Chapter 8
Cancer Risks and Screening with Current and Emerging Drug Therapies in Inflammatory Bowel Diseases

Helen Lee, Yecheskel Schneider, and Gary R. Lichtenstein

What's the Risk of Lymphomas in the General Population?

The two main categories of lymphomas, cancers of the immune system, are non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL). HL arises from mature B cells, while NHL can come from mature B, T, and/or NK cells [1, 2]. NHL, the seventh most common cancer in the USA, occurs more frequently than HL, but together they account for about 5% of new cancers diagnosed in the USA annually [1–3]. The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program estimates that there will be 74,680 new cases of NHL in the USA in 2018, accounting for 4.3% of all new cancers, and 19,910 (3.3%) estimated deaths from all cancers (see Table 8.1) [3]. SEER estimates that there will be 8500 new cases of HL diagnosed in the USA in 2018 accounting for 0.5% of new

Helen Lee and Yecheskel Schneider contributed equally to the work and are co-first authors.

H. Lee · Y. Schneider
Division of Gastroenterology, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

University of Pennsylvania School of Medicine, Philadelphia, PA, USA
e-mail: Helen.Lee2@uphs.upenn.edu; Yecheskel.Schneider@pennmedicine.upenn.edu

G. R. Lichtenstein (✉)
Division of Gastroenterology, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Center for Inflammatory Bowel Diseases, The Raymond and Ruth Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA

Gastroenterology Division, Department of Internal Medicine, Perelman Center for Advanced Medicine, Philadelphia, PA, USA
e-mail: Gary.lichtenstein@uphs.upenn.edu

J. D. Feuerstein, A. S. Cheifetz (eds.), *Cancer Screening in Inflammatory Bowel Disease*, https://doi.org/10.1007/978-3-030-15301-4_8

Table 8.1 Epidemiology of NHL and HL [3]

	NHL	HL
Prevalence compared to other types of cancer in the USA	#7	#26
Estimated new cases in 2018 (%)	74,680 (4.3)	8500 (0.5)
Estimated deaths in 2018 (%)	19, 910 (3.3)	1, 020 (0.2)
Lifetime risk (%)	2.1	0.2
New cases per 100,000 people per year (between 2011 and 2015)	19.4	2.5
New deaths per 100,000 people per year (between 2011 and 2015)	5.7	0.3

Source: Surveillance, Epidemiology, and End Results (SEER) Program. https://seer.cancer.gov/

cancers and 1050 estimated deaths from HL or 0.2% of all cancer deaths [3]. Some risk factors for NHL include older age (median age of diagnosis is 67 years old), race (Caucasian >black), gender (slight predominance in males over females), inherited or acquired immunocompromised status (patients with human immunodeficiency virus, organ transplant, or autoimmune disorder or on immunosuppressants), and infections (Epstein-Barr virus, HTLV-1, HIV, *Helicobacter pylori*, hepatitis C, human herpesvirus 8) [1, 3]. The estimated lifetime risk for developing NHL is 2.1% [3]. Some risk factors for HL include race (Caucasian, black), age (young adults between 20 and 34 years old; median age of diagnosis is 39-SEER), gender (males over females), and presence of an inherited or acquired immunocompromised condition similar to the risk factors for NHL [2–4]. The estimated lifetime risk for developing HL is 0.2% [3].

Does Having IBD Increase a Patient's Risk for Lymphoma?

Although some earlier observational studies that were conducted largely at referral centers reported there was an associated increased risk for lymphoma among patients with IBD, several population-based studies later revealed that the risk of lymphomas for IBD patients who are not on immunosuppressive therapies is similar to the general population [5–16]. In 2000, Loftus et al. published the results of a population-based cohort study on IBD patients diagnosed between 1940 and 1993 in Olmsted County, Minnesota, before the advent of immunomodulators and biologic therapies to assess whether those patients with IBD had a higher risk for NHL [17]. They found that the absolute risk was negligible at 0.01% per person-year [17]. A subsequent retrospective cohort study by Lewis et al. in 2001 using the General Practice Research Database (GPRD) from the UK reached a similar conclusion [18]. The GPRD was felt to be representative of the country's entire population [18]. The study included over 16,000 patients with IBD and compared them to greater than 60,000 matched control patients without IBD to determine if there was a

greater incidence of NHL or HL in patients with IBD [18]. They found that the relative risk (RR) of lymphoma (either NHL or HL) in IBD patients compared to matched controls was not statistically significant with RR of 1.2 and 95% confidence interval (CI) of 0.7–2.1 [18]. Another large population-based study from Sweden that included more than 47,000 patients with IBD with prospectively collected data found that the standardized incidence ratio of lymphomas was 0.8 with 95% CI of 0.5–1.3 in patients with UC and 1.3 with 95% CI of 0.8–2.0 in patients with Crohn's [19].

