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Risk of Melanoma and Nonmelanoma Skin Cancer Among Patients With Inflammatory Bowel Disease

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This article has an accompanying continuing medical education activity on page e14. Learning Objective: Upon completion of this exam, successful learners will be able to interpret and communicate skin cancer risks in patients with inflammatory bowel disease (IBD).

See Covering the Cover synopsis on page 276.

BACKGROUND & AIMS: Patients with inflammatory bowel disease (IBD) are at risk for certain malignancies. We aimed to determine the risk of melanoma and nonmelanoma skin cancer (NMSC) in patients with IBD and how medications affect these risks. **METHODS:** We performed retrospective cohort and nested case-control studies using administrative data from the LifeLink Health Plan Claims Database from 1997 to 2009. The cohort comprised 108,579 patients with IBD, and each was matched to 4 individuals without IBD. The risk of melanoma and NMSC was evaluated by incidence rate ratio (IRR) and by adjusted Cox proportional hazard ratio (HR) modeling. In nested case-control studies, patients with melanoma or NMSC were matched to 4 patients with IBD without melanoma or NMSC. Conditional logistic regression was used to determine associations between medications and both skin cancers. **RESULTS:** In the cohort, IBD was associated with an increased incidence of melanoma (IRR, 1.29; 95% confidence interval [CI], 1.09–1.53). Risk was greatest among individuals with Crohn's disease (IRR, 1.45; 95% CI, 1.13–1.85; adjusted HR, 1.28; 95% CI, 1.00–1.64). The incidence of NMSC also increased among patients with IBD (IRR, 1.46; 95% CI, 1.40–1.53) and was greatest among those with CD (IRR, 1.64; 95% CI, 1.54–1.74). In the nested case-control studies, therapy with biologics increased the risk of melanoma (odds ratio [OR], 1.88; 95% CI, 1.08–3.29). Patients who had been treated with thiopurines had an increased risk of NMSC (OR, 1.85; 95% CI, 1.66–2.05). **CONCLUSIONS: Immunosuppression increases the risk of melanoma and NMSC among patients with IBD. The risk of melanoma is increased by use of biologics, and the risk of NMSC is increased by use of thiopurines. Patients with IBD should be counseled and monitored for skin cancer.**

Keywords: Malignancy; Cancer Risk; Epidemiology; Side Effect.

It is estimated that 68,130 Americans were diagnosed with melanoma and 8700 Americans died of melanoma in 2010. The age-adjusted incidence rate for melanoma in the United States from 2004 to 2008 was 20.8 cases per 100,000 men and women per year. The rate of melanoma has nearly tripled in the white population over the past 20 years.[1,2] Nonmelanoma skin cancer (NMSC) is also on the rise. From 2002 to 2006, there was a 16% increase in procedures for NMSC. In 2006, the total number of NMSCs in the US population was estimated to be 3,507,693.[3]

The risk factors for skin cancers include both environmental and genetic factors. Epidemiologic evidence has shown an increased risk of melanoma among those with extensive exposure to sunlight.[4] Intermittent intense sun exposure in adolescence, often associated with a sunburn, confers an increased risk of melanoma.[5] Sites closer to the equator have an increased risk,[6] and a north-south gradient of melanoma has been shown in the United States.[1] In contrast, NMSC is associated with cumulative sun exposure risk, rather than the intensity of the exposure, as is seen with melanoma. High numbers of nevi on the body and fair complexion are also associated with increased risk of skin cancer.[7]

Immunosuppressive medications are another important risk factor for skin cancers. Solid-organ transplant recipients have a 3.4-fold increased risk of melanoma[8]; the risk of NMSC in this population is estimated to be even higher. For example, squamous cell skin cancer is 65–250 times more common in posttransplant populations.[9] In general, the risk of skin cancer correlates with degree of immunosuppression.[8] Consequently, it is recommended that organ transplant recipients undergo routine skin

Abbreviations used in this paper: 5-ASA, 5-aminosalicylic acid; anti-TNF, anti–tumor necrosis factor α; CI, confidence interval; CPT-4, Current Procedural Terminology, 4th edition; HR, hazard ratio; ICD-9, International Classification of Diseases, 9th Revision, Clinical Modification; IRR, incidence rate ratio; NMSC, nonmelanoma skin cancer; OR, odds ratio.

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2012.05.004

surveillance due to the increased risk of skin cancer in this population.[10] Recent data have shown an increased risk of NMSC in patients with inflammatory bowel disease (IBD),[11–13] particularly associated with the thiopurine class of medications. Little is known about the risk of melanoma in patients with IBD and the specific risks of various immunosuppressive medications used in the treatment of IBD, including the biologic anti–tumor necrosis factor α (anti-TNF) medications. Case reports and a recent meta-analysis have suggested an association between biologic anti-TNF medications and risk of melanoma.[14–16] Defining the risk of melanoma in patients with IBD is paramount, because preventive measures (such as sunscreen use) have been shown to reduce the incidence of melanoma.[17]

The specific aims of this study were (1) to quantify the risk of melanoma and NMSC among a US cohort of patients with IBD as compared with a non-IBD cohort and (2) to evaluate the risk of melanoma and NMSC among patients with IBD who use immunosuppressive or biologic anti-TNF medications as compared with patients with IBD who have not used these medications.

