems to have fallen in the 1970s and has plateaued since the 1980s (see Figure 2D). This may be explained by changes in classification of different types of lymphoma. With treatment, prognosis for Hodgkin's lymphoma is good with around 78% of patients with HL diagnosed in 2007 in the UK predicted to survive for at least 10 years according to calculations by Cancer Research UK. The overall age-standardised survival rate for patients diagnosed with HL in England between 1996 and 1999 was 80% (Coleman, 1999). The Nodular Sclerosis subtype of classical HL is the commonest occurring in 60% of cases and is associated with younger age and more affluent populations.

Many of the risk factors for Hodgkin's lymphoma are similar to those of NHL but certain factors may be more important in the development of HL:

- **Genetic susceptibility** – a family history of Hodgkin's lymphoma appears to have a much more dramatic effect on risk when compared to NHL. Monozygotic twin studies suggest a 99-fold increased risk (Mack et al., 1995) and a first degree relative diagnosed with any haematological malignancy confers a two to three-fold increased risk (Chang

et al., 2005, Goldin et al., 2004). Studies from the USA suggest racial differences in susceptibility with lower risk in blacks than whites (Glaser, 1991).

- **Epstein-Barr virus** – EBV infection has long been implicated in the development of Hodgkin's lymphoma. EBV DNA can be found in 40% of cases with higher rates of association found in the paediatric population (Jarrett et al., 1996). EBV positivity is more commonly found in the Mixed Cellularity than the Nodular Sclerosis subtypes of classical HL. A previous history of infectious mononucleosis confers an increased risk of HL with an SIR of 3.49 in patients aged 15 to 34 years (Hjalgrim et al., 2000).
- **Previous non-Hodgkin's lymphoma** – Studies suggest that patients who have previously been treated for NHL are at increased risk of subsequently developing HL with a magnitude in the order of four- to twelve-fold (Travis et al., 1991, Travis et al., 1993).

4. Pathogenesis of lymphoma in IBD

Lymphoma is a clonal expansion of B- and T- lymphocytes caused by the accumulation of a series of genetic mutations affecting proto-oncogenes and tumour suppressor genes. This results in dysregulated proliferation, evasion of immune surveillance mechanisms and inhibition of apoptosis (Jaffe et al., 2001). Significant progress has been made in to the understanding of these mechanisms at a molecular level. The activation of oncogenes by aberrant chromosomal translocations as well as the inactivation of tumour suppressor genes by chromosomal deletion or mutation are both important mechanisms of lymphomagenesis (Kuppers et al., 1999). Oncogenic viruses such as EBV and HTLV1 can also introduce foreign genetic sequences into the lymphocyte genome causing disruption of normal function (Neri et al., 1991).

There are a number of genetic, environmental, infectious and iatrogenic factors amongst patients with inflammatory bowel disease which can predispose to increased susceptibility to these mechanisms for the development of lymphoma:

- **Chronic inflammation** – The pathogenesis of IBD is not completely understood but aberrations in the innate and adaptive immune response to luminal antigens has been the focus of much research. It can be postulated that the dysregulation of these immune systems seen in the chronic inflammation associated with IBD may lead to antigen-driven lymphocyte proliferation and a relatively unhindered risk of genetic and chromosomal deviations (Sokol and Beaugerie, 2009). Another possibility is that the combination of metabolites, cytokines and chemokines seen in the mucosa of IBD patients promotes mutagenesis in bystander cells. These theories may help to explain the increased risk of lymphoma seen in a variety of different auto-immune conditions and their concordance to sites of inflammation (Smedby et al., 2006). EBV related lymphoma has been reported in longstanding pyothorax of over 20 years duration (Aozasa et al., 2005). This is a condition which is regarded to be due to chronic suppuration with no autoimmunity and it is suggested that any chronic inflammatory state may predispose to lymphoma development.
- **Genetic susceptibility** – Linkage studies and genome wide association studies have identified a large array of susceptibility genes for IBD (Barrett et al., 2008). These genetic changes may also be involved in the pathogenesis of lymphoma in certain individuals. For example, the first susceptibility gene identified, IBD1, encodes for the protein

NOD1 which in its wild-type activates nuclear factor kappa B (NF-κB) (Ogura et al., 2001). NF-κB is a tightly regulated mediator of T- and B-lymphocytes and alterations in its signalling pathway have been implicated in a number of malignancies including lymphoma (Jost and Ruland, 2007). Although some plausibility exists, this link remains to be established.

- **Therapeutic immune modulation –** Immunomodulatory drugs such as the thiopurines, (azathioprine and mercaptopurine), methotrexate, and the anti-TNF drugs (infliximab, adalimumab and certolizumab) have become standard treatment for complicated IBD. These drugs exert their effects through a number of mechanisms which are incompletely understood. It is recognised that AZA and its metabolites suppress intracellular inosinic acid synthesis which interferes with intracellular purine synthesis resulting in a down regulation of B- and T-cell proliferation (Bacon and Salmon, 1987). Thiopurine nucleotides also incorporate into lymphocyte DNA disrupting structure, repair mechanisms and promoting mutagenesis (Ling et al., 1992). There is also evidence that azathioprine renders DNA highly sensitive to damage to ultraviolet (UVA) radiation and this may account for the increased risk of non-melanomatous skin cancer in patients treated with thiopurines (O'Donovan et al., 2005). A recent study showed that IBD patients on thiopurine therapy had significantly more somatic mutations in circulating T-lymphocytes than in a thiopurine-naïve control group (Nguyen et al., 2009).

  The impact of anti-TNF drugs on the risk of mutagenesis has not been adequately studied. It is conceivable that interruption of TNF signalling disrupts immune surveillance mechanisms and alters the normal detection and elimination of cells with chromosomal abnormalities.

  At higher doses, methotrexate is cytotoxic, whereas the lower doses used in IBD patients are known to alter T-cell derived cytokines in inflammatory states. It inhibits pro-inflammatory cytokines such as interleukin-12, interferon-γ and tumour necrosis factor-α whilst promoting anti-inflammatory cytokines such as interleukin-10 (van Dieren et al., 2006). These cytokines have fundamental effects on lymphocyte proliferation and function but the specific mechanisms which may contribute to potential lymphoma development are not known.
- **Immunosuppression –** The increased risk of lymphoma in patients with immunodeficiency states such as HIV infection (Serraino et al., 1992) and post-transplant immunosuppression (Grulich et al., 2007a) is well recognised and many of these cases are EBV positive. The increased risk of opportunistic infections amongst IBD patients on immunomodulators therapy is also well documented. Toruner et al identified 100 cases of opportunistic infections over an 8 year period on their database of IBD patients from the Mayo Clinic and found that treatment with thiopurines conferred an Odds Ratio of 3.1 (Toruner et al., 2008). The majority of these opportunistic infections were caused by viruses including cytomegalovirus, Herpes simplex virus and Epstein-Barr virus.

  EBV is a widely disseminated human Herpes virus which has been associated with a number of different types of B-cell lymphoma, particularly mixed cellularity and lymphocyte depleted classical Hodgkin's lymphoma, Burkitt's lymphoma and post-transplant lymphoproliferative disorder (PTLD). EBV viral load can predict risk of PTLD (Stevens et al., 2001) and cases of infectious mononucleosis with early transformation to lymphoma have been described (Owen et al., 2010). Interestingly,

Wong et al describe a case of synchronous colonic adenocarcinoma and lymphoma and demonstrated that EBV was present in the lymphomatous tissue but not in the invasive adenomatous tissue (Wong et al., 2003). A series of IBD patients from the Mayo clinic identified 12 patients diagnosed with lymphoma between 1993 and 2000, half of whom were on azathioprine therapy. The lymphomas of five out of these six patients on azathioprine were EBV positive whereas only one out of the six azathioprine-naïve patients was EBV positive (Dayharsh et al., 2002). This study suggests a link between azathioprine therapy and EBV driven lymphoma in IBD though the numbers were too small to reach statistical significance. In the CESAME prospective study of over 21,000 French IBD patients, 9 of the 13 cases of lymphoma in patients on azathioprine were EBV positive with up to 16 years exposure to the drug (Beaugerie et al., 2009a). Reijasse et al measured EBV viral loads in patients with Crohn's disease and EBV sero-positive controls. There was no difference in viral loads between the two groups irrespective of immunomodulator or biological therapy but a minority of patients did have transient, very high EBV viral loads (Reijasse et al., 2004). It is not clear, whether these peaks in EBV viral load are associated with lymphoma risk but this does appear to be the case in post-transplant patients where EBV viral load can predict this outcome (Stevens et al., 2001).

The pathobiology of EBV and its role in lymphomagenesis is complex. The host-incorporated EBV genome encodes a number of proteins with similarities to a variety of cytokines, anti-apoptotic molecules and signal transducers that can immortalise and mutate infected cells (Sokol and Beaugerie, 2009).

The risk of other oncogenic viruses such as HLTV1 is not well described in the IBD literature. A recent meta-analysis suggested a lower prevalence of *Helicobacter Pylori* infection in IBD patients compared to control groups but its association with gastric MALT-oma is well documented (Luther et al., 2010).

5. Lymphoma risk in the literature

In order to evaluate any causality between IBD and the risk of lymphoma, it is extremely important to appreciate the quality of safety data available. Frequently, this information is flawed and difficult to interpret.

5.1 Quality of data

Randomised controlled drug trials collate information regarding adverse events but they are powered to elucidate differences in efficacy and not safety. They also tend to have relatively small numbers and a short follow up period which may not reflect the true incidence of late or delayed adverse events. Some useful safety information is available from observational studies of large populations. These have large numbers and long follow up but are susceptible to indication bias and often have other confounding factors. Case controlled series have an efficient methodology but may be hampered by the shortcomings of control selection. The most common form of safety data comes from case reports and case series which are able to identify rare risks. However, the inherent positive bias with this form of evidence, does not allow it to be utilised for risk quantification or for providing proof of causality. Post marketing surveillance, a form of *pharmaco-vigilence*, is another important source of safety data. This information may be made available through institutional

reporting schemes, such as the FDA's Adverse Events Recording System (AERS) in the United States (FDA, 2011) or the MHRA's Yellow Card System in the United Kingdom (MHRA, 2011). Important information may come from drug specific data such as the TREAT registry (Lichtenstein et al., 2006), which is an on-going large-scale observational registry that was designed to examine the safety of Crohn's Disease therapies including infliximab. This type of data provides a *real world* experience with a heterogeneous group of patients suffering a variety of co-morbidities and taking concomitant medication. However, such schemes are generally voluntary systems which are prone to under-reporting and hence an under estimation of true incidence.

The low incidence of lymphoma, even in higher risk populations, poses a challenge to evaluating this risk. The incidence of all types of lymphoma diagnosed in the United Kingdom in 2007 was about 17 cases per 100,000 population (Cancer-Research-UK, 2011). A study of almost 3 million individuals would be necessary to detect an adverse event of this frequency with a confidence interval of 95%. No studies of this magnitude are available nor are likely to be available in the future.

5.2 Available data

The literature pertaining to the risk of lymphoma amongst IBD patients is dominated by case reports and case series. However, a number of large population studies have also been published over the last three decades which have been extremely valuable because they allow approximation of the risk of lymphoma (Loftus et al., 2000, Lewis et al., 2001, Beaugerie et al., 2009a, Greenstein et al., 1985). This information must be considered within the limitations of this type of study. A small number of meta-analyses have attempted to combine information from these population-based studies (Kandiel et al., 2005, Siegel et al., 2009). Post-marketing surveillance for drugs such as azathioprine, mercaptopurine and methotrexate are not available but some data regarding the newer anti-TNF therapies in IBD now exists (Lichtenstein et al., 2006).

Interest in the risk of developing lymphoma in the context of IBD and its treatment has grown exponentially (see Figure 3). This coincides with increasing use of immunomodulators in the management of IBD and concerns over their safety. Prior to the 1990s, only sporadic case reports and case series were available. More recently, a number of population based studies, review articles and meta-analyses have been published which are discussed in this report.

Additionally, changes in the classification of lymphoid neoplasia makes evaluation of the literature difficult in certain circumstances where there are overlapping features between diagnoses (Swerdlow et al., 2008).

6. Presentation of lymphoma in IBD

The presentation of lymphoma amongst IBD patients is very heterogenous and occurs in both Crohn's disease and ulcerative colitis.

There are abundant reports of lymphoma of the gastro-intestinal tract mimicking presentations of Crohn's disease (Kashi et al., 2010, Kang et al., 2007, Hurlstone, 2002, Jouini et al., 2001, Vincenzi et al., 2001, Camera et al., 1997, Maaravi et al., 1993, Scully et al., 1993,

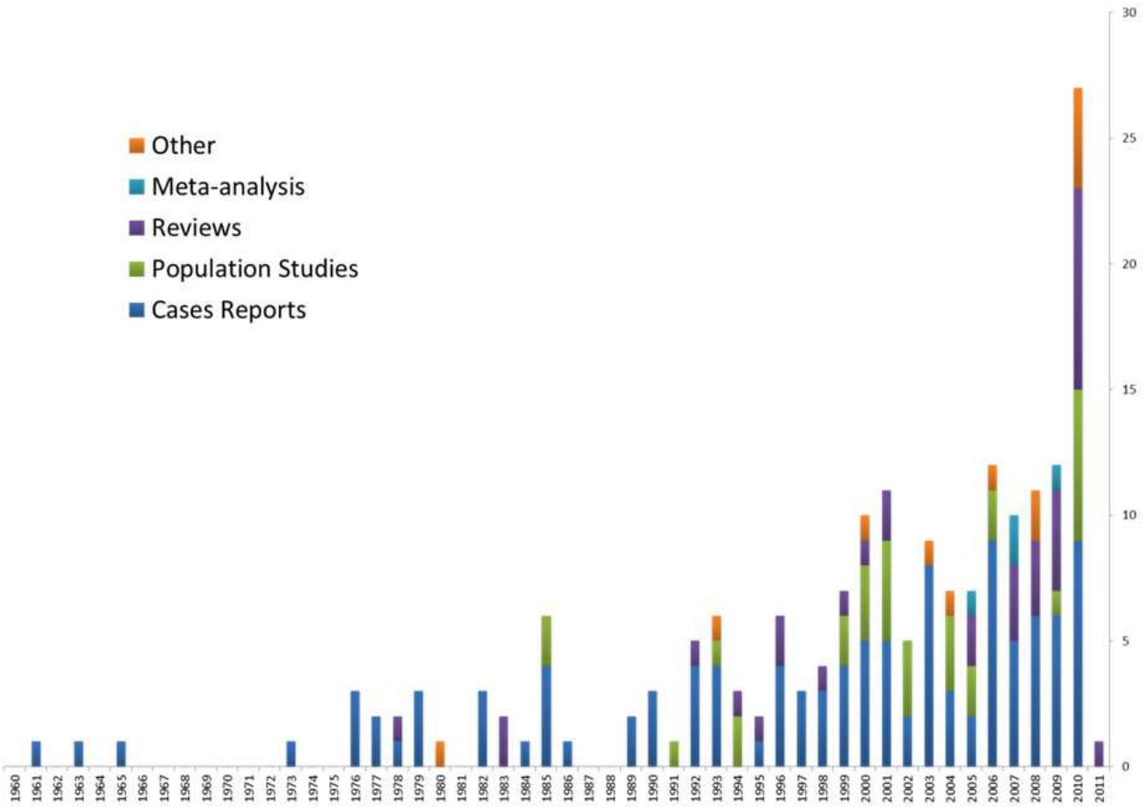

Fig. 3. Medline cited publications regarding lymphoma risk in IBD patients since 1950.

McCullough et al., 1992, Pohl et al., 1991, Bartram and Chrispin, 1973) and ulcerative colitis (Isomoto et al., 2003, Luo et al., 1997, Wagonfeld et al., 1976, Myerson et al., 1974, Parnes et al., 1974, Friedman et al., 1968, Federman et al., 1963). Clearly, lymphoma of the GI tract frequently occurs in the absence of inflammatory bowel disease. In a series from the Mayo Clinic spanning 40 years in the pre-biologic era, of the 2,332 cases of primary intestinal lymphoma identified, only 15 patients had concomitant inflammatory bowel disease (Holubar et al., 2010). These cases are not discussed further here.

6.1 Intestinal and extra-intestinal lymphoma

Lymphoma may present at a variety of sites amongst IBD patient but these can broadly be classified as intestinal and extra-intestinal.

Up to 15% of extra-nodal lymphoma involves the GI tract (Newton et al., 1997). In a series of 15 cases of intestinal lymphoma, 60% were colorectal, 27% involved the small bowel and there were individual cases in the stomach, duodenum and ileal pouch, each constituting 6.25% of this series (Holubar et al., 2010). In 80% of these cases, the location of the lymphoma was congruous to the site of IBD. In another series of 14 colorectal lymphomas, the commonest sites were the caecum and rectosigmoid but these were not IBD patients (Wong and Eu, 2006). Gastric mantle cell lymphoma has also been reported by Raderer et al in a patient with a 14 year history of Crohn's disease (Raderer et al., 2004). Ileal pouch lymphoma has also been reported in a number of other publications (Sengul et al., 2008,

Frizzi et al., 2000, Nyam et al., 1997) and one publication suggests EBV may be involved in the aetiology (Schwartz et al., 2006). Lymphoma at an ileostomy site has also been reported (Pranesh, 2002). Metachronous colonic lymphoma (Hill et al., 1993) as well as synchronous colonic adenocarcinoma and lymphoma (Hope-Ross et al., 1985, Nishigami et al., 2010) have been described in IBD patients.

In addition, a number of extra-intestinal sites of lymphoma amongst IBD patients have been reported. Hepatosplenic T-cell lymphoma (HSTCL) has become a concern amongst IBD physicians and this will be discussed in further detail. Owen et al reports a patient with UC treated with azathioprine who develops a B-cell lymphoproliferative disorder on her eyelid following a recent illness diagnosed as infectious mononucleosis (Owen et al., 2010). Deneau et al recently described the case of a child with an EBV-driven NK-cell lymphoma involving the skin and GI tract causing hepatosplenomegaly (Deneau et al., 2010). Other cutaneous lymphomas are described in the literature (Adams et al., 2004, Martinez Tirado et al., 2001). Vulval and peri-anal lymphoma has also been identified (Winnicki et al., 2009, Sivarajasingham et al., 2003). Kastner et al present a young lady with ulcerative colitis, previously treated with azathioprine, who presents with seizures and is found to have cerebral lesions of high grade B cell lymphoma (Kastner et al., 2007). Plamacytoma (a mature B-cell lymphoma) can present as a paravertebral mass (Redmond et al., 2007).

