SYSTEMATIC REVIEWS AND META-ANALYSES

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Inflammatory Bowel Disease Is Associated With an Increased Risk of Melanoma: A Systematic Review and Meta-analysis

Siddharth Singh,* Sajan Jiv Singh Nagpal,* Mohammad H. Murad,‡ Siddhant Yadav,* Sunanda V. Kane,* Darrell S. Pardi,* Jayant A. Talwalkar,* and Edward V. Loftus Jr*

*Division of Gastroenterology and Hepatology, ‡Department of Preventive Medicine, Mayo Clinic, Rochester, Minnesota

BACKGROUND & AIMS: **Inflammatory bowel disease (IBD) has been associated with an increased risk of nonmelanoma skin cancer, particularly among patients treated with thiopurines. It is unclear whether IBD affects risk for melanoma. We performed a systematic review and meta-analysis of cohort studies to determine the risk of melanoma in patients with IBD.**

METHODS: **We conducted a systematic search of bibliographic databases through March 2013. Cohort studies reporting incident melanoma after IBD diagnosis and an estimate of incidence rate ratio or standardized incidence rate were included in the analysis. Pooled relative risk (RR) estimates with 95% confidence intervals (CIs) were calculated using the random-effects model.**

RESULTS: **Our analysis included 12 studies, comprising a total of 172,837 patients with IBD; 179 cases of melanoma were reported from 1940 to 2009. The pooled crude incidence rate of melanoma in patients with IBD was 27.5 cases/100,000 person-years (95% CI, 19.9–37.0). Overall, IBD was associated with a 37% increase in risk of melanoma (12 studies: RR, 1.37; 95% CI, 1.10–1.70). The risk was increased among patients with Crohn's disease (7 studies: RR, 1.80; 95% CI, 1.17–2.75) and ulcerative colitis (7 studies: RR, 1.23; 95% CI, 1.01–1.50). The risk of melanoma was higher in studies performed before introduction of biologic therapies (before 1998) (8 studies: RR, 1.52; 95% CI, 1.02–2.25) but not in studies performed after 1998 (2 studies: RR, 1.08; 95% CI, 0.59–1.96).**

CONCLUSIONS: **Based on a meta-analysis, IBD has been associated with an increased risk of melanoma, independent of the use of biologic therapy. Patients diagnosed with IBD should be counseled on their risk for melanoma.**

Keywords: Skin Cancer; Colitis; Risk Factors; Tumor Necrosis Factor Therapy; Thiopurines.

See related article by Kappelman MD et al on page 265 in this issue of *CGH*; see editorial on page 274.

Melanoma is the fifth most common cancer in men in the United States, with more than 76,000 cases diagnosed annually, and the incidence is increasing.[1] Although melanoma is amenable to early detection, there has been no decrease in the mortality rate, with about 9000 Americans dying of melanoma every year. Risk factors for melanoma include the presence of atypical and multiple nevi, a personal history of nonmelanoma skin cancer, family history of melanoma, and intermittent intense sun exposure.[2]

It is well known that inflammatory bowel disease (IBD) is associated with an increased risk of nonmelanoma skin cancers (squamous cell cancer and basal cell cancer), particularly with the use of thiopurine analogs.[3,4] However, it is unclear whether IBD or its treatment is associated with an increased risk of melanoma. Some population-based studies have suggested an increased risk of melanoma in patients with IBD,[5] whereas others have not observed such an association.[6,7] More recently, the use of anti-tumor necrosis factor (TNF)-α agents for rheumatoid arthritis or IBD has been associated with an increased risk of melanoma,[8,9] although the data are conflicting.[10–12]

To better understand this issue, we performed a systematic review with a meta-analysis of cohort studies that investigated the association between IBD and risk of incident melanoma.

Abbreviations used in this paper: **CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; IRR, incidence rate ratio; RR, relative risk; SIR, standardized incidence ratio; TNF, tumor necrosis factor; UC, ulcerative colitis.**

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Methods

This systematic review was conducted following guidance provided by the Cochrane Handbook[13] and Kanwal and White[14] and was reported according to the Meta-analysis Of Observational Studies in Epidemiology guidelines.[15]