There were two population-based studies that showed different conclusions. One from Manitoba, Canada, found that there is an increased risk of lymphoma in male Crohn's patients, while another study from Florence, Italy, noted an increased risk of HL in patients with ulcerative colitis [20, 21]. However, these conflicting findings were not confirmed by other population-based studies.

Based on the large amount of evidence amassed from several population-based studies conducted in the past two decades, having IBD likely confers an insignificant to no increased risk for lymphoproliferative diseases [22–25].

What's the Risk of Skin Cancers in the General Population?

Melanomas and nonmelanoma skin cancers (NMSC) are the two main categories of cancer of the skin. Melanoma, cancer of melanocytes, is the fifth most common type of cancer in the USA [3]. According to SEER, the estimated number of new melanoma cases in 2018 is 91,270 which accounts for 5.3% of all cancers [3]. A similar estimated number of new cases of melanoma-in-situ will be diagnosed (87,290) in 2018 [26]. The estimated number of deaths from melanoma in 2018 is 9320 or 1.5% of all cancer deaths [3]. 2.3% of population will be diagnosed with melanoma in their lifetime [3]. Risk factors for melanomas include male gender, fair complexion, older age, cumulative exposure to ultraviolet light, history of sunburns, family or personal history of melanomas, presence of multiple atypical large nevi, congenital melanocytic nevi, certain geographic locations (highest incidence in New Zealand and Australia where the ozone layer is the thinnest), presence of mutation or deletion of cyclin-dependent kinase inhibitor 2A (CDKN2A), and/or presence of a variant melanocortin-1 receptor (MC1R) that produces melanins that are not sun-protective [3, 27, 28].

Although NMSC is the most commonly occurring cancer, its exact incidence in the USA is not clear as this information is not currently routinely collected and recorded in cancer registries [28]. There is an estimated annual incidence of at least 1.5–2 million cases of NMSC in the USA though that is likely an underestimate. One study estimated the total number of NMSC in the USA in 2012 to be greater than five million after analyzing administrative data from Centers for Medicare & Medicaid Services Physicians Claims database and population-based data from National Ambulatory Medical Care Survey database [28, 29]. NMSC encompasses both basal cell skin cancers and squamous cell skin cancers [28]. The

majority of NMSC are basal cell skin cancers (70–80%), while squamous cell skin cancers comprise much of the remaining NMSC [28]. It is estimated that 20% of Americans will develop a skin cancer in their lifetime [30, 31]. Risk factors for developing NMSC are similar to melanomas, including cumulative and childhood ultraviolet light exposure, geographic location (relative to ozone layer thickness), older age, male gender, fair complexion, presence of certain skin conditions (xeroderma pigmentosum, epidermodysplasia verruciformis, nevoid basal cell cancer syndrome), exposures to ionizing radiation, immunosuppressed status, human papillomavirus infection, and chemical carcinogens like tobacco and arsenic [28, 31, 32].

Does Having IBD Increase a Patient's Risk for Skin Cancers?

IBD appears to be a risk factor for melanomas independent of immunomodulator (IMM) and biologic therapy exposure. A meta-analysis of 12 studies which included a total of 172,837 patients and 179 cases of melanoma diagnosed between 1940 and 2009 by Singh et al. in 2014 found that there is a 37% increased risk of melanoma in patients with Crohn's disease and ulcerative colitis over the general population [33]. The increased risk was seen in cohort studies predating the use of immunomodulators and anti-tumor necrosis factor alpha therapy as well as in subgroup analysis where hospital-based studies were excluded leaving only population-based cohorts [33]. Extensive disease was noted to be a possible risk factor for melanoma among patients with IBD [34].

Patients with IBD are not likely to be at increased risk for NMSC over the general population if they have not had exposure to immunomodulators or biologic therapies [35]. Although there were few cohort studies that noted an association between IBD and NMSC, they either did not account for the confounder of exposure to IMM like thiopurines or increased healthcare utilization [9, 35–39]. One study did note that there may be an increased risk for basal cell skin cancer in certain group of IBD patients; males younger than age 50 with Crohn's disease were found to have a threefold increase risk of NMSC compared to those without IBD [38].

The Risk of Lymphoproliferative Disorders After Exposure to Thiopurines and Anti-TNF Alpha Therapies

One of the greatest concerns when using immunomodulators or biologics for the treatment of inflammatory bowel disease, whether alone or in combination, is the concern regarding the risk of lymphoma. Although effective at inducing or maintaining remission, the risk of lymphoma may impose significant concern on both the patient and the physician when selecting a therapy. In particular, combination

therapy with a thiopurine and an anti-TNF agent may carry a greater risk than when each individual agent is used alone. Much of the data we have examining the risk of lymphoma for individuals receiving therapy for their IBD relies on individual cohort studies and meta-analyses of these studies.

Thiopurines

A large nationwide cohort study from France, by Lemaitre et al., examined the risk of lymphoma for individuals on thiopurines and found that the risk of lymphoma was increased in those exposed to thiopurine monotherapy compared to those unexposed to thiopurine or anti-TNF agents, with an adjusted hazard ratio of 2.6 [40]. Another cohort study examining nationwide data in the USA over a 10-year period for individuals with ulcerative colitis treated with thiopurines found that patients on thiopurine had a fourfold increase in the risk of lymphoma while in therapy, compared to individuals not exposed, and this risk increased with ongoing use of the medication [41]. Additionally, a meta-analysis looking at the risk of lymphoma in individuals with IBD on thiopurines found an increased risk of lymphoma in those taking thiopurines, compared to those unexposed to medication. It found that the risk did not persist after discontinuation of therapy. Additionally, the risk was greatest in those over the age of 50 or men under the age of 35. Additionally, the meta-analysis found that the risk increased after one year of thiopurine use, but it was not increased when the duration of use was less than one year [42]. Thiopurines, either alone or in combination with anti-TNF therapy, may also be associated with the risk of developing Hepatosplenic T-cell lymphoma (HSTCL), a rare but aggressive lymphoma with a high risk of mortality. A systematic review of 36 reported cases of patients who developed HSTCL found that most patients were men, were younger than 35 years of age, and had received either thiopurine monotherapy or thiopurine combination therapy with an anti-TNF agent. Overall, the use of thiopurines does appear to be associated with a small but increased risk of lymphoma. This risk does appear to decrease overtime after discontinuation of the medication.

Anti-TNF Agents

The literature regarding the risk of anti-TNF therapy and the development of lymphoma has been conflicting. Data from the Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT™) Registry did not find an increased risk of lymphoma for individuals treated with infliximab therapy alone [43]. In addition, a large nationwide cohort study in Denmark found that exposure to an anti-TNF agent was not associated with an increased risk of lymphoma [44]. However, in the cohort study from Lemaitre et al., the risk of lymphoma for those who received anti-TNF therapy, compared to those who were unexposed to anti-TNF therapy or

thiopurines, was increased, with an adjusted hazard ratio of 2.41 [40]. This risk was slightly lower for those who received anti-TNF monotherapy, as opposed to those who received thiopurine monotherapy. At this time, it is difficult to say whether anti-TNF therapy alone is associated with an increased risk of lymphoma; however, any such risk would likely be small and less than the risk of lymphoma when exposed to thiopurines.

Combination Therapy of a Thiopurine with an Anti-TNF

In the study by Lemaitre et al., the risk of lymphoma was greatest when exposed to combination therapy with a thiopurine and anti-TNF, with an adjusted hazard ratio of 6.11 [40]. Another study examining data in the USA from 1996 to 2009 and including 16,023 patients with IBD found that combination therapy of anti-TNF with thiopurine was associated with an increased risk [45]. A meta-analysis from 2010 examined the risk of lymphoma for individuals who had received an immunomodulator and an anti-TNF agent for the treatment of Crohn's, including 26 studies in their analysis, with 8905 patients and 1178 patient-years of follow-up. The authors found that the use of combination therapy was associated with a small but increased risk of lymphoma, with a standardized incidence ratio of 3.23 [46]. Notably, combination therapy has also been seen in individuals who have developed HSTCL, as mentioned above in the thiopurine subsection. Combination therapy may be associated with an increased risk of lymphoma, greater than the risk of thiopurines or anti-TNF therapy alone.

Additional Therapies

Methotrexate

There are no adequately powered studies specifically examining the risk of lymphoma in patients with inflammatory bowel disease receiving methotrexate. One study by Farrell et al. studied 782 patients with IBD, 238 of whom had received immunosuppressive therapy. Two of four patients who developed lymphoma had previously received methotrexate, either alone or in combination with cyclosporine [47]. However, given the limited data regarding the risk of lymphoma for individuals on methotrexate, it is difficult to draw a conclusion regarding the risk based on this one study.

Tofacitinib

Tofacitinib, a small molecule JAK-kinase inhibitor, approved by the Food and Drug Administration for UC and for rheumatoid arthritis, has limited data evaluating the risk of malignancy for patients with IBD. Data pooled from studies evaluating

tofacitinib for individuals with rheumatoid arthritis and did not show an increased risk of lymphoma for those on therapy when compared to standardized incidence ratios from the Surveillance, Epidemiology and End Results data [48]. In the randomized controlled trial evaluating tofacitinib for the treatment of UC, there was one reported lymphoma [49, 50]. Data examining the risk of lymphoma for individuals with rheumatoid arthritis on Tofacitinib have found the rate of lymphoma to be within the expected range of patients with moderate-to-severe rheumatoid arthritis [48]. Additional studies are needed in the future to better evaluate the risk of lymphoma for individuals with IBD who are receiving this medication.

