

The Authors Reply

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We thank Stang and Jöckel for their letter [1] concerning our recent paper about time trends in the incidence of ocular melanoma in the United States [2]. They begin by stating that they wish to propose ‘an alternative explanation for the observed decrease of the incidence in the SEER program.’ It is not clear how the issues they raise constitute an ‘alternative’ to the points we discuss on pages 254 and 255 of our paper [2], other than to extend them forward in time. We reported the decreasing trend over time in the proportion of ocular melanomas that were microscopically confirmed, particularly for choroidal and ciliary body tumors, and noted that this could create a downward bias in measured incidence rates if clinically diagnosed ocular melanomas are under-ascertained by SEER. The only difference is that, whereas we stated that most of the decrease in the proportion of tumors with microscopic diagnosis had occurred by the early 1990s, they argue that a downward trend continued through the 1990s and that this might thereby obscure a recent increase in incidence due to some other cause, such as use of cellular (mobile) telephones.

To clarify this issue, we examined the proportion of ocular melanomas with a microscopic diagnosis among whites for individual years from 1985 to 2000, for the two most common anatomic subsites, the choroid and ciliary body (Table 1). There is no evidence of a continued downward trend in the relative frequency of microscopic diagnoses for choroidal or ciliary body tumors from 1992 to 2000. As we noted previously [2], lesions in the back of the eye are biopsied more readily now than in earlier decades [4], and surgical specimens are no longer required for a microscopic diagnosis. SEER data indicate an increase in diagnoses based on cytology beginning in 1988, although the number of such diagnoses is still small relative to the number based on histology (data not shown).

Although the 1981–1993 incidence data from the Florida Cancer Registry cited by Stang and Jöckel are not directly relevant to recent incidence trends in the SEER data, if anything, they tend to support the patterns we observed for earlier years. The first year of operation of the Florida Registry was 1981, and the high incidence rate for 1981 is an outlier with respect to all subsequent years [5], possibly due to the inclusion of prevalent cases. The incidence rate for microscopically confirmed cases was generally higher in the 1980s than the 1990s, but no trend was apparent from 1990 to 1993 [5].

In Table 2, we update data shown in the lower half of Table 1 in our earlier paper [2] concerning trends in incidence among non-Hispanic whites. This includes new incidence data for 1999 and 2000, the most recent years for which data are available, and changes to 1992–1998 data to reflect reporting delay and updated case ascertainment for those years [6]. The increases in rates for 1996–1998 compared to our previous paper suggest a lag in the completeness of ascertainment or recording of the most recent cases in SEER, and one can infer that the rates for 1999–2000 also are underestimates. However, even an upward adjustment of 10–20% would not alter the conclusion that there has been no increase in the incidence of ocular melanoma through 2000.

In a second point, Stang and Jöckel question whether the analysis of incidence trends in the general population is sufficiently sensitive to detect changes related to relative risks of the order they observed if the prevalence of exposure is low. They note that the relative risk for mobile phone use presented in their paper [7] pertained only to persons who had used phones at their work place ‘for at least six months and for at least several hours per day’, and that the prevalence of exposure defined in this way was low. They do not mention that their question asked about use of ‘radio sets, mobile phones or similar devices.’ It did not discriminate between devices, was ambiguous about what proportion of the time a mobile phone or radio set was actually being used to converse (or transmit), and included no results by level of use, thus precluding any inferences as to dose–response or a

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Table 1. Percent microscopic confirmation of ocular melanomas reported to SEER, by anatomic sub-site of melanoma and calendar year, for years 1985–2000 (all whites)

Year	Microscopic confirmation (%)	
	Choroid ^a (n = 1307)	Ciliary body ^a (n = 304)
1985	75	77
1986	73	73
1987	75	56
1988	81	79
1989	82	89
1990	82	91
1991	77	95
1992	66	79
1993	79	75
1994	68	75
1995	66	75
1996	69	82
1997	63	80
1998	74	92
1999	66	89
2000	60	92

^a ICD-O-2 topography codes are choroid (693) and ciliary body (694) [3]. The category for ciliary body includes site specified as iris, lens, sclera, uveal tract, intraocular and eyeball.