Search Strategy

First, a systematic literature search of PubMed (1966 to October 31, 2012), Embase (1988 to October 31, 2012), and Web of Science (1993 to October 31, 2012) databases was conducted by 2 study investigators (S.S. and S.J.S.N.), independently, for all relevant articles on the risk of melanoma in patients with IBD. Medical subject terms used in the search included "cancer," "melanoma" combined with "inflammatory bowel disease/epidemiology," "ulcerative colitis/epidemiology" (UC), or "Crohn's disease/epidemiology" (CD). The title and abstract of studies identified in the search were reviewed by 2 authors independently to exclude studies that did not answer the research question of interest. The full text of the remaining articles was examined to determine whether it contained relevant information. The κ-coefficient of agreement between the reviewers on initial article selection was 0.82. Next, the reference sections of the selected articles, as well as review articles on the topic, were searched manually for additional articles. Finally, abstracts from major gastroenterology conferences (Digestive Diseases Week; annual meeting of the American College of Gastroenterology; Advances in IBD, the annual meeting of the Crohn's and Colitis Foundation of America from 2004 to 2012; European Crohn's and Colitis Organization Annual Meeting from 2007 to 2012; and United European Gastroenterology Week from 2009 to 2012) were searched manually for additional relevant abstracts on the topic. An updated search of the primary bibliographic database, PubMed, was conducted on March 18, 2013, but no additional relevant articles were identified.

Selection Criteria

Studies considered in this meta-analysis were cohort studies that met the following inclusion criteria: (1) diagnosed IBD (CD and/or UC) according to well-defined criteria; (2) reported incident cases of melanoma after the diagnosis of IBD; and (3) reported incidence rate ratios (IRR) (by comparing the number of cases of melanoma occurring in the IBD cohort during follow-up evaluation with the number of cases of melanoma in a matched, non-IBD, background population) or standardized incidence ratios (SIRs) (by comparing the rates of observed to expected melanoma cases), with 95% confidence intervals (CIs), or provided data for their calculation. Inclusion was not otherwise restricted by study size, setting, language, or publication type. Case reports or case series were excluded. When there were multiple publications from the same population, only data from the most recent, comprehensive report were included. The flow diagram summarizing study identification and selection is shown in Figure 1.

The quality of observational studies was assessed using the Newcastle–Ottawa scale by 2 investigators (S.S. and S.J.S.N.) independently.[16] In this scale, observational studies were scored across 3 categories: selection

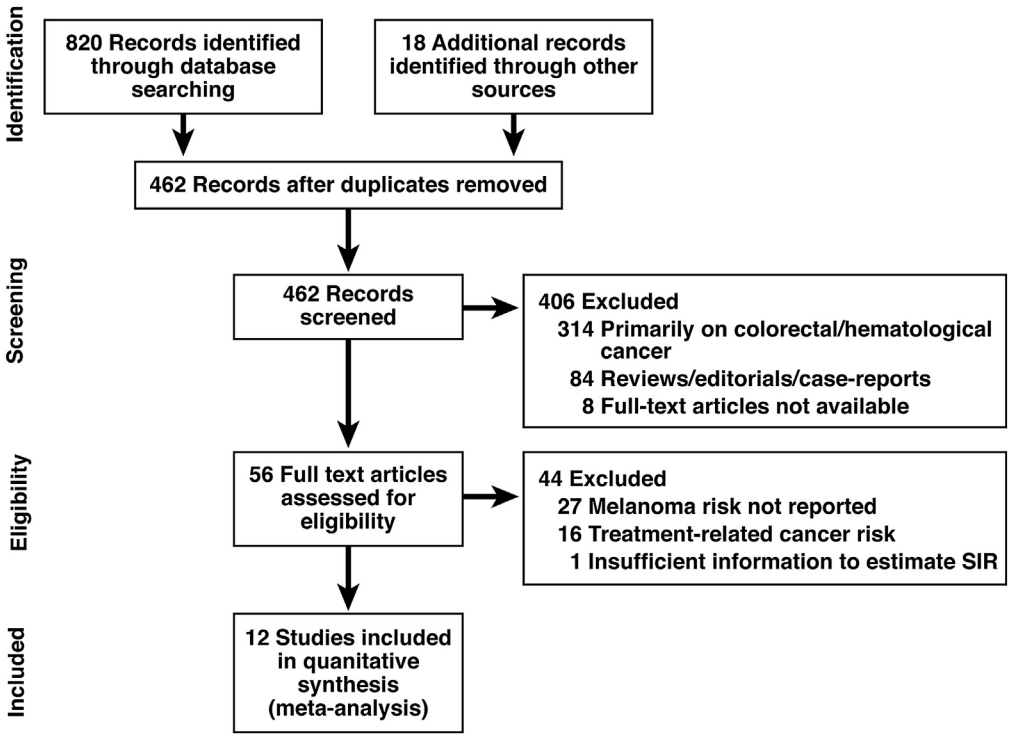

Figure 1. Flow diagram summarizing study identification and selection.