Patients and Methods

We analyzed the inpatient and outpatient procedural and outpatient pharmaceutical insurance claims contained in the LifeLink Health Plan Claims Database (IMS Health, Norwalk, CT) for the period January 1, 1997, through December 31, 2009. The source database contains enrollment information on more than 60 million persons from more than 98 health plans across the United States. This longitudinal, patient-level database has also been used in previous epidemiologic studies of IBD.[11,18] The specific data extract used for this study includes data covering a long period to better study newer medications used in the treatment of IBD. Prior studies have reported the LifeLink Health Plan Claims Database to be representative of the commercially insured US population on a variety of demographic measures.[19]

Study Design

We performed a retrospective cohort study to determine the overall risk of melanoma and NMSC in patients with IBD compared with a non-IBD cohort. We then performed nested case-control studies to determine the independent effects of medication use (immunosuppressive and biologic anti-TNF therapy) on melanoma and NMSC among patients with IBD. A similar design has previously been used by our group[11] and also by Gupta et al[20] to evaluate the incidence of disorders in patients with IBD and the effects of various medications.

Cohort Study

Patient selection. Eligibility criteria for inclusion in the cohort were at least 12 months of continuous health plan enrollment with pharmacy benefits, no history of human immunodeficiency virus (HIV) due to inherent immune system differences, and age younger than 64 years. We chose 64 years as the upper age limit to avoid the possibility of missing data resulting from Medicare dual eligibility (which begins at age 65 years). We identified cases of Crohn's disease (CD) and ulcerative colitis (UC) using a previously reported administrative definition updated to include medications recently approved for IBD indications.[21] Specifically, patients with IBD were identified by either of 2 definitions: (1) a minimum of 3 health care contacts, on different dates, associated with an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9) diagnosis code for CD (555.xx) or UC (556.xx) or (2) at least one claim for CD or UC plus a pharmacy claim for any of the following medications: mesalamine, olsalazine, balsalazide, sulfasalazine, 6-mercaptopurine, azathioprine, methotrexate, infliximab, adalimumab, certolizumab pegol, natalizumab, and enteral budesonide. For patients who had claims for both CD and UC, disease assignment was made according to the majority of the last 9 claims or, if there were fewer than 9 claims, the majority of available claims. Those with equal numbers of CD and UC claims were categorized as unknown IBD type. For the comparison cohort, each patient with IBD was matched to 4 non-IBD persons by age, sex, and month of enrollment ($\pm$6 months). Persons having any IBD claims (based on ICD-9) who did not meet our definition of IBD were ineligible for the comparison cohort.

Cohort lead time and follow-up. For the entire cohort, we required 6 months of lead time or screening time before the start of follow-up for outcome ascertainment to minimize possible inclusion of prevalent outcomes and to allow assessment of potentially confounding patient characteristics at the time of entry into the cohort. Thus, for patients with IBD, we required 6 months of enrollment before the first qualifying IBD claim; for non-IBD, we required 6 months of enrollment before the enrollment date of the case to whom they were matched.

Each member of the cohort was followed up until the first diagnosis of melanoma or, if none, until censoring at the earlier of one of 2 events: discontinuation of primary or pharmacy insurance coverage or age older than 64 years.

Assessment of melanoma outcome. The primary outcome of interest was first diagnosis of melanoma. The standard definition included both pathologic and surgical components, requiring 2 separate elements within 30 days: (1) a claim containing a Current Procedural Terminology, 4th edition (CPT-4) code for interpretation of pathology from an office or surgical setting (88301–88309) accompanied by an ICD-9 diagnosis code of melanoma (172.0–172.9) on the same line AND (2) within 30 days, a claim containing a CPT-4 code for excision of malignant lesions (11600–11646) or a CPT-4 code for Mohs stage 1 excision (17311 or 17313).

To assess the adequacy of our primary definition, we also specified 2 alternate definitions, one more sensitive and one more specific. The more sensitive definition was any single ICD-9 code for melanoma (172.0–172.9). This definition has been validated within Medicare administrative data via linkage to the Surveillance, Epidemiology, and End Result (SEER) tumor registry and has been found to have a sensitivity of 90.1%.[22] The more specific definition required all 3 diagnostic, pathologic, and surgical components (CPT-4 code for pathology AND ICD-9 for melanoma AND CPT-4 for surgery or excision) on the same date. These alternate definitions were used to perform sensitivity analyses of our primary definition of melanoma. Persons with any melanoma claim (ICD-9 172.0–172.9) during the 6-month lead or screening period (before start of follow-up) were excluded to minimize possible inclusion of prevalent cases.

Assessment of NMSC outcome. The definition of NMSC was based on a definition we used in prior work, updated to account for changes in procedure codes for Mohs excision that went into effect in 2007.[11] The NMSC definition consisted