Malignant melanoma associated with chronic once-daily aspirin exposure in males: A large, single-center, urban, US patient population cohort study from the "Research on Adverse Drug events And Report" (RADAR) project

To the Editor: Conflicting evidence exists for the risk of malignant melanoma (MM) subsequent to chronic aspirin exposure.[1-3] Although a study in the *Journal of the American Academy of Dermatology* demonstrated that chronic aspirin exposure before and after MM diagnosis in a large midwestern US population was associated with overall prolonged survival,[4] the risk of MM subsequent to chronic aspirin exposure remains uncertain. The aim of this study, which was also conducted within a large midwestern US patient population, was to determine whether there was a detectable risk for MM after 1 year or more of chronic aspirin exposure.

Using the methodology of the "Research on Adverse Drug events And Report",[5] the Northwestern Medicine Enterprise Data Warehouse, which is a large, urban, single-center medical record data repository (>5 million patients), was searched (January 2005-December 2006). The Northwestern Medicine Enterprise Data Warehouse includes clinical data from all patients receiving treatment through Northwestern Healthcare affiliates. Most patients are from metropolitan Chicago; however, some travel from nearby states. Privately insured, Medicare, Medicaid, and uninsured patients are all included. The study population consisted of all patients age 18 to 89 years with no history of MM and a minimum follow-up time of 5 years after continuous once-daily aspirin exposure for 1 year or more. The control population consisted of all patients within the same time frame but with no documented aspirin exposure. The data collected included age, race, sex, documentation of aspirin exposure and daily aspirin dose (81 mg or 325 mg), duration of follow-up, and concurrent use of a nonsteroidal anti-inflammatory drug. The outcome of interest was an incident MM diagnosis occurring 12 months or more after the index date (first recorded prescription date for the exposed population and first encounter date for the nonexposed population) determined by using International Classification of

Table I. Characteristics of aspirin-exposed and nonaspirin-exposed populations

	Aspirin-exposed		Nonaspirin-exposed	
	Non-MM	MM	Non-MM	MM
Characteristic	n (%)	n (%)	n (%)	n (%)
Total	1161 (100)	26 (100)	192,277 (100)	1676 (100)
Sex				
Male	641 (55.2)	23 (88.5)	64,800 (33.7)	670 (40)
Female	520 (44.8)	3 (11.5)	127,447 (66.3)	1005 (60)
Not specified	—	—	30	1 (0.1)
Age, y				
Mean ± SD (range)	69.12 ± 11.3 (29-89)	76.8 ± 6.7 (64-88)	53.6 ± 14.5 (18-89)	61.6 ± 14.3 (25-89)
Race				
White	667 (57.5)	15 (57.7)	117,760 (61.2)	1393 (83.1)
Black	191 (16.5)	0 (0)	23,112 (12)	13 (0.8)
Other	67 (5.7)	0 (0)	15,241 (7.9)	65 (3.9)
Not specified	236 (20.3)	11 (42.3)	36,164 (18.8)	205 (12.2)
NSAIDs				
Exposed	309 (26.6)	7 (26.9)	16,760 (8.7)	218 (13)
Not exposed	852 (73.4)	19 (73.1)	175,517 (91.3)	1458 (87)
Aspirin dose				
81 mg	714 (61.5)	16 (61.5)	—	—
325 mg	447 (38.5)	10 (38.5)	—	—
Median duration of clinic encounter follow-up, mo	120 (IQR, 111-127)	123.5 (IQR, 115.7-131)	119 (IQR, 101-129)	127 (IQR, 118-133)
Median duration of exposure, mo	45 (IQR, 24-77)	41 (IQR, 24.5-74)	—	—
Median time from index date to MM diagnosis, mo	—	79.5 (IQR, 31.7-85.2)	—	93 (IQR, 62-113)

IQR, Interquartile range; *MM*, malignant melanoma; *NSAID*, nonsteroidal anti-inflammatory drug.

Table II. Crude and adjusted relative risk by sex

RR	Reference	MM
Total		
Unadjusted RR	1	2.54 (95% CI, 1.73-3.74); $P < .0001$
Adjusted RR	1	1.48 (95% CI, 1.01-2.18); $P = .046$
Male		
Unadjusted RR	1	3.38 (95% CI, 2.25-5.09); $P < .0001$
Adjusted RR	1	1.83 (95% CI, 1.22-2.76); $P = .004$
Female		
Unadjusted RR	1	0.73 (95% CI, 0.24-2.27); $P = .590$
Adjusted RR	1	0.53 (95% CI, 0.17-1.63); $P = .266$

Relative risk adjusted for age, race, sex, and concurrent exposure to a nonsteroidal anti-inflammatory drug.
CI, Confidence interval; *MM*, malignant melanoma; *RR*, relative risk.

Diseases, Ninth Revision, codes 172.0 to 172.9 and International Classification of Diseases, Tenth Revision, codes C43.0 to C43.9.

Relative risk for MM after aspirin exposure was determined by logistic regression analysis with a 95% confidence interval.

Patient characteristics are shown in Table I.

For the study population as a whole, there was a significant association between aspirin exposure and subsequent diagnosis of MM, but after stratification by sex, a significant association was present only for males and not for females (Table II). No dose-response relationship was evident.

The findings of this study suggest that chronic once-daily aspirin exposure is associated with an overall increased risk for development of MM and that the risk is dose independent. Importantly, in contrast to the findings of some other reports,[1-3] these findings demonstrate an increased risk for development of MM in males. These inconsistent results might be explained in part by the limitations of pharmacoepidemiologic research, including differences in study design, duration of drug exposure, duration of follow-up, dose-response relationship, and assessment of patient compliance with adherence to drug administration.[6]

Limitations of this study include the inability to verify both patient adherence to a daily aspirin regimen and assignment of diagnostic codes. Moreover, other relevant MM risk factors, such as history of sun exposure and skin phototype, were not collected. Strengths of this study include the large cohort size; representation across age, sex, and race; and a multiyear follow-up period.

Although the mechanism for these findings is unclear, given the potential clinical impact, further exploration of the risk related to chronic, once-daily aspirin exposure and subsequent diagnosis of melanoma is warranted.

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Wound care for Stevens-Johnson syndrome and toxic epidermal necrolysis

To the Editor: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute and life-threatening drug reactions characterized by extensive mucocutaneous exfoliation. SJS and TEN occur rarely, with an annual incidence of 1.2 to 9.2 and 0.4 to 1.9 per million, respectively.[1,2] Wound care for SJS and/or TEN mirrors local trends in burn management, as current guidelines lack strong evidence for these pathologic processes.[3-5] The aim of this review is to assess the effects of dressings used in the wound care in patients with SJS and/or TEN and present evidence rated according to the Strength of Recommendation Taxonomy criteria that will aid clinicians in determining the best approach to wound care for their patients with SJS and/or TEN.

A review of the literature describing wound management in patients with SJS and TEN was conducted as outlined in Supplemental Fig 1 (available at http://www.jaad.org). The search terms used were (((“*toxic epidermal necrolysis*” [Supplementary Concept]) OR “*toxic epidermal necrosis*” OR “*Stevens Johnson syndrome*”) AND (*biosynthetic OR collagen OR debridement OR dressing OR silver OR topical OR wound*)). All retrospective studies, case reports, and case series describing wound management in patients with SJS and/or TEN were included. A total of 22 articles that included the primary outcome of time to re-epithelialization (average time, 14.16 ± 9.42 days) were selected. Table I[6-27] summarizes the results.

Simple dressings (topical creams or ointments covered with bandages) and modern dressings (fiber, biologic, and synthetic) were studied. The most commonly used dressings in the wound care of patients with SJS and/or TEN were biosynthetic dressings, followed by silver-impregnated fiber dressings. Table II describes the characteristics of the dressings reported. Although all the included articles reported survival rates, only 15 reported length of stay (which varied by hospital setting, such as critical care unit or ward floor) or total hospital stay. The number of weekly dressing changes was obtained in all studies, either directly from the articles or by calculation to the closest decimal point. Pain severity during dressing changes was reported in 5 studies. Compared with simple dressings, modern dressings offer the advantage of a reduced number of dressing changes, which results in improved patient comfort. However, there is no apparent impact of their use on healing time. Most studies did not report side effects or cost of dressings. No adverse events related to the dressings were documented.

A total of 13 studies used a concomitant systemic medication. Systemic steroids and intravenous immunoglobulin were the most frequently used. Whether any of these systemic medications affected time to re-epithelialization remains to be determined. No randomized clinical trials or studies with large power were found in our search. No studies met grade A or B Strength of Recommendation Taxonomy criteria (Table I). The limitations of the studies selected include small sample sizes, use of systemic medication, and variation of time to diagnosis and time to placement of dressings. There was a lack of studies comparing 2 or more wound care interventions.

In conclusion, the use of modern dressings should be considered as part of standard therapy because of less frequent dressing changes and improved reported patient comfort. Further clinical studies are warranted, as their influence on healing time is yet to be determined.

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