6.2 Clinical presentation

Many of the symptoms of intestinal lymphoma are very similar to those caused by inflammatory bowel disease. The most commonly presenting symptom is bloody diarrhoea occurring in almost three quarters of cases (Holubar et al., 2010, Wong and Eu, 2006). Other common symptoms include abdominal pain, weight loss and sweats. Presentation with bowel obstruction and perforation occurs less frequently (Holubar et al., 2010, Bourikas et al., 2008). Diagnosis of lymphoma is frequently made following laparotomy. Endoscopic appearances can be diverse, manifesting as ulceration, polyps or masses.

Duration of IBD before development of lymphoma appears to be very variable between individual cases. Shepherd et al reported 10 cases of colorectal lymphoma complicating inflammatory bowel disease (6 patients with UC and 4 with CD) (Shepherd et al., 1989). The duration of inflammatory bowel disease varied from 30 months to 20 years in these cases. In the CESAME study, there was between 1 to 16 years of exposure to thiopurines before lymphoma diagnosis (Beaugerie et al., 2009a).

More unusual presentations of lymphoma include jaundice due to a nodal mass at the porta hepatis in a patient with Crohn's disease (Parasher et al., 1999), spontaneous tumour lysis syndrome in a Crohn's patient with a plasmacytoma (Froilan Torres et al., 2009), nephrotic syndrome in a patient with Hodgkin's lymphoma and UC (Basic-Jukic et al., 2002), and jaundice due to vanishing bile duct syndrome in a patient with Hodgkin's lymphoma and IBD (DeBenedet et al., 2008).

7. Population and cohort studies

A number of population and cohort studies have been published and are described below. The standardised incidence ratio (SIR) is defined as the ratio between observed and

expected events in a study population. This is a useful comparator to analyse the risk of lymphoma in IBD patients and has been used in much of the literature.

Incidence and Risk Factors for Lymphoma in a Single-Center Inflammatory Bowel Disease Population (Chiorean et al 2010)

A cohort study identified 3,585 patients attending a single IBD centre in Indianapolis, USA. Data was collected retrospectively between 1990 and 2005. Since 2005, the registry was updated prospectively. An electronic database was interrogated for diagnoses of Hodgkin's and non-Hodgkin's lymphoma and compared to expected age-standardised incident rates from the SEER registry. This study also used a case matched control group with a ratio of 1:10 to determine risk factors for lymphoma development. The population consisted of 2,277 Crohn's patients and 1,308 UC patients with no significant demographic differences between groups. 8 patients were identified with a diagnosis of lymphoma (6 NHL and 2 HL). Only 3 patients had thiopurine exposure but 2 of these patients had also received TNF antagonists and were EBV positive. The study did not find any statistically significant relationship between diagnosis of lymphoma with demographics, drug therapy, duration of treatment and length of diagnosis. Based on SEER statistics, the overall SIR for lymphoma was 1.6 (95% CI 0.6 to 3.0) but this was not significant. (Chiorean et al., 2010)

Risk of Cancer in Inflammatory Bowel Disease Treated with Azathioprine: A UK Population-Based Case-Control Study (Armstrong et al 2010)

This was a nested case-control study using the General Practice Research Database (GPRD) in the UK which was interrogated for patients with a diagnosis of IBD, any previous prescriptions for azathioprine or mercaptopurine and a subsequent diagnosis of any cancer. The GPRD is the largest longitudinal primary care database in the world containing approximately 50 million patient years of data. The control group consisted of all IBD patients who had not been diagnosed with a cancer. The total number of patients included in the study was 15,471 and 15 patients had diagnoses of lymphoma (2 HL, 6 NHL and 7 unspecified). The group found the risk of lymphoma for patients who had ever received thiopurines versus those that had never received such drugs was increased by an OR of 3.22 (95% CI 1.01 to 10.18). An SIR was not calculated for the risk of lymphoma compared to the background population in this study. (Armstrong et al., 2010)

Lymphoproliferative Disorders in an Inflammatory Bowel Disease Unit (Van Domselaar et al 2010)

This was a retrospective study of 911 patients attending a tertiary IBD clinic in Madrid followed up for a mean of 32.3 months. There were 7 cases of lymphoma identified in the cohort (6 NHL and 1 HL). The mean age at diagnosis was 53 years and the mean time from IBD to lymphoma diagnosis was 4.82 years (range 0 to 20 years). Three cases were associated with EBV. An SIR of 3.72 can be calculated from the figures presented though this was not calculated by the authors. (Van Domselaar et al., 2010)

Risk of Malignant Lymphoma in Patients with Inflammatory Bowel Diseases: A Dutch Nationwide Study (Vos et al)

The authors identified all IBD patients diagnosed with lymphoma between 1997 and 2004 from a Dutch nationwide histo- and cyto-pathology database known as PALGA. Age adjusted incidence of lymphoma was obtained from the Netherlands Central Bureau for

Statistics between these years. After excluding incomplete data, 44 cases of lymphoma were identified in 17,834 IBD patients. The calculated SIR was 1.27 (95% CI 0.92 to 1.68) and the authors concluded that there was no increased risk of lymphoma in IBD patients. However, the SIRs in the age groups 35-39 years and 45-49 years were 9.32 and 3.99 respectively and these did reach significance. Only 43% of patients were exposed to thiopurines. Of the patients in whom EBV status could be obtained, 92% (11/12) with EBV positive lymphoma were taking a thiopurine compared to 19% (4/21) who were EBV negative ($p<0.001$). (Vos et al., 2010)

Lymphoproliferative Disorders in Patients Receiving Thiopurines for Inflammatory Bowel Disease: A Prospective Observational Cohort Study (Beaugerie et al 2009)

This is a frequently quoted study which set out to objectively clarify the risk of cancer in IBD patients. 19,486 patients were enrolled into a prospective French nationwide database called CESAME (Cancers et Surrisque Associé aux Maladies inflammatoires intestinales En France) between May 2004 and June 2005 and followed up until 31st December 2007. This equated to almost 50,000 patient-years of follow up. Details regarding patient demographics, type of IBD, date of diagnosis, disease location, history of malignancy and exposure to immunosuppressive therapy including thiopurines, methotrexate and anti-TNF agents were collected. A total of 23 patients were identified who developed lymphoma (22 NHL, 1 HL). The SIR is not presented in this study but later discussed in a review article by the same author at 1.86 (95% CI 1.1 to 3.0) (Sokol and Beaugerie, 2009). The HR for patients taking AZA versus those who were not was 5.28 (95% CI 2.01 to 13.9). There was a trend towards increased risk of lymphoma with anti-TNF therapy but this did not reach statistical significance. No patients taking methotrexate developed lymphoma in this study. (Beaugerie et al., 2009a)

Risk of Haematopoietic Cancer in Patients with Inflammatory Bowel Disease (Askling et al 2005)

This was a huge population based cohort study using prospectively recorded data from a number of large Swedish IBD databases (Uppsala cohort, Stockholm County cohort, Stockholm pan-colitis register and Swedish in-patient register). 47, 679 patients were recruited in total and 180 lymphomas were detected. Compared to national Swedish cancer statistics, the calculated SIR was 1.09 in this study. (Askling et al., 2005)

Intestinal and Extra-Intestinal Cancer in Crohn's Disease: Follow-up of a Population-based Cohort in Copenhagen, Denmark (Jess et al 2004)

374 patients with a diagnosis of Crohn's disease were followed up for a median of 17 years in Copenhagen County. No lymphomas were observed in this population. (Jess et al., 2004)

Long-term Risk of Cancer in Ulcerative Colitis : A Population-based Cohort Study from Copenhagen County (Winther et al 2004)

This study is from the same cohort of patients investigated in the above study by Jess et al. In the sample of 1160 UC patients, the median follow up was 19 years. A total of 124 malignancies were observed including only 1 lymphoma. The SIR for lymphoma risk works out at 0.5 (95% CI 0.1 to 0.8) in this study. This suggests a protective role of UC in lymphomagenesis which is not demonstrated in any other studies. This result is likely to be artefactual due to the finding of only 1 case of lymphoma in the study. (Winther et al., 2004)

Inflammatory Bowel Disease is not Associated with an Increased Risk of Lymphoma (Lewis et al 2001)

This is an important large retrospective cohort study utilising the General Practice Research Database that was also used by Armstrong et al above. All patients coded with a diagnosis of UC or CD were eligible for inclusion and cross-matched for a diagnosis of HL and NHL. Prescriptions for AZA and 6MP were also analysed and an average dose per day was calculated. A control cohort was randomly selected but matched for age, sex and primary care practice. The study identified 6,605 patients with CD, 10,391 patients with UC and there were 60,506 patients in the control group. 18 patients were identified with lymphoma in this cohort compared with an expected 13.6 cases and an SIR of 1.32 (95% CI 0.78 to 2.10). The relative risk compared to the control group was 1.20 (96% CI 0.67 to 2.06). The authors concluded that IBD was not associated with an increased risk of lymphoma. Even on sub-analysis of patients prescribed thiopurines, there was no significant increased risk of lymphoma. (Lewis et al., 2001)

Cancer Risk in Patients with Inflammatory Bowel Disease – A Population-based Study (Bernstein et al 2001)

Population-based data was obtained from the University of Manitoba IBD database which was extracted from the Manitoba Health administrative databases in Winnipeg, Canada. An age and gender matched non-IBD control group was randomly selected with a ratio of 1:10. 5,529 patients were included in the study and the overall incidence of cancer was 690.2 per 100,000 population. 16 cases of NHL were identified but no cases of HL. This study found an incident rate ratio of 1.59 (95% CI 0.6 to 3.3) for the risk of lymphoma. The risk of developing lymphoma was highest in male patients with Crohn's disease where the IRR was calculated at 3.63 (95% CI 1.53 to 8.62). (Bernstein et al., 2001)

The Incidence of Lymphoid and Myeloid Malignancies Among Hospitalized Crohn's Disease Patients (Arseneau et al 2001)

This was a retrospective cohort study. Discharge data for all in-patients in the Commonwealth of Virginia and the State of California was analysed to identify patients who were admitted to hospital with a diagnosis code for Crohn's disease. These patients were then followed up for 2 years examining for new diagnostic codes for lymphoma. The patients were matched with a control group who had admissions to hospital over the same period with no history of CD. 5,426 patients were discharged from hospital in the study period with a diagnosis of CD. 10 cases of NHL were identified and an OR of 2.04 (95% CI 1.33 to 3.14) was calculated. (Arseneau et al., 2001)

Hodgkin's Disease Risk is Increased in Patients with Ulcerative Colitis (Palli et al 2000)

This is a population based study of all patients with IBD residing in Florence, Italy between 1978 and 1992. A total of 920 patients were followed up for a median of 11 years. An increased risk of Hodgkin's disease was observed in patients with UC with 6 cases identified and an SIR calculated at 9.3 (95% CI 2.5 to 23.8). The broad confidence interval makes it difficult to assess the validity of these findings in this study. (Palli et al., 2000)

Risk of Lymphoma in Inflammatory Bowel Disease (Loftus et al 2000)

This was a retrospective study of all incidence cases of IBD in Olmsted County, Minnesota between 1950 and 1993 examined for the diagnosis of lymphoma. The authors comment that

the use of immunomodulators during this time frame was rare and hoped to be able to demonstrate the baseline risk of lymphoma in IBD patients. Expected cases of lymphoma were derived from published Olmsted County age-standardised incidence rates. 454 patients were diagnosed with IBD in the study period. Only 1 case of NHL was identified in the entire cohort and an SIR of 1.0 (95% CI 0.03 to 5.6) was calculated. The observed number of patients with lymphoma is so small in this study that the results are very difficult to interpret. (Loftus et al., 2000)

Increased Incidence of non-Hodgkin's Lymphoma in Inflammatory Bowel Disease Patients on Immunosuppressive Therapy but Overall Risk is Low (Farrell et al 2000)

This study interrogated an IBD database of 782 IBD patients in Dublin. 30% of patients were taking immunomodulators therapy with the majority on azathioprine. A total of 30 cancers were identified with 4 cases of NHL compared with the expected 0.53 cases. These figures produced an SIR of 31.2 (95% CI 2.0 to 85.0). All these patients were on immunosuppressive therapy (2 on MTX and 2 on AZA). Calculating an SIR for patients on immunosuppressive therapy, the authors found a 58.8 –fold increased risk. These rather alarming results have not been duplicated. The confidence intervals are very broad and difficult to interpret. A possible explanation for these outlying results is that this retrospective study was initiated shortly after two new cases of lymphoma had been identified in this cohort. This clustering of cases may have had a significant impact on risk calculations. (Farrell et al., 2000)

Increased Risk of Cancer in Ulcerative Colitis: A Population-based Cohort Study (Karlén et al 1999)

A cohort of 1547 patients with UC in Stockholm County diagnosed between 1955 and 1984 were followed on the National Cancer Register and the National Cause of Death Register until 1989. Comparisons were made with regional cancer statistics. 3 lymphomas were identified in the cohort with an SIR of 1.2 (95% CI 0.3 to 2.5). (Karlen et al., 1999)

Long-term Neoplasia Risk after Azathioprine Treatment in Inflammatory Bowel Disease (Connell et al 1994)

This study from St Mark's Hospital in London followed up 755 IBD patients taking azathioprine for a median of 12.5 months. The overall risk of cancer was similar to that of the background population with an SIR of 1.27 but there was an increased risk of colorectal malignancy with an SIR of 6.7. No cases of lymphoma were identified in this cohort. (Connell et al., 1994)

Crohn's Disease and Cancer: A Population-based Cohort Study (Persson et al 1994)

This study was performed by the same group and used similar methodology to the Karlén study from Stockholm described above. 1251 patients with Crohn's disease were followed up. There was an increased incidence of small bowel and upper GI tract malignancies. 4 cases of lymphoma were identified with an SIR of 1.4 (95% CI 0.4 to 3.5). (Persson et al., 1994)

Extracolonic Malignancies in Inflammatory Bowel Disease (Ekbom et al 1991)

This was a population based cohort with IBD consisting of 4776 patients from the Uppsala Health Care Region in central Sweden. All patients were followed up in the Swedish Cancer Registry and the Registry of Causes of Death for a diagnosis of malignancy. 9 cases of

lymphoma were found in this cohort with an expected 8.9 cases. The SIR was 1.0 (95% CI 0.5 to 1.6). (Ekbom et al., 1991)

Extraintestinal Cancers in Inflammatory Bowel Disease (Greenstein et al 1985)

This was a retrospective case note review of patients with a diagnosis of IBD at the Mount Sinai Hospital, New York. 1961 patients were studied with a total of 8 lymphomas (6 NHL and 2 HL). The expected frequency of lymphoma expected was 1.67 giving an SIR of 4.79. (Greenstein et al., 1985)

8. Baseline risk of lymphoma in IBD

An estimate of the baseline lymphoma risk has been made for this chapter using a meta-analysis technique. Populations and cohort studies were identified using the MEDLINE database provided by the US National Library of Medicine (NLM). Statistical analysis was carried out using the Review Manager (RevMan) Version 5 software which is provided by The Cochrane Collaboration, Copenhagen, for preparing and maintaining Cochrane reviews and meta-analyses. Dichotomous data was entered and analysed using the Mantel-Haentszel statistical technique and a 95% confidence interval assuming a Poisson distribution of lymphoma incidence. Studies were only weighted by their size. Graphical representation of results is performed with a Forest plot indicating 95% confidence intervals.

A total of 145,208 patients from 16 trials were included in the meta-analysis (see Figure 4). This produced a cumulative Risk Ratio of 1.29 (95% CI of 1.10 to 1.51, p=0.002). However, this included hospital-based and specialist clinic cohorts which can introduce selection bias. The meta-analysis was repeated only including the 12 population-based studies (see Figure 5). 133,463 patients were included. This did not have a very large effect on the results and the Risk Ratio falls slightly to 1.23 (95% CI 1.05 to 1.45, p=0.01). In both analyses, the test for heterogeneity was not significant and the test for overall effect was 3.15 and 2.52 respectively.

	Observed		Expected			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year
Greenstein et al 1985	8	1961	2	1961	0.7%	4.00 [0.85, 18.81]	1985
Ekbom et al 1991	9	4776	9	4776	3.3%	1.00 [0.40, 2.52]	1991
Persson et al 1994	4	1251	3	1251	1.1%	1.33 [0.30, 5.95]	1994
Karlen et al 1999	3	1547	3	1547	1.1%	1.00 [0.20, 4.95]	1999
Farrell et al 2000	4	782	0	782	0.2%	9.00 [0.49, 166.88]	2000
Loftus et al 2000	1	454	1	454	0.4%	1.00 [0.06, 15.94]	2000
Arseneau et al 2001	10	5426	5	5426	1.8%	2.00 [0.68, 5.85]	2001
Bernstein et al 2001	16	5529	10	5529	3.7%	1.60 [0.73, 3.52]	2001
Lewis et al 2001	18	16996	14	16996	5.1%	1.29 [0.64, 2.58]	2001
Winther et al 2004	1	1160	2	1160	0.7%	0.50 [0.05, 5.51]	2004
Askling et al 2005	180	47679	166	47679	60.9%	1.08 [0.88, 1.34]	2005
Beaugerie et al 2009	23	19846	12	19486	4.4%	1.88 [0.94, 3.78]	2009
Armstrong et al 2010	15	15471	3	15471	1.1%	5.00 [1.45, 17.27]	2010
Chiorean et al 2010	8	3585	5	3585	1.8%	1.60 [0.52, 4.89]	2010
Vos et al 2010	44	17834	35	17834	12.8%	1.26 [0.81, 1.96]	2010
Von Domselaar et al 2010	7	911	2	911	0.7%	3.50 [0.73, 16.80]	2010
Total (95% CI)		**145208**		**144848**	**100.0%**	**1.29 [1.10, 1.51]**	
Total events	351		272				

Heterogeneity: Chi² = 15.74, df = 15 (P = 0.40); I² = 5%
Test for overall effect: Z = 3.15 (P = 0.002)

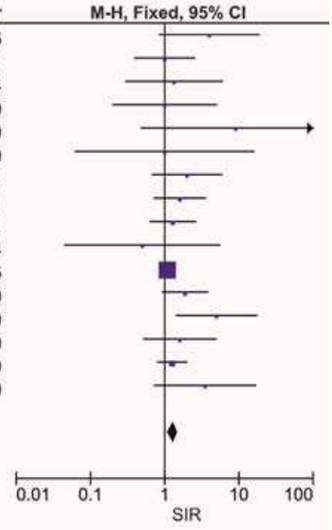

Fig. 4. Meta-analysis of population and cohort studies to evaluate the baseline risk of lymphoma.

