Author Response: Is Drusen Area Really So Important?

We appreciate Dr Ying’s questions and comments regarding our paper and acknowledge his criticism. Our results indicated that an increase in drusen area does not necessarily impart an additional risk for choroidal neovascularization (CNV). We pointed out that the risk of an event in our study does increase with increasing drusen area but it did not do so without limits, as we discussed in our concluding paragraph. We are well aware of the publications from Age-Related Eye Disease Study (AREDS) as the UPMC Eye Center was one of the 11 original centers in this pivotal trial and Dr Friberg was the principal investigator at our site.

In the Table 2 provided by Dr Ying in his letter query, the drusen are characterized and the area categories increase from 0 to greater than 1 disc area of drusen in the central 3000 micrometers of the macula. Essentially, his categorical table covers subjects with no or very few small drusen, which are typically category 1 AREDS subjects, to category 3 subjects with many drusen. The event rate for choroidal neovascularization in his table entries increases from 0.1% to 8.6%, to 12.2%, and finally to 12.9%. We graphed his extracted data here in Figure A.

The slope of the plotted curve is steep initially and then flattens as the equivalent drusen area reaches that equal to approximately 70 large drusen. In Figure 1 in our IOVS article, we estimated the probability of neovascularization versus drusen area in the 3000-micrometer region of regard in fellow eye not affected AREDS eyes and show it with a dotted line. That figure is reproduced here (Fig. B).

These figures are similar. Flattening of the slope to zero in our published curve occurs at approximately 0.80 mm², which is equivalent to an area of approximately 60 large drusen. Before this drusen area is reached, the slope is steeper, indicating increased risk of CNV with increasing drusen area. Essentially, the relationship between drusen area and risk in both our figure and that derived from Dr Ying’s table depends upon the region of the curve to which one is referring.

We also pointed out that using categories to denote drusen area rather than using continuous data yields statistical results that can be skewed or biased and are generally not as robust. We did not assert that drusen area is never important. However, we challenge the implicit historical assumption that an increasing drusen area in a subject’s eye exposes it to an ever-increasing risk of conversion to CNV. This is important clinically, as retinal specialists often see patients with drusen spread across the entire posterior pole. As more drusen develop, our study results refute the notion that this increