Accepted Manuscript

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PII: S0190-9622(18)30485-7

DOI: 10.1016/j.jaad.2018.03.031

Reference: YMJD 12420

To appear in: *Journal of the American Academy of Dermatology*

Received Date: 14 September 2017

Revised Date: 13 March 2018

Accepted Date: 14 March 2018

Please cite this article as: Orrell KA, Cices AD, Guido N, Majewski S, Ibler E, Huynh T, Rangel SM, Laumann AE, Martini MC, Rademaker AW, West DP, Nardone B, Malignant melanoma associated with chronic once daily aspirin exposure in males: a large, single-center, urban, U.S. patient population cohort study from the Research on Adverse Drug events And Reports (RADAR) project, *Journal of the American Academy of Dermatology* (2018), doi: 10.1016/j.jaad.2018.03.031.

Malignant melanoma associated with chronic once daily aspirin exposure in males: a large, single-center, urban, U.S. patient population cohort study from the Research on Adverse Drug events And Reports (RADAR) project

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Funding sources: None

IRB approval status: Northwestern University Institutional Review Board approved study.

Conflicts of Interest: The authors have no conflict of interest to declare

Manuscript word count: 528

References: 6

Figures: 0

Tables: 2

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Dear Editor,

Conflicting evidence exists for the risk of melanoma (MM) subsequent to chronic aspirin (ASA) exposure[1-3]. Although a study in this Journal demonstrated that chronic aspirin exposure after MM diagnosis in a large Midwestern U.S. population was associated with overall prolonged survival[4], the risk of MM subsequent to chronic aspirin exposure remains uncertain. The aim of this study, also within a large Midwestern U.S. patient population, was to determine if there was or was not a detectable risk for MM after 1 year or more of chronic aspirin exposure.

Using the Research on Adverse Drug events And Reports (RADAR) methodology[5], the Northwestern Medicine Enterprise Data Warehouse (NMEDW), a large, urban, single-center medical record data repository (> 5 million patients), was searched (January 2005 - December 2006). The NMEDW 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. Study inclusion criteria consisted of all patients, aged 18-89 years, no prior history of MM and a minimum follow-up time of 5 years after continuous once daily ASA exposure for 1 year or more. The control population consisted of all patients within the same time frame but with no documented ASA exposure. Data collected included age, race, gender, documentation of ASA exposure and daily dose (81mg or 325 mg), duration of follow-up, and concurrent use of a non-steroidal anti-inflammatory drug (NSAID). The outcome of interest was incident MM diagnosis occurring $\geq$ 12 months after the index date (first recorded prescription date for exposed population and first encounter date for non-exposed population) using ICD-9: 172.0-172.9 and ICD-10: C43.0-C43.9.

Relative risk (RR) for MM after ASA exposure was determined by logistic regression analysis with a 95% CI.

Patient characteristics are shown in Table 1.

Over the whole population, there was a significant association between ASA exposure and subsequent diagnosis of MM but after stratification by gender, a significant association was present only for males and not for females (table 2). No dose response relationship was evident.

Findings of this study suggest that chronic once daily aspirin exposure is associated with an overall increased risk of MM and that the risk is dose-independent. Importantly, in contrast to some other reports[1-3], these findings demonstrate an increased risk of MM in males. These inconsistent results might be explained in part by the limitations of pharmacoepidemiology 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 inability to verify both patient adherence to daily ASA 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, gender and race, and a multi-year 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.

Acknowledgements

Northwestern Medicine Enterprise Data Warehouse (NMEDW), is supported by the National Institutes of Health's National Center for Advancing Translational Sciences, Grant Number UL1TR001422. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

84 **Abbreviations:**

85 MM (Melanoma), COX (Cyclooxygenase), RADAR (Research on Adverse Drug Events and
86 Reports), NSAID (Nonsteroidal anti-inflammatory drug), NMEDW (Northwestern Medicine
87 Enterprise Data Warehouse), EMR (Electronic medical record), ICD (International Classification
88 of Disease), RR (Relative risk), VITAL (Vitamins and Lifestyle)

89

Table legend

Table 1. Characteristics of ASA-exposed and ASA–unexposed populations

Table 2. Crude and adjusted* relative risk by gender

Table 1. Characteristics of ASA-exposed and ASA–unexposed populations

	ASA-exposed		ASA-unexposed	
	Non-MM	**MM**	**Non-MM**	**MM**
	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Total	1,161 (100)	26 (100)	192,277 (100)	1,676 (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)	1,005 (60)
Not specified	-	-	30	1 (0.1)
Age (years):				
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)	1,393 (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)
unexposed	852 (73.4)	19 (73.1)	175,517 (91.3)	1,458 (87)
ASA dose:				
81mg	714 (61.5)	16 (61.5)	-	-
325mg	447 (38.5)	10 (38.5)	-	-
Median duration of clinic encounter follow-up (months):	120 (IQR 111-127)	123.5 (IQR 115.7-131)	119 (IQR 101-129)	127 (IQR 118-133)
Median duration of exposure (months):	45 (IQR 24-77)	41 (IQR 24.5-74)	-	-
Median time from index date to MM diagnosis (months):	-	79.5 (IQR 31.7-85.2)	-	93 (IQR 62-113)

ASA=aspirin; MM= Malignant Melanoma; IQR= interquartile range; NSAIDs = nonsteroidal anti-inflammatory drug

Table 2. Crude and adjusted* relative risk by gender

*adjusted for age, race, gender, and concurrent NSAID exposure; CI=confidence intervals; RR=relative risk; MM=malignant melanoma

		Reference	MM
Total	**Unadjusted RR (95% CI); p value**	1	2.54; 95% CI 1.73-3.74; p<0.0001
	Adjusted RR (95% CI); p value	1	1.48; 95% CI 1.01-2.18; p=0.046
Male	**Unadjusted RR (95% CI); p value**	1	3.38 (2.25-5.09); p<0.0001
	Adjusted RR (95% CI); p value	1	1.83; 95% CI 1.22-2.76; p=0.004
Female	**Unadjusted RR (95% CI); p value**	1	0.73 (0.24-2.27); p=0.590
	Adjusted RR (95% CI); p value	1	0.53; 95% CI 0.17-1.63; p=0.266

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