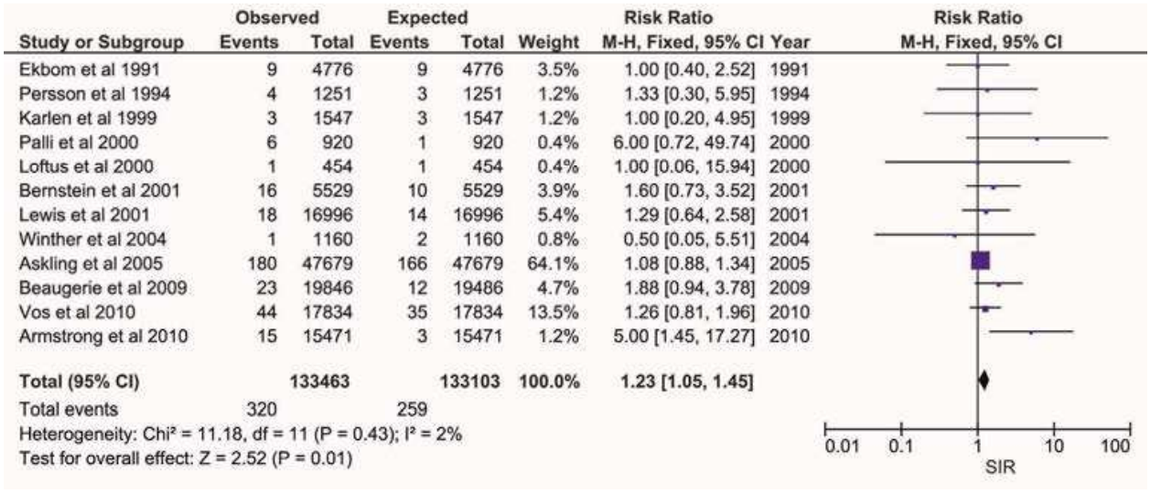

Fig. 5. Meta-analysis of population studies only to evaluate risk of lymphoma.

These findings would suggest that there is only a small (if any) increased risk of lymphoma in IBD patients compared to the general population.

9. Risk of lymphoma with thiopurines

The risk of lymphoma in patients treated with thiopurines has been analysed by including all cohort and population-based studies (see Figure 6). There were 35805 patients included from 7 studies. The test for heterogeneity was not significant and the test for overall effect was 4.03. Overall Risk Ratio is calculated at 3.54 (95% CI 1.91 to 6.54, $p<0.0001$) confirming the suspected increased risk of lymphoma in patients treated with azathioprine or mercaptopurine.

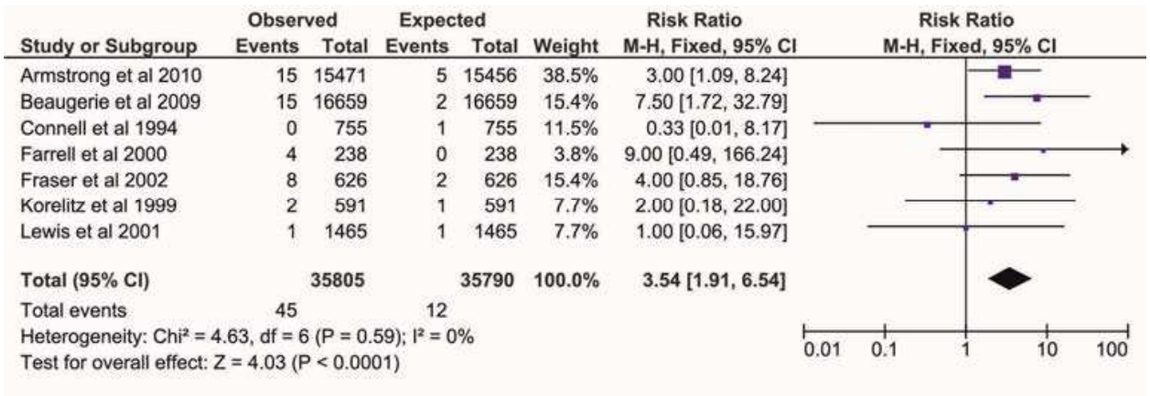

Fig. 6. Meta-analysis to evaluate the risk of lymphoma in patients treated with thiopurines.

10. Comparison to other published meta-analyses

Only three meta-analyses have investigated the background risk and the thiopurine-associated risk of lymphoma in IBD patients. Results from Von Roon et al and Kandiel et al support the findings of the meta-analyses produced here but the work by Masunaga et al shows some disparity.

The Risk of Cancer in Patients with Crohn's Disease (Von Roon et al 2007)

Meta-analytical techniques were used to quantify the risk of intestinal, extra-intestinal and haemopoietic malignancies in Crohn's patients. 34 studies were included with a total of 61,122 patients. Overall pooled estimates were obtained using a random-effects model. The relative risk of lymphoma was 1.42 (95% CI 1.16 to 1.73). This publication, similar to the meta-analysis presented in this dissertation, suggests only a slight increased baseline risk of lymphoma compared to the general population. (von Roon et al., 2007)

Increased Risk of Lymphoma among Inflammatory Bowel Disease Patients Treated with Azathioprine and 6-Mercaptopurine (Kandiel et al 2005)

This meta-analysis sought to provide an estimate of the relative risk of lymphoma among IBD patients treated with thiopurine therapy. Inclusion criteria were strict with only cohort studies in the English language, where the exposed group had received AZA or 6MP and the study had been specifically designed to evaluate the risk of cancer. 6 studies were included with a total of 3891 IBD patients. Similar methodology was used to the presented meta-analysis in this dissertation. Results were also pooled using a Mantzel-Haenszel method but weighting was proportioned to the inverse variance rather than the population size.

The pooled data identified 11 cases of lymphoma whilst the expected number of cases was 2.63, resulting in an SIR of 4.18 (95% CI 2.07 to 7.51). This is similar in magnitude to the SIR in the meta-analysis presented here at 3.54. However, Kandiel et al found a significant test of heterogeneity explained by the substantially higher rates of lymphoma in two of the included studies (Farrell et al 2000 and Connell et al 1994). Exclusion of these studies did not produce a large impact on the pooled SIR. (Kandiel et al., 2005)

Meta-Analysis of Risk of Malignancy with Immunosuppressive Drugs in Inflammatory Bowel Disease (Masunaga et al 2007)

This group aimed to compare the risks of developing malignancy in IBD patients receiving immunosuppressants with those who were not. 9 cohort studies met the inclusion criteria. Where a control group for comparison was not available in these studies, Masunaga et al compared incidence of lymphoma with that of the University of Manitoba IBD Database used by Bernstein et al in their population study. The meta-analysis technique calculated a Weighted Mean Difference (WMD) rather than SIR at 0.0 (95% CI -0.8 to 0.7). These results were not significant and the authors concluded that there was no increased risk of lymphoma in IBD patients treated with immunosuppressives. This result seems to deviate from the findings of the larger recent population studies (such as the CESAME study), that of the meta-analysis performed by Kandiel et al and the meta-analysis presented in this dissertation. This may be due to bias introduced by the arbitrary control method used to calculate expected lymphoma rates in control groups in this meta-analysis. (Masunaga et al., 2007)

11. Risk of lymphoma in patients treated with methotrexate

There is virtually no data for the risk of lymphoma in IBD patients taking methotrexate. Only 2 cases of lymphoma associated with MTX treatment for inflammatory bowel disease have been reported in the literature (Farrell et al., 2000). In this study, 31 patients were receiving methotrexate and two of them were subsequently diagnosed with lymphoma. One

of these patients had also received cyclosporin A. As discussed earlier, the authors of this study found risk of lymphoma in their IBD cohort to be much higher than is reported elsewhere and this deviation may have resulted from a clustering of lymphoma diagnosis at the time of investigation. No reliable determination of risk can be obtained from this study.

In the large CESAME study, almost 700 patients (4%) had on-going or previous MTX use but no cases of lymphoma were identified in these patients (Beaugerie et al., 2009a).

Some information can be extrapolated from studies of other inflammatory conditions though this data must be applied with caution in IBD because the risk of the drug cannot be easily separated from the risk of the disease itself. Lymphoma associated with methotrexate has been reported in the rheumatology literature.

A large observational study of rheumatoid arthritis patients treated with methotrexate and/or anti-TNF drugs followed up 18,572 patients biannually found an SIR of 1.7 (95% CI 0.9 to 3.2). The authors concluded that there was no significant increased risk of lymphoma with methotrexate therapy over baseline (Wolfe and Michaud, 2004). A French 3 year prospective population study of RA patients treated with methotrexate identified 18 cases of NHL and 7 cases of HL. Compared to national population statistics, the authors found no increased risk of NHL but a Standardised Mortality Ratio of 7.4 (95% CI 3.0 to 15.3) for HL in their cohort (Mariette et al., 2002).

There are no similar studies in IBD and it is not possible to evaluate a relative or absolute risk of lymphoma with methotrexate therapy. However, it would appear that the risk of lymphoma in this patient group is low.

12. Risk of lymphoma in patients treated with anti-TNF drugs

It is difficult to assess the specific risk of anti-TNF drugs in IBD patients because most patients will have had thiopurine or methotrexate exposure prior to using this modality of treatment. The bulk of the literature regarding anti-TNF drugs is for the use of infliximab in Crohn's disease and little is known regarding differences in safety when used in UC.

A meta-analysis has recently been carried out by Siegel et al with very comprehensive methodology (Siegel et al., 2009). In this meta-analysis, 26 studies with a total of 8905 patients with 21,178 patient-years of exposure to anti-TNF drugs were included (see Table 2). 22 studies were regarding infliximab, 3 regarding adalimumab and only one regarding certolizumab. All the included studies were for the treatment of Crohn's disease through randomised controlled trials, cohort studies and case series. There were 13 cases of NHL with a mean age at presentation of 52 years and 62% male. 10 out of the 13 patients with NHL had received dual therapy with immunomodulators and anti-TNFs. The SIR for the risk of lymphoma in patients treated with anti-TNF drugs was 3.23 (95% CI 1.5 to 6.9) compared to SEER statistics (see Table 3). However, the majority of the lymphoma patients had previously had exposure to immunomodulators and the SIR calculated for anti-TNF therapy should actually be referred to as the risk of combination therapy. This numerical result is in the same order of magnitude as the risk for immunomodulator therapy alone (as calculated by the meta-analysis in this dissertation and other studies). This may suggest that immunomodulator therapy may play the dominant role in lymphoma risk even in settings where combination therapy is used.

Study	Year	Setting	Drug	N	Median f/u (weeks)	NHL cases
Colombel et al	2007	PRECISE RCT	CTZ	905	53	0
Colombel et al	2007	OLE of GAIN and CHARM	ADA	1169	58	0
Sandborn et al	2007	CLASSIC II RCT	ADA	276	56	1
Lemann et al	2006	RCT IXB + AZA	IXB	57	52	0
Schroder et al	2006	Controlled pilot study of IXB + MTX	IXB	19	48	0
Mantzaris et al	2004	RCT IXB + AZA	IXB	45	60	0
Sands et al	2004	IXB for fistulising CD	IXB	282	54	0
Hanauer et al	2002	ACCENT I	IXB	573	54	1
Rutgeerts et al	1999	RCT	IXB	73	48	6
Lichtenstein et al	2007	TREAT registry	IXB	3396	201	0
Biancome et al	2006	Matched pair study	IXB	404	109	1
Doumit et al	2004	Cohort study	IXB	322	104	0
Carbone et al	2007	Case series	IXB	34	52	0
Peyrin-Biroulet et al	2007	Case series for switch to ADA	ADA	52	52	0
Hyder et al	2006	Case series for fistulising CD	IXB	22	91	0
Pacault et al	2006	Case series	IXB	137	150	0
Talbot et al	2005	Case series for perianal CD	IXB	21	87	0
Choi et al	2005	Case series from Korea	IXB	13	57	0
Ardizzone et al	2004	Case series for perianal CD	IXB	20	67	0
Colombel et al	2004	Case series from Mayo Clinic	IXB	500	74	1
Rodrigo et al	2004	Case series for fistulising CD	IXB	44	72	0
Schroder et al	2004	Case series IXBMTX in fistulising CD	IXB	12	57.6	0
Sciderer et al	2004	Cohort study	IXB	92	113	0
Ljung et al	2003	Population-based cohort	IXB	191	52	3
Kinney et al	2003	Case series	IXB	117	52	0
Cohen et al	2000	Case series	IXB	129	52	0

Table 2. Studies included in meta-analysis By Siegel et al 2009. (ADA adalimumab; CTZ certolizumab, MTX methotrexate, AZA azathioprine, CD Crohn's disease, RCT randomised controlled trial, f/u follow up, OLE open label extension).

	NHL rate per 10,000 patient-years	SIR	95% CI
SEER (all ages)	1.9		
IM alone	3.6		
Anti-TNF vs SEER	6.1	3.23	1.5 to 6.9
Anti-TNF vs IM alone	6.1	1.7	0.5 to 7.1

Table 3. Results of meta-analysis by Siegel et al 2009.

The majority of these studies have relatively small numbers of patients, short follow up and were not designed to evaluate efficacy. However, the TREAT registry data includes the largest number of patients and has the longest follow up. The TREAT (Crohn's Therapy, Resource, Evaluation and Assessment Tool) registry is a large prospective, observational, multi-centre, long-term registry of Crohn's disease patients designed to evaluate the safety of infliximab and is a form of post-marketing surveillance. The TREAT registry is hoped to represent *real world* patients without the biases inherent to patients included in trials. No cases of lymphoma were reported in the registry.

The CESAME study data was not included in the meta-analysis by Siegel et al. Beaugerie et al calculated SIRs depending on anti-TNF and thiopurine combination or mono-therapy as well as whether drugs were continued or discontinued (Beaugerie et al., 2009a). These results are presented in Table 4. The results cannot confirm an increased risk of lymphoma in those continuing anti-TNF therapy because the confidence interval crosses 1.0. However, there does appear to be an increased risk when anti-TNF drugs have been used with thiopurines, particularly when combination therapy is continued.

	NHL cases	SIR	95% CI
Continuing anti-TNF therapy	2	4.53	0.55 to 16.4
Discontinued anti-TNF therapy	3	6.92	1.43 to 20.2
Continuing thiopurines and anti-TNF therapy	2	10.2	1.24 to 36.9
Continuing thiopurines but discontinued or never anti-TNFs	13	6.53	3.48 to 11.2

Table 4. SIRs in patients treated with thiopurines and anti-TNF drugs (Beaugerie et al 2009)

13. Hepatosplenic T-cell lymphoma

Hepatosplenic T-cell lymphoma (HSTCL) is a rare form of peripheral non-Hodgkin's lymphoma. In the majority of incidences, it results from a clonal expansion of γ/δ T-cells but α/β T-cell receptors can also be expressed in some cases (Gaulard et al., 1990). Only 100 to 200 cases of HSTCL in the entire medical literature have been reported (Belhadj et al., 2003) but there has been recent concern regarding the safety of thiopurines and anti-TNF therapy, particularly when used in combination, for the management of IBD. To date, 36 cases of HSTCL have been reported in IBD patients (Kotlyar et al., 2011), mostly affecting young men and the prognosis has been invariably fatal. Despite treatment with chemotherapy and stem cell transplantation, median survival is only 11 months (Falchook et al., 2009) but novel treatment strategies have shown some promise in isolated cases (Jaeger

et al., 2008, Tey et al., 2008). Diagnosis is made by liver, splenic or bone marrow biopsy exhibiting atypical medium-sized lymphoid cells with round nuclei, small distinct nucleoli, loosely condensed chromatin, moderate pale cytoplasm and particular immunophenotypic expression which will be discussed further (Swerdlow et al., 2008).

13.1 Clinical presentation

The aberrant cells infiltrate into the sinusoids of the spleen, liver and bone marrow resulting in the classical presentation of hepatosplenomegaly with thrombocytopenia but no lymphadenopathy. Systemic B symptoms of fever, night sweats and weight loss may affect up to 80% of patients. Other findings may include anaemia, abnormal liver function tests and less frequently atypical lymphocytes on peripheral blood film (Falchook et al., 2009).

13.2 Immunophenotypic and genetic features

The tumour cells express CD2, surface CD3, CD7 and CD16 but there is absence of CD4, CD5, CD8 and the B-cell surface marker CD20 (Swerdlow et al., 2008). Most cases express the γ/δ T-cell receptor (TCR-γ positive) but rarer cases express the α/β T-cell receptor (TCR-β positive) and studies demonstrate clonal rearrangements of the TCR gene.

A recent systematic review investigating chromosomal abnormalities in IBD patients diagnosed with HSTCL identified the development of isochrome 7q in 57.1%, aberrations of chromosome 8 in 35.7%, trisomy 8 in 21.4% and loss of the Y chromosome in 14.3 % of cases (Kotlyar et al., 2010). The group were intrigued by the cases with loss of the Y chromosome as almost all cases of HSTCL have presented in men. These chromosomal abnormalities are not specific to IBD patients.

13.3 HSTCL in IBD

HSTCL is not linked to EBV infection. However, the risk of HSTCL does seem to be related to thiopurine and anti-TNF therapy. DNA damage specific to chromosome 7 has been seen in a dose dependent manner with thiopurine agents (Piccin et al., 2010) and inhibition of TNF may result in decreased effectiveness of immune surveillance eliminating cells with aberrant abnormal chromosomal pattern (Shale et al., 2008).

Early concern was regarding a risk of HSTCL in IBD patients who had previous exposure to both thiopurines and anti-TNF drugs but more and more cases have been identified with only thiopurine exposure. Anti-TNF drugs are frequently used in non-IBD conditions, such as rheumatoid arthritis, ankylosing spondylitis and psoriasis, but they are rarely used in combination with other immunomodulators. It is interesting that, HSTCL has only been reported in a single non-IBD patient who received adalimumab for rheumatoid arthritis (Shale et al., 2008). Conversely, there are a number of case reports of patients developing HSTCL whilst on immunosuppression in the post-transplant setting (Roelandt et al., 2009, Tey et al., 2008, Steurer et al., 2002) where anti-TNF drugs are not used.

Kotlyar et al recently presented a systematic review investigating medications, duration of therapy and ages of IBD patients diagnosed with HSTCL (Kotlyar et al., 2011). 36 cases of HSTCL have occurred in IBD patients since 1996, all of whom had a history of thiopurine exposure. 20 of these patients also had also received anti-TNF therapy. Four patients had

previously received both infliximab and adalimumab and an additional patient had received a third biologic, natalizumab. There were no patients who had received an anti-TNF drug alone. Most patients had received at least 2 years therapy with a thiopurine and of those patients who had received infliximab, the number of previous infusions ranged from 1 to 20 up to 5 years prior to the diagnosis of HSTCL. The age range of patients was 12 to 58 years with a median of 23 years. The majority of patients were under 35 years old and the older patient appears to be an isolated case. Of the 31 patients in whom gender was known, only two were female.

13.4 Clinical application

From the limited information available, HSTCL seems to be linked to previous prolonged thiopurine exposure and the risk may be higher in those who have also received an anti-TNF drug. This seems to compete with conclusions drawn from recent efficacy trials. The SONIC trial found that combination therapy with azathioprine and infliximab reached significantly higher rates of steroid-free clinical remission than either of these drugs as monotherapy for a cohort of naïve patients with moderate to severe Crohn's disease (24.1% vs 34.9% vs 46.2% AZA vs IXB vs AZA+IXB at 50 weeks) (Colombel et al., 2010).

Whilst it is not possible to estimate the relative risk of HSTCL in IBD patients, Kotlyar et al attempted to derive the absolute risk of HSTCL in men using epidemiology data from the US and Europe as well as an estimate of thiopurine use in IBD patients from the French CESAME trial (Beaugerie et al., 2009a, Kotlyar et al., 2010). The group concluded that more than 99.99% of patients in immunomodulatory treatment will not develop HSTCL. Further reassurance comes from the CESAME study in that no cases of HSTCL were found despite analysis of over 50,000 patient-years follow up.

A vigilant approach must be taken when using thiopurines for the treatment of male patients under 35 years. Kotlyar et al recommended careful monitoring in patients who have been on thiopurine treatment for more than 2 years but this may be difficult to put in to practice as no pre-malignant markers have been identified. Decisions between the use of combination or monotherapy must be made in the context of clinical severity of disease and poor prognostic markers for complicated IBD. The risk of HSTCL is extremely low and patients should be made aware of this when making choices regarding their treatment. Highly efficacious therapeutic strategies should not be rejected based entirely on the low risk of HSTCL. Somewhat reassuringly, despite the rapidly increasing number of patients on anti-TNF drugs, exceeding 5 million patient-years exposure, the rate at which new cases of HSTCL have been diagnosed has not changed over the last 15 years.

14. Confounding factors and limitations

There are a number of limitations to the data which has been pooled for the meta-analyses presented in this chapter. There are also confounding factors which are not taken in to account by the source studies.

14.1 Age

Data from the US and UK clearly demonstrates that the incidence of non-Hodgkin's lymphoma, the predominant form of lymphoid neoplasm seen in IBD patients, increases

with advancing age (see Figure 2). Most of the studies reviewed in this chapter use age standardised statistics to estimate risk of lymphoma in IBD patients. An earlier meta-analysis carried out by Kandiel et al, found a relative risk for the development of lymphoma in IBD patients treated with thiopurines of 4.18 (95% CI 2.07 to 7.51) which is comparable to the findings of the meta-analysis presented here. The authors went on to calculate the number of patients that would need to be treated for each new diagnosis of lymphoma i.e. the number needed to harm (NNH). Approximating to a relative risk of 4, the NNH varied from 4357 in 20-29 year olds to just 355 in 70-79 year olds (Kandiel et al., 2005). The risk of lymphoma is not uniform across all age groups and this needs to be taken in to account when this information is applied to a clinical setting.

14.2 Gender

Gender also appears to be a further factor when analysing the risk of both Hodgkin's and non-Hodgkin's lymphoma. Although other autoimmune conditions tend to affect more women, the gender difference for IBD is small. Men have an increased risk of lymphoma (see Figure 2 and Figure 3) but the magnitude of the gender difference varies with age and type of lymphoma. In NHL there is only a slight preponderance for males but in HL, the incidence is three times greater in males in certain age groups. As discussed, HSTCL occurs almost exclusively in young men. Many of the studies in this analysis did not separate results for male and female patients but this may have made analysis difficult because of the generally small number of cases of lymphoma detected in these cohorts. Vos et al, in their nationwide Dutch study, calculated SIRs for male and female patients separately but did not find a substantial difference when they took both groups as a whole. However, in the 35-39 years age range, males had an SIR of 10.25 (95% CI 2.56 to 23.05) and females, 6.74 (95% CI 1.20 to 16.77) and this difference was significant (Vos et al., 2010).

14.3 Type of lymphoma

Non-Hodgkin's lymphoma appears to be the predominant lymphoid malignancy detected in IBD patients, particularly diffuse large B-cell lymphoma (DLBCL). The CESAME study group found 22 cases of NHL and only 1 HL in their large cohort of patients from France (Beaugerie et al., 2009a). Few studies have attempted to separate findings for HL and NHL. Palli et al did find an increased risk of HL in patients with UC but the confidence interval was large and the validity of these results has been put in to question (Palli et al., 2000).

14.4 Type of IBD

Whether Crohn's disease or ulcerative colitis confers a higher risk of lymphoma has not been established. Two publications from the same population-based cohort in Copenhagen, Denmark distinguished their analysis between CD and UC patients. In the CD group no lymphomas were identified and only 1 lymphoma was found in the UC group (SIR 0.5) (Winther et al., 2004, Jess et al., 2004). A further population-based cohort from Stockholm, Sweden also analysed UC and CD separately in two different publications. Again no cases of lymphoma were seen in the CD group but there were 3 in the UC group (SIR 1.2) (Persson et al., 1994, Karlen et al., 1999). Interpreting these findings with such small numbers is

fraught with difficulty. In the CESAME study, 16 of the 23 lymphomas were in patients with Crohn's disease (Beaugerie et al., 2009a).

14.5 Exposure to immunomodulators

Not all studies have attempted to evaluate the risk of lymphoma associated with immunomodulator therapy. The studies which have attempted to make this estimation are heterogenous and frequently there is a lack of distinction between lifetime exposure to these drugs, the cumulative doses received and whether cessation of a drug returns any lymphoma risk back to baseline. The CESAME study group attempted to answer some of these questions (Beaugerie et al., 2009a) by analysing patients who have *continuing*, *discontinued* or *never received* thiopurines. The SIRs for these three groups were 6.86 (95% CI 3.94 to 11.31), 1.44 (95% CI 0.17 to 5.20) and 1.43 (CI 95% 0.53 to 3.12) respectively. This may suggest that discontinuation of thiopurines returns risk to baseline but the results were not statistically significant.

14.6 Disease severity

It is not clear whether it is the disease itself, its treatment or a combination of the two which might put IBD patients at increased risk of lymphoma. It is possible that the use of drugs such as thiopurines and biologics are a marker of more aggressive disease and it is disease severity which disposes to lymphoma development. However, modern management of IBD has led to earlier use of these drugs, often in patients who do not have severe disease but possess risk factors for complicated disease, in an attempt to alter the natural history of the condition.

Severity of disease as a risk factor for lymphoma has not been analysed in any depth in IBD patients but there is some evidence available from other autoimmune diseases. A study of 378 RA patients diagnosed with lymphoma found no significant association with individual drugs but a marked increased risk with high disease activity which conferred a 70-fold increased risk (Baecklund et al., 2006). The authors concluded that it was the disease activity, not its treatment that was important in lymphomagenesis. In the CESAME study, some data regarding disease activity was collated but was not linked to lymphoma risk (Beaugerie et al., 2009a).

15. Other risk factors for lymphoma development

It is important to recognise a number of other risk factors for lymphoma development which are relevant to the IBD population but have not been well studied yet.

15.1 Pharmacogenomics of thiopurine therapy

Azathioprine is a pro-drug which is metabolised to 6-mercaptopurine and then to a number of further metabolites including 6-thioguanine (6TG) and 6-methylmercaptopurine (6MMP) which are associated with myelo- and hepato-toxicity when they accumulate at high levels. Important enzymes in this pathway include thiopurine methyl transferase (TPMT) and hypoxanthine phosphoribosyltransferase (HPRT). It is recognised that polymorphisms of TPMT can influence TPMT activity and hence levels of 6TG and 6MMP. About 1 in 300 individuals have homozygote TPMT mutations and AZA or 6MP therapy results in very

high levels of 6TG causing myelo-toxicity. Those with heterozygote mutations have intermediate TPMT activity and dose adjustment of AZA and 6MP may be required.

