Corresponding Author: Jean-David Bouaziz, MD, PhD, Dermatology Department, Hôpital Saint Louis, 1 av Claude Vellefaux, Paris, France 75010 (jean-david.bouaziz@aphp.fr).

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COMMENT & RESPONSE

Study on the Risk of Cutaneous Squamous Cell Carcinoma After Vismodegib Therapy for Basal Cell Carcinoma: Not a Case-Control Study

To the Editor In the May 2016 issue of *JAMA Dermatology*, Mohan et al[1] report an increased risk of cutaneous squamous cell carcinoma (CSCC) after vismodegib therapy for basal cell carcinoma (BCC).[1] They collected data from a cohort of 55 patients with BCC treated with vismodegib and compared the risk of CSCC with that in a cohort of 125 patients with BCC not treated with vismodegib. The authors present the study as a case-control study, which it is not.

The definition of a case-control study can be found in any textbook in basic epidemiology: A case-control study is a type of observational study in which 2 existing groups differing in outcome are identified and compared on the basis of some supposed causal attribute.[2] The 2 groups in the study by Mohan et al[1] were selected on the basis of a difference in a possible risk exposure (ie, vismodegib treatment) and, when compared, found to differ in outcome (ie, CSCC).[1] With this design, the study is a cohort study in which 2 cohorts were followed longitudinally to compare outcomes. Data were collected retrospectively, but this does not make it a case-control study.

The study has other and more important methodological concerns than being mislabeled a case-control study. These are, however, nicely discussed by the authors[1] and in an accompanying editorial by Rübben et al.[3]

Petter Gjersvik, MD, PhD

Author Affiliation: Institute of Clinical Medicine, University of Oslo, Oslo, Norway.

Corresponding Author: Petter Gjersvik, MD, PhD, Institute of Clinical Medicine, University of Oslo, Department of Dermatology, Oslo University Hospital, P.B. 4950 Nydalen, N-0424 Oslo, Norway (petter.gjersvik@medisin.uio.no).

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1. Mohan SV, Chang J, Li S, Henry AS, Wood DJ, Chang AL. Increased risk of cutaneous squamous cell carcinoma after vismodegib therapy for basal cell carcinoma. *JAMA Dermatol*. 2016;152(5):527-532.

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To the Editor We read with concern the article by Mohan et al.[1] First, this is not a case-control study in which participants are sampled based on the presence (case) or absence (control) of a given disease. Instead this is a retrospective cohort study of patients exposed or not exposed to vismodegib.

In addition, non-basal cell carcinoma (BCC) secondary cancers were defined as being associated with vismodegib therapy if they were diagnosed at least 2 weeks after the first exposure to vismodegib. Is it possible to include events occurring so early after treatment?

According to the crude analysis, the rate of subsequent cancers was much lower in exposed (29.1%) than in nonexposed (40.0%) patients. Is it possible that in the Cox model, owing to adjustment, the result is completely reversed leading to a hazard ratio of 6.37?

Clinical follow-up durations were not statistically different, although the follow-up duration of exposed patients was much longer than that of nonexposed patients (median 8.5 years vs 5.5 years). This could be a possible source of bias and should be discussed.

The same observation is valid for latency period, which was longer (even though not statistically significant) in exposed than in nonexposed patients. This means that in exposed patients, it took longer to develop secondary cancers, which is the opposite of what was stated in the article. There is no information about patients lost to follow-up or those who died. Similar cohorts of patients with advanced BCC have an annual mortality of more than 7%.[2]

Finally, the Kaplan-Meier curve shown in Figure 2[1] is inappropriate because only patients who developed cutaneous squamous cell carcinomas were included. In a survival curve, it is necessary to include all participants. It seems that all exposed and all nonexposed patients developed a cutaneous squamous cell carcinoma. However, the numbers of patients at risk do not match the figure.

Taking into account all the criticisms of the report by Mohan et al,[1] we believe that there is inadequate evidence to suggest that vismodegib treatment increases the risk of non-BCC secondary cancers.

Susana Puig, MD, PhD
Francesca Sampogna, PhD
Antonio Tejera-Vaquerizo, MD

Author Affiliations: Melanoma Unit, Dermatology Department, Hospital Clínic, Universidad de Barcelona, Barcelona, Spain (Puig); Institut d'investigacions biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain (Puig); Clinical Epidemiology Unit, Istituto Dermopatico dell'Immacolata-IRCCS, Rome, Italy (Sampogna); Dermatology Department, Instituto Dermatológico GlobalDerm, Córdoba, Spain (Tejera-Vaquerizo).

Corresponding Author: Susana Puig, MD, PhD, Melanoma Unit, Dermatology Department, Hospital Clinic, Universidad de Barcelona, Barcelona, Villarroel 170, 08036, Barcelona, Spain (susipuig@gmail.com).

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Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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In Reply We agree with Gjersvik and Puig et al that our study[1] is a retrospective cohort study and thank the writers for clarifying this. According to the textbook *Epidemiology in Medicine* by Hennekens et al,

Considerable confusion has arisen concerning the terms retrospective and prospective as applied to epidemiologic studies. Some investigators have used these terms synonymously with case-control and cohort, respectively, reasoning that the former looks backward from a disease to a possible cause, while the latter looks forward from an exposure to an outcome... While this terminology is theoretically applicable to case-control studies, it has the greatest practical utility for differentiating two main types of cohort studies, i.e. retrospective and prospective cohort studies.[2(p23)]

Therefore, the more useful way to label our study is *retrospective cohort study*, rather than case-control. The exposure is a Smoothened inhibitor, and the outcome is second cancer. The cohort consisted of patients with basal cell carcinoma (BCC). The study is retrospective as it analyzed data from 1998 to 2014.

To address the question raised by Puig et al regarding rapid appearance of squamous cell carcinoma (SCC) being defined as 2 weeks after Hedgehog blockade, we have observed the new onset of SCCs 2 weeks after initiation of Hedgehog blockade in a patient who clearly did not have a lesion prior to Smoothened initiation (unpublished data). In addition, examples of other similar observations in the literature where SCC develops rapidly after targeted therapy include (1) the onset of SCC after vemurafenib within 1 to 6 months after start of vemurafenib therapy[3] and (2) the onset of SCC after 3 months of ustekinumab treatment.[4] This was the reasoning behind defining second cancer after 2 weeks in our study.

Regarding the question raised by Puig et al on the primary objective of the study, the findings of crude analysis of all non-BCC secondary cancers were indeed 29.1% in exposed and 40.0% in nonexposed patients. However, this does not account for time to exposure (vismodegib) and time to event (second cancer). The Cox proportional hazard ratio accounted for time and treated vismodegib exposure (or nonexposure) as a time-dependent variable.

Puig et al raised concern about the variation in follow-up time (despite the lack of statistical significance). To further convince readers that the variation in follow-up time was not significant, we conducted a subset analysis that included patients whose BCC diagnosis was in the year 2008 or after. The median follow-up times were 2.4 (range, 0.1-6.3) years and 1.4 (range, 0.3-6.1) years for nonexposed (n = 56) and exposed groups (n = 24), respectively (P = .49). Nevertheless, the hazard ratio was still significant, at 3.24 (95% CI, 1.28-8.22) (P = .01).

To clarify Figure 2 in our study,[1] because we handled vismodegib exposure as a time-dependent variable, the observed Kaplan-Meier survival curves could not be generated. Instead, the survival function was estimated, and the predicted survival curves were generated. Thus, this may have led to confusion with the more commonly used Kaplan-Meier curves. We apologize that this was not made clear in the article.

In summary, my coauthors and I believe that the results of our study are correct, even though we agree that terminology and explanations could have been more clear. We thank the writers for their comments and hope that our responses have clarified the questions.

Shufeng Li, MS
Anne Lynn S. Chang, MD

Author Affiliations: Department of Dermatology and Urology, Stanford University School of Medicine, Redwood City, California (Li); Department of Dermatology, Stanford University School of Medicine, Redwood City, California (Chang).

Corresponding Author: Anne Lynn S. Chang, MD, Department of Dermatology, Stanford University School of Medicine, 450 Broadway St, MC 5334, Pavilion C, 2nd Floor, Redwood City, CA 94063 (alschang@stanford.edu).

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CORRECTION

Errors in Tables: In the Original Investigation titled "Association Between Changes in Coronary Artery Disease Progression and Treatment With Biologic Agents for Severe Psoriasis,"[1] published online July 7, 2016, there were errors in the tables. Table 1 should have a footnote defining "ever smoked" that reads as follows: "Defined as current tobacco use or smoked at least 100 cigarettes/approximately