Ustekinumab

Ustekinumab which is a monoclonal antibody directed against the p40 component of the interleukins 12 and 23 is currently approved for the treatment of Crohn's disease. Data focusing on the lymphoma risk is limited to randomized controlled studies evaluating the efficacy of the medication for the treatment of Crohn's disease, which have not shown an increased risk of lymphoma [51]. To date, there are no large cohort studies in patients with IBD which have evaluated the risk of lymphoma for individuals receiving this therapy.

Vedolizumab

Vedolizumab is a selective anti-integrin, which targets alpha4-beta7 and is approved for both UC and Crohn's disease. A large prospective cohort study evaluating the safety of vedolizumab for one year of use in 294 patients did not reveal any incident lymphomas [52]. A systematic review including 2830 patients exposed to vedolizumab also did not reveal an increased risk of lymphoma [53].

The Risk of Skin Cancer After Exposure to Thiopurines and Anti-TNF Alpha Therapies: Discordant Results

Anti-TNF Alpha Therapies

Melanoma

There were a few retrospective studies that seem to indicate that use of anti-TNF alpha therapies is linked to an increase risk for developing melanomas [39, 54]. In their 2012 retrospective study, Long and her colleagues analyzed data from an insurance claims database and showed that there was an increased incidence of melanoma (IRR 1.29 with 95% CI 1.09–1.53) in IBD patients who used biologics, especially those with Crohn's disease (IRR 1.45 with 95% CI 1.13–1.85, adjusted HR 1.28 with 95% CI 1.00–1.64) [39]. Querying the Food and Drug Administration

(FDA) Adverse Event Reporting System, McKenna et al. also noted that there was an increased odds of melanoma for IBD patients on anti-TNF monotherapy and for those who received combination therapy with thiopurines [54].

However, there is an equally if not stronger and more compelling collection of data to show that there is no increased risk for melanomas in patients exposed to anti-TNF therapy. A population-based cohort study from Denmark in 2012 that included more than 56,000 IBD patients who were followed for a median of 3.7 years found no increased risk for any cancers including melanomas [44]. Another population-based study of IBD patients in Olmsted County, Minnesota, diagnosed between 1940 and 2004 by the Mayo Clinic researchers reported no cases of melanoma were found in patients treated with anti-TNF inhibitor [55]. The TREAT registry's prospectively collected data also revealed that there is no increased incidence of melanoma in Crohn's patients treated with infliximab when compared to other treatment groups and the SEER database [43].

NMSC

There are also conflicting results on whether use of anti-TNF inhibitors increases the risk of NMSC. A 2–3-fold increase in risk was observed in Crohn's patients who had recent (≤90 days) or persistent (>365 days) use of TNF monotherapy or combination therapy [37]. Although a subsequent study by Long and colleagues using a different insurance claims database in 2012 came to the opposite conclusion, there was no increased risk after all [39]. An increased risk for NMSC was also found in a query of the FDA Adverse Event Reporting System for anti-TNF inhibitors [54]. Interestingly, a meta-analysis that pooled data from randomized control trials for adalimumab in patients with Crohn's disease found no increase in NMSC risk on TNF monotherapy SIR 1.2 with 95% CI 0.39–2.80 [56].

After reviewing the available data, the risk of either melanomas or NMSC in IBD patients is not likely to be increased above the general population after exposure to anti-TNF alpha therapy as it was previously believed to be [57]. It should be noted that some older studies did not distinguish between patients on anti-TNF therapy who had prior exposure to antimetabolite therapy versus those who were naïve to it. The use of prior antimetabolite therapy is a known risk factor for the development of NMSC.

Thiopurines

Melanomas

There are very few studies to address the question of whether thiopurines increase the risk for melanoma development. Prospectively collected data from Cancers Et Surrisue Associé aux Maladies inflammatories intestinales En France (CESAME)

cohort showed that there was no associated increased risk for melanomas in patient who were receiving thiopurines (SIR 1.09 with 95% CI 0.13–3.94), and interestingly, it also showed that there was no increase in risk for patients who had previously been exposed to thiopurines [58]. Long and colleagues' retrospective study examining insurance claims data also noted no increased risk for melanoma in IBD patients on thiopurines (OR 1.10 with 95% CI 0.72–1.67) [39]. On the other hand, Yadav and colleagues observed an association between melanomas and the use of IMM, which in this study included azathioprine and 6-mercaptopurine among other medications [55]. When they examined the Olmsted County cohort's risk, they determined that there was an IRR of 5.3 (with 95% CI 1.1–24.8) although it is not clear how much of that increased risk could be attributed to thiopurines only compared to the other IMM as the researchers did not include a breakdown of the frequency of exposure for each individual IMM [55]. One of the strengths of this retrospective study was that it had a long median follow-up of 18 years.

NMSC

There have been multiple studies published over the past decade that clearly link NMSC and thiopurine exposure together [37–39, 56, 59–61]. IBD patients who take thiopurines have at least a twofold greater risk of developing NMSC when compared to general population [37, 39, 62]. Younger age of exposure confers a greater risk when compared to older age of exposure [62]. We have also learned that longer cumulative duration of thiopurine exposure increases one's risk for the development of NMSC [37, 62, 63]. Although the data is conflicting, that risk may decrease but is not perceived to return to baseline upon discontinuation of thiopurine therapy [55, 61–63].

It is not clear that exposure to thiopurines leads to an increased risk for melanomas, but there is no doubt that thiopurine use is associated with increased risk for NMSC.

Methods to Help Decrease the Risk of Skin Cancers Among IBD Patients

(i) Sun-protective measures – It is recommended that IBD patients, similar to the general population, should engage in avoidance of artificial or natural ultraviolet (UV) light or use a broad-spectrum sunscreen that is protective against UVA and UVB light with a sun protection factor (SPF) of 30 or greater [35, 64]. Reapplication of sunscreen should be done at least every 2 hours if continuous exposure to UV rays is expected [64]. Additionally, patients should routinely wear sun-protective clothing that cover the exposed skin as well as hats and sunglasses [64].

(ii) Skin exam – In the recently published preventative care guidelines for IBD patients by the American College of Gastroenterology (ACG), a skin exam performed by a dermatologist is recommended on initiation of immunosuppressive therapy [35]. Timing of subsequent skin exams for surveillance should then be individualized based on each patient's risk factors [35]. The guideline also suggests that IBD patients maintained on thiopurine therapy who are 50 years or older should receive skin exam to screen for NMSC based on data from the CESAME group that indicated there was an increased risk after that age. CESAME group found that before the age of 50, the incidence of NMSC in patients who were taking thiopurines was 0.66/1000 patient-years, while those who were previously on thiopurines had an incidence of 0.38/1000 patient-years [65]. They also found that from age 50 to 65, the incidences of NMSC in patients who were taking thiopurines and those had been on it previously were 2.59/1000 patient-years and 1.96/1000 patient-years, respectively, and beyond the age of 65, the incidence was greater at 4.04/1000 patient-years and 5.70/1000 patient-years, respectively [65]. However, it is important for IBD patients to continue to receive regular skin exams even after immunosuppressive therapy is later discontinued since it is not clear that their risk for skin cancer decreases or return to a baseline population risk [35]. The recommendation for patients to receive regular skin exams, performed by a physician or themselves, is not based upon data from any randomized control trials, but given the known increased risk for skin cancer on immunosuppressive therapy, it makes sense to engage IBD patients in measures to allow for early detection, rapid referral to dermatology for diagnosis, and treatment of a skin cancer [35].

A recent cost-effective analysis for skin exams showed that they can be effective but costly tool for skin cancer surveillance [66]. The authors found that it is more cost-effective for patients to undergo a skin exam every other year compared to annual surveillance. The same group also showed that there is currently a low rate of adherence to skin cancer screening in IBD patients from their center. Even though 21.3% of their IBD patients had a healthcare encounter with a dermatologist, only 2.6% had at least one total body exam during the study period [67].

(iii) Education on skin cancer risk – Patients should be informed about their individual risk factors for developing a skin cancer and counseled on appropriate preventative measures [35]. One survey-based study performed at a tertiary care center showed that while IBD patients are generally aware of a link between IBD and skin cancer, they lacked knowledge pertaining to prevention, protection, and sun exposure practices [68]. This study highlights a crucial area of IBD patient care that needs further improvement. Development of better methods to convey important educational information regarding skin cancer risk and preventive measures is critical to help bridge this large gap in patient knowledge.

References

1. Jacobson CA, Longo DL. Non-Hodgkin's lymphoma. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, editors. Harrison's principles of internal medicine, 20e. New York: McGraw-Hill. http://accessmedicine.mhmedical.com/content.aspx?bookid=2129&sectionid=192018038. Accessed 16 July 2018.
2. Jacobson CA, Longo DL. Hodgkin's lymphoma. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, editors. Harrison's principles of internal medicine, 20e. New York: McGraw-Hill. http://accessmedicine.mhmedical.com/content.aspx?bookid=2129&sectionid=192018130. Accessed 16 July 2018.
3. The National Cancer Institute: Surveillance, Epidemiology, and End Results Program (2018). https://seer.cancer.gov/. Accessed 23 July 2018.
4. American Cancer Society: Lymphoma (2018). https://www.cancer.org/cancer/lymphoma.html. Accessed 23 July 2018.
5. Bargen JA. Chronic ulcerative colitis associated with malignant disease. Arch Surg. 1928;17:561–76.
6. Greenstein AJ, Gennuso R, Sachar DB, Heimann T, Smith H, Janowitz HD, et al. Extraintestinal cancers in inflammatory bowel disease. Cancer. 1985;56:2914–21. https://doi.org/10.1002/1097-0142(19851215)56:12<2914::AID-CNCR2820561232>3.0.CO;2-J.
7. Masel S, Hanauer S. Increased association of lymphoma and inflammatory bowel disease. Gastroenterology. 2000;118:A119.
8. Farrell RJ, Ang Y, Kileen P, O'Briain DS, Kelleher D, Keeling PWN, et al. Increased incidence of non-Hodgkin's lymphomas in inflammatory bowel disease patients on immunosuppressive therapy but overall risk is low. Gut. 2000;47:514–9.
9. Ekbom A, Helmick C, Zack M, Adami HO. Extracolonic malignancies in inflammatory bowel disease. Cancer. 1991;67:2015–9.
10. Persson PG, Karlen P, Bernell O, Leijonmarck CE, Brostom O, Ahlbom A, et al. Crohn's disease and cancer: a population-based cohort study. Gastroenterology. 1994;107:1675–9.
11. Karlen P, Lofberg R, Brostrom O, Leijonmarck CE, Helllers G, Persson PG. Increased risk of cancer in ulcerative colitis: a population-based cohort study. Am J Gastroenterol. 1999;94:1047–52.
12. Winther KV, Jess T, Langholz E, Munkholm P, Binder V. Long-term risk of cancer in ulcerative colitis: a population-based cohort study from Copenhagen County. Clin Gastroenterol Hepatol. 2004;2(2):1088–95.
13. Jess T, Winther KV, Munkholm P, Langholz E, Binder V. Intestinal and extra-intestinal cancer in Crohn's disease: follow-up of a population-based cohort in Copenhagen County. Denmark Aliment Pharmacrol Ther. 2004;19:287–93.
14. Beaugerie L, Brousse N, Bouvier AM, Colombel JF, Lemann M, Cosnes J, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet. 2009;374:1617–25.
15. Sokol H, Beaugerie L. Inflammatory bowel disease and lymphoproliferative disorders: the dust is starting to settle. Gut. 2009;58:1427–36.
16. Vos ACW, Bakkal N, Minnee RC, Casparie MK, de Jong DJ, Dijkstra G, et al. Risk of malignant lymphoma in patients with inflammatory bowel diseases: a Dutch nationwide study. Inflamm Bowel Dis. 2011;17:1837–45.
17. Loftus EV Jr, Tremaine WJ, Habermann TM, Harmsen WS, Zinsmeister AR, Sandborn WJ. Risk of lymphoma in inflammatory bowel disease. Am J Gastroenterol. 2000;95(9):2308–12.
18. Lewis JD, Bilker WB, Brensinger C, Deren JJ, Vaughn DJ, Strom BL. Inflammatory bowel disease is not associated with an increased risk of lymphoma. Gastroenterology. 2001;121:1080–7.

19. Askling J, Brandt L, Lapidus A, Karlen P, Bjorkholm M, Lofberg R, et al. Risk of haematopoietic cancer in patients with inflammatory bowel disease. Gut. 2005;54:617–22.
20. Bernstein CN, Blanchard JF, Kliewer E, Wajda A. Cancer risk in patients with inflammatory bowel disease: a population-based study. Cancer. 2001;91:854–62.
21. Palli D, Trallori G, Bagnoli S, Saieva C, Tarantino O, Ceroti M, et al. Hodgkin's disease risk is increased in patients with ulcerative colitis. Gastroenterology. 2000;119:647–53.
22. Loftus EV Jr. Lymphoma risk in inflammatory bowel disease: influences of referral bias and therapy. Gastroenterology. 2001;121:1240–1.
23. Jones JL, Loftus EV Jr. Lymphoma risk in inflammatory bowel disease: is it the disease or the treatment? Inflamm Bowel Dis. 2007;13:1299–307.
24. Bewtra M. Lymphoma in inflammatory bowel disease and treatment decisions. Am J Gastroenterol. 2012;107:964–70.
25. Subramaniam K, D'Rozario J, Pavli P. Lymphoma and other lymphoproliferative disorders in inflammatory bowel disease: a review. J Gastroenterol Hepatol. 2013;28(1):24–30.
26. American Cancer Society. Cancer facts and figures (2018). https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf. Accessed 23 July 2018.
27. American Cancer Society. Melanoma skin cancer (2018). https://www.cancer.org/cancer/melanoma-skin-cancer.html. Accessed 23 July 2018.
28. Curti BD, Leachman S, Urba WJ. Cancer of the skin. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, editors. Harrison's principles of internal medicine, 20e. New York: McGraw-Hill. http://accessmedicine.mhmedical.com/content.aspx?bookid=2129&sectionid=192015390. Accessed 16 July 2018.
29. Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas) in the US population, 2012. JAMA Dermatol. 2015;151(10):1081–6.
30. World Health Organization. Skin cancers. http://www.who.int/uv/faq/skincancer/en/index2.html. Accessed 23 July 2018.
31. Skin Cancer Foundation. Skin cancer facts & statistics. https://www.skincancer.org/skin-cancer-information/skin-cancer-facts. Accessed 23 July 2018.
32. Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. Arch Dermatol. 2000;136(12):1524–30.
33. Singh S, Nagpal SJS, Murad MH, Yadav S, Kane SV, Pardi DS, et al. Inflammatory bowel disease is associated with an increased risk of melanoma: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2014;12:210–8.
34. Nissen LHC, Pierik M, Derikx LAAP, de Jong E, Kievit W, van den Heuvel TR, et al. Risk factors and clinical outcomes in patients with IBD with melanoma. Inflamm Bowel Dis. 2017;23:2018–26.
35. Farraye FA, Melmed GY, Lichtenstein GR, Kane SV. ACG clinical guideline: preventative care in inflammatory bowel disease. Am J Gastroenterol. 2017;112:241–58.
36. Mellemkjaer L, Olsen JH, Frisch M, Johansen C, Gridley G, McLaughlin JK. Cancer in patients with ulcerative colitis. Ing J Cancer. 1995;60:330–3.
37. Long MD, Herfarth HH, Pipkin C, Porter CQ, Sandler RS, Kappelman M. Increased risk for non-melanoma skin cancer in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2010;8(3):268–74.
38. Singh H, Nugent Z, Demers AA, Bernstein CN. Increased risk of nonmelanoma skin cancers among individuals with inflammatory bowel disease. Gastroenterology. 2011;141:1612–20.
39. Long MD, Martin CF, Pipkin CA, Herfarth HH, Sandler RS, Kappelman MD. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. Gastroenterology. 2012;143(3):390–9.
40. Lemaitre M, Kirchgesner J, Rudnichi A, Carrat F, Zureik M, Carbonnel F, et al. Association between use of thiopurines or tumor necrosis factor antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease. JAMA. 2017;318(17):1679–86.

41. Khan N, Abbas AM, Lichtenstein GR, Loftus EV Jr, Bazzano LA. Risk of lymphoma in patients with ulcerative colitis treated with thiopurines: a nationwide retrospective cohort study. Gastroenterology. 2013;145(5):1007–15.
42. Kotlyar DS, Lewis JD, Beaugerie L, Tierney A, Brensinger CM, Gisbert JP, et al. Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis. Clin Gastroenterol Hepatol. 2015;13(5):847–58.
43. Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Langholff W, et al. Drug therapies and the risk of malignancy in Crohn's disease: results from the TREAT™ registry. Am J Gastroenterol. 2014;109:212–23.
44. Nyboe Andersen N, Pasternak B, Basit S, Andersson M, Svanstrom H, Capsersen S, et al. Association between tumor necrosis factor-α antagonists and risk of cancer in patients with inflammatory bowel disease. JAMA. 2014;311(23):2406–13.
45. Herrinton LJ, Liu L, Weng X, Lewis JD, Hutfless S, Allison JE. Role of thiopurine and anti-TNF therapy in lymphoma in inflammatory bowel disease. Am J Gastroenterol. 2011;106(12):2146–53.
46. Siegel CA, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. Clin Gastroenterol Hepatol. 2009;7:874–81.
47. Farrell RJ, Ang Y, Kileen P, O'Briain DS, Kelleher D, Keeling PW, et al. Increased incidence of non-Hodgkin's lymphoma in inflammatory bowel disease patients on immunosuppressive therapy but overall risk is low. Gut. 2000;47:514–9.
48. Curtis JR, Lee EB, Kaplan IV, Kwok K, Geier J, Benda B, et al. Tofacitinib, an oral Janus kinase inhibitor: analysis of malignancies across the rheumatoid arthritis clinical development programme. Ann Rheum Dis. 2016;75(5):831–41.
49. Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2017;376(18):1723–36.
50. Lichtenstein GR, Loftus EV, Bloom S, Lawendy N, Friedman GS, Zhang H, et al. Tofacitinib, an Oral Janus kinase inhibitor, in the treatment of ulcerative colitis: open-label, Long-term extension study. Poster presentation Digestive Diseases Week. October 2017.
51. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2016;375(20):1946–60.
52. Amiot A, Serrero M, Peyrin-Biroulet L, Filippi J, Pariente B, Roblin X, et al. One-year effectiveness and safety of vedolizumab therapy for inflammatory bowel disease: a prospective multicentre cohort study. Aliment Pharmacol Ther. 2017;46(3):310–21.
53. Bye WA, Jairath V, Travis SPL. Systematic review: the safety of vedolizumab for the treatment of inflammatory bowel disease. Aliment Pharmacol Ther. 2017;46(1):3–15.
54. McKenna MR, Stobaugh DJ, Deepak P. Melanoma and non-melanoma skin cancer in inflammatory bowel disease patients following tumor necrosis factor-α inhibitor monotherapy and in combination with thiopurines: analysis of the food and drug administration adverse event reporting system. J Gastrointestin Liv Dis. 2014;23(3):267–71.
55. Yadav S, Singh S, Harmsen WS, Varayil JE, Tremaine WJ, Loftus EV Jr. Effects of medications on risk of cancer in patients with inflammatory bowel diseases: a population-based cohort study from Olmsted County. Minnesota Mayo Clin Proc. 2015;90(6):738–46.
56. Osterman MT, Sandborn WJ, Colombel JF, Robinson AM, Lau W, Huang B, et al. Increased risk of malignancy with adalimumab combination therapy, compared with monotherapy, for Crohn's disease. Gastroenterology. 2014;146(4):941–9.
57. Cohn HM, Dave M, Loftus EV Jr. Understanding the cautions and contraindications of immunomodulator and biologic therapies for use in inflammatory bowel disease. Inflamm Bowel Dis. 2017;23(8):1301–15.
58. Peyrin-Biroulet L, Chevaux JB, Bouvier AM, Carrat F, Beaugerie L. Risk of melanoma in patients who receive thiopurines for inflammatory bowel disease is not increased. Am J Gastroenterol. 2012;107:1443–4.
59. Ariyaratnam J, Subramanian V. Association between thiopurine use and nonmelanoma skin cancers in patients with inflammatory bowel disease: a meta-analysis. Am J Gastroenterol. 2014;109:163–9.

60. Scott FI, Mamtani R, Brensinger CM, Haynes K, Chiesa-Fuxench Z, Zhang J, et al. Risk of nonmelanoma skin cancer associated with the use of immunosuppressant and biologic agents in patients with a history of autoimmune disease and nonmelanoma skin cancer. JAMA Dermatol. 2016;152(2):164–72.
61. Hagen JW, Pugliano-Mauro MA. Nonmelanoma skin cancer risk in patients with inflammatory bowel disease undergoing thiopurine therapy: a systematic review of the literature. Dermatol Surg. 2018;44(4):469–80.
62. Abbas AM, Almuktar RM, Loftus EV Jr, Lichenstein GR, Khan N. Risk of melanoma and non-melanoma skin cancer in ulcerative colitis patients treated with thiopurines: a nationwide retrospective cohort. Am J Gastroenterol. 2014;109(11):1781–93.
63. Kopylov U, Vutcovici M, Kezouh A, Seidman E, Bitton A, Afif W. Risk of lymphoma, colorectal and skin cancer in patients with IBD treated with immunomodulators and biologics: a Quebec claims database study. Inflamm Bowel Dis. 2015;21:1847–53.
64. Long MD, Kappelman MD, Pipkin CA. Non-melanoma skin cancer in inflammatory bowel disease: a review. Inflamm Bowel Dis. 2011;17(6):1423–7.
65. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, Bouvier AM, Chevaux JB, Simon T, et al. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. Gastroenterology. 2011;141(5):1621–8.
66. Anderson AJ, Ferris LK, Binion DG, Smith KJ. Cost-effectiveness of melanoma screening in inflammatory bowel disease. Dig Dis Sci. 2018;63(10):2564–72.
67. Anderson AJ, Ferris LK, Click B, Ramos-Rivera C, Koutroubakis IE, Hashash JG, et al. Low rates of dermatologic care and skin cancer screening among inflammatory bowel disease patients. Dig Dis Sci. 2018;63(10):2729–39.
68. Kimmel JN, Taft TH, Keefer L. Inflammatory bowel disease and skin cancer: an assessment of patient risk factors, knowledge and skin practices. J Skin Cancer. 2016;2016:4632037.