Thiopurines are also commonly used drugs for the management of acute lymphoblastic leukaemia (ALL) in paediatric patients. Following treatment, these patients have an increased risk of subsequently developing secondary myelodysplasia or acute myeloid leukaemia but it had been thought that this risk is associated with alkylating agents, epipodophyllotoxins or radiation therapy rather than due to AZA. However, Bo et al showed that paediatric patients with allelic variations of the TPMT gene (and lower TPMT levels) had a higher rate of secondary leukaemias in this setting (Bo et al., 1999). Thiopurines result in the incorporation of 6TG, a purine analogue, into lymphocyte DNA which can activate DNA repair mechanisms. This introduces the risk of point mutations and chromosomal abnormalities during repair processes. It follows that higher levels of 6TG may increase this risk further, possibly explaining the link with lymphomagenesis in IBD patients treated with thiopurines.

Disanti et al made an interesting observation in a cohort of IBD patients treated with 6MP over a 37 year period. The investigators divided the group of over 600 patients in to those who developed a sustained leukopenia of $<4.0x10^9/l$ for 20 or more days and those who did not. They found that there was an increased risk of haematological malignancies in the group with sustained leukopenia ($p=0.014$) (Disanti et al., 2006).

Although, the TPMT levels were not known in these patients, further investigation in to the association between TPMT and lymphoma risk may be intriguing.

15.2 Radiation exposure

The use of imaging modalities such as computed tomography and fluoroscopy have been an important component for the diagnosis and assessment of IBD but there has been increasing concern regarding the cancer risk associated with diagnostic ionising radiation (Brenner and Hall, 2007). Much of the risk of medical radiation exposure is extrapolated from studies of populations near nuclear explosions and occupational exposure but there is some evidence in certain medical settings (Brenner et al., 2003). For example, young patients with scoliosis who have had repeated chest x-rays were at increased risk of breast malignancy (Doody et al., 2000).

Recent evidence suggests that CT imaging is being used more frequently in IBD patients, particularly those with Crohn's disease (Newnham et al., 2007, Kroeker et al., 2011). Leukaemia is well recognised as a long term consequence of radiation exposure and this risk is higher in children (Darby et al., 1992, Shimizu et al., 1990). However, there is little evidence to confirm an increased risk of lymphoma in patients exposed to diagnostic ionising radiation though the mechanisms of oncogenesis may be similar. There was no increased risk of lymphoma seen in patients receiving radiotherapy for uterine cancer nor amongst tuberculosis patients with repeated pneumothorax who had an average of 77 chest x-rays on follow up (Boice, 1992). A study including 318 NHL patients found no increased exposure to diagnostic radiation compared to controls if imaging from the 12 months immediately prior to lymphoma diagnosis was excluded. The authors felt that radiological procedures within this period were performed to investigate the lymphoma rather than a causative factor (Boice et al., 1991).

15.3 Vitamin D and sunlight exposure

Vitamin D deficiency is common amongst IBD patients. Recent studies have shown suboptimal levels of Vitamin D in 57 to 78% of recently diagnosed patients with IBD (Leslie et al., 2008, Bours et al., 2010). The protective role of Vitamin D has been investigated in a number of malignancies including prostate, colon, lung, pancreatic, endometrial, breast and even skin cancer (Schwartz and Skinner, 2007). The paracrine and autocrine effects of extra-renal 25-hydroxy-Vitamin-D_3 via the nuclear Vitamin D Receptor (VDR) include regulation of cell cycle proliferation, induction of apoptosis and increased cell differentiation signalling.

Recent epidemiologic studies demonstrate a reduction in NHL risk with increased sunlight exposure (Armstrong and Kricker, 2007). As sunlight is a major vitamin D source, it has been suggested that vitamin D status may mediate this observed association. A recent review of the literature could not conclude or dismiss a link between vitamin D insufficiency and lymphoma due to confounding findings in a number of studies and the limitations on the accuracy of dietary history taking which was the most frequent methodology in these studies (Kelly et al., 2009).

The role of Vitamin D in lymphomagenesis in the IBD population has not been investigated and warrants further study.

16. Summary of findings and application to clinical practice

This systematic review and the meta-analyses carried out in this chapter have made some key findings:

- There is only a small (if any) increased overall risk of lymphoma in IBD patients.
- Thiopurine therapy results in a 3 to 4-fold increased risk of lymphoma in IBD patients.
- The risk of lymphoma with methotrexate therapy cannot be evaluated adequately but appears to be low.
- Treatment with anti-TNF drugs appears to confer an increased risk of lymphoma in IBD patients. However, this may reflect previous or concurrent immunomodulator exposure rather than the risk of anti-TNFs alone.
- HSTCL is associated with long term thiopurine therapy. Additionally, anti-TNF therapy may increase this risk.

It is the role of the IBD physician to help patients balance up the risks and benefits of these drugs and make the right choice for themselves. Due to the significant morbidity associated with IBD, simply avoiding these drugs is frequently not an option. It is mandatory to provide clear communication of risks and benefits and to individualise this to the patient because lymphoma risk in IBD patients is not uniform nor is the risk of complicated disease. A recent study found that patients were more likely to tolerate the risk of adverse events due to IBD drug therapy for moderately symptomatic Crohn's disease than gastroenterologists would choose for their patients (Johnson et al., 2010).

Patient selection is paramount. The risk of most forms of lymphoma appears to be higher in males and in older age groups. HSTCL is particularly relevant to men under the age of 35 years. Special consideration of the risks must be made in these groups. A number of predictors

for severe or complicated disease are now being identified which should allow selection of patients who are most likely to gain from aggressive treatment (Beaugerie et al., 2006).

There is ample evidence that immunomodulators and anti-TNF drugs are very effective for the treatment of IBD. In a 30 year review, Fraser et al found that there were 64% and 87% remission rates at 6 months for patients treated with AZA for Crohn's disease and ulcerative colitis respectively (Fraser et al., 2002). Feagan et al found 65% remission at 40 weeks with MTX for Crohn's disease (Feagan et al., 2000). In the SONIC study, there was 57% remission at 1 year for combined AZA and IXB therapy (Colombel et al., 2010). The CHARM study and its open label extension, ADHERE, for adalimumab in Crohn's disease found improved fistula healing rates, 57% decreased hospitalisation and improved Work Productivity Scores (Panaccione et al., 2010). A Markov model found that the benefits of azathioprine for the treatment of Crohn's disease outweighed the risk of lymphoma but such calculations are inherently based on estimations and assumptions (Lewis et al., 2000).

Additionally, there is evidence that stopping these drugs may be harmful to patients. Azathioprine withdrawal leads to relapse within 18 months at 21% vs 8% (p=0.02, NNH=8) (Lemann et al., 2005). Methotrexate withdrawal leads to relapse within 40 weeks in 61% vs 35% (p=0.04, NNH=4) (Feagan et al., 2000). Infliximab withdrawal leads to hospitalisation within 1 year in 38% vs 23% (p=0.05, NNH=7) (Rutgeerts et al., 2004). However, the CESAME study did suggest that stopping immunomodulator therapy did return the risk of lymphoma back to baseline.

No form of screening is able to predict lymphoma development. Although, the role of vitamin D status and TPMT expression on lymphoma risk is intriguing, there is insufficient evidence to recommend the routine testing of these parameters to guide patient management. Prophylactic use of antivirals in renal transplant recipients has been shown to reduce the risk of post-transplant lymphoproliferative disorders by as much as 83% and the use of this strategy in IBD patients on immunosuppression is warranted (Funch et al., 2005).

The morbidity associated with IBD, the efficacy of these drugs and the risks of stopping them are important factors in making management decisions with patients. In many patients, the benefits will outweigh the risks.

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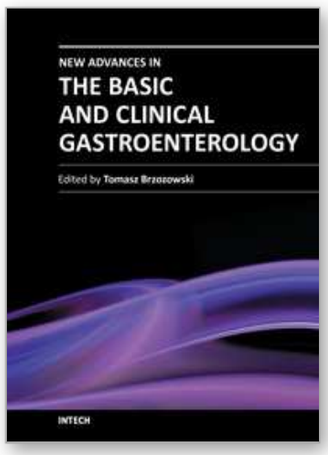

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The purpose of this book was to present the integrative, basic and clinical approaches based on recent developments in the field of gastroenterology. The most important advances in the pathophysiology and treatment of gastrointestinal disorders are discussed including; gastroesophageal reflux disease (GERD), peptic ulcer disease, irritable bowel disease (IBD), NSAIDs-induced gastroenteropathy and pancreatitis. Special focus was addressed to microbial aspects in the gut including recent achievements in the understanding of function of probiotic bacteria, their interaction with gastrointestinal epithelium and usefulness in the treatment of human disorders. We hope that this book will provide relevant new information useful to clinicians and basic scientists as well as to medical students, all looking for new advancements in the field of gastroenterology.

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