Table 2. Numbers of malignant ocular melanoma cases and incidence rates among non-Hispanic whites for 11 SEER reporting areas, by sex and year of diagnosis

Year of diagnosis	Males		Females		Both sexes	
	Cases ^a	Rate ^{a,b}	Cases ^a	Rate ^{a,b}	Cases ^a	Rate ^{a,b}
1992	80	0.67	75	0.49	155	0.57
1993	81	0.66	86	0.58	167	0.61
1994	97	0.78	77	0.50	174	0.62
1995	115	0.92	83	0.59	198	0.74
1996	83	0.66	80	0.55	163	0.60
1997	106	0.82	76	0.51	182	0.64
1998	89	0.68	97	0.61	186	0.65
1999	85	0.66	76	0.51	161	0.57
2000	68	0.52	73	0.47	141	0.50

^a Numbers of cases and incidence rates for 1992–1998 do not exactly match the numbers in our previous paper [2] due to updated case ascertainment in SEER [5] (see text).

^b Per 100,000 per year (age-adjusted, 1970 US standard).

possible threshold. Even if one assumes that there was non-differential reporting of use by cases and controls, the manner in which exposure was defined and quantified makes it difficult to generalize from their data to other populations.

Nonetheless, their general point that a moderate effect confined to a small subset would be difficult to detect at the national level is valid. Of course, people also use cellular telephones outside of the workplace, and any

cancers related to such use would be captured in national rates. Depending on what one believes about the dose–response relationship and latency for ocular melanoma associated with cellular phones, an argument can be made that our analysis was conducted too soon to detect an effect of heavy or long-term use, as we noted on page 254 of our paper [2]. The prevalence of heavy, daily cellular phone use in the general population is no longer low and has not been for some time, but evaluations of incidence data in the United States and other western countries [8] have revealed no evidence of an upturn in incidence rates.

In summary, we found no evidence of a continuing, strong downward trend in the fraction of ocular melanomas reported to SEER that are confirmed microscopically, so it is unlikely that a recent increase in the incidence rate of ocular melanoma has been obscured by a secular decrease in microscopic diagnosis. Although we concur that population-level data are of limited utility in testing causal hypotheses, and that incidence trends can be influenced by many factors, it would be surprising if a new factor had fortuitously emerged to exert a downward bias on the incidence trends for ocular melanoma of sufficient magnitude to mask recent increases in incidence that would be anticipated based on the relative risk estimates reported by Stang *et al.* [6], particularly in view of the explosive worldwide growth in heavy use of cellular telephones.

References

1. Stang A, Jöckel K-H. Re: Trends in the incidence of ocular melanoma in the United States, 1974–1998. *Cancer Causes Control* (this issue).
2. Inskip PD, Devesa SS, Fraumeni JF Jr (2003) Trends in the incidence of ocular melanoma in the United States, 1974–1998. *Cancer Causes Control* **14**: 251–257.
3. Percy C, Van Holten V, Muir C, eds (1990) *ICD-0, International Classification of Diseases for Oncology*, 2nd edn. Geneva (Switzerland): World Health Organization.
4. Cohen VM, Dinakaran S, Parsons MA, Rennie IG (2001) Transvitreal fine needle aspiration biopsy: the influence of intraocular lesion size on diagnostic biopsy result. *Eye* **15**(pt 2): 143–147.
5. Margo CE, Mulla Z, Billiris K (1998) Incidence of surgically treated uveal melanoma by race and ethnicity. *Ophthalmology* **105**: 1087–1090.
6. Ries LAG, Eisner MP, Kosary CL, *et al.* eds (2003) *SEER Cancer Statistics Review, 1975–2000*, Bethesda, MD: National Cancer Institute. <http://seer.cancer.gov/csr/1975–2000>, 2003.
7. Stang A, Anastassiou G, Ahrens W, Bromen K, Bornfeld N, Jöckel K-H (2001) The possible role of radio-frequency radiation in the development of uveal melanoma. *Epidemiology* **12**: 7–12.
8. Johansen C, Boice JD Jr, McLaughlin JK, Christensen HC, Olsen JH (2002) Mobile phones and malignant melanoma of the eye. *Br J Cancer* **86**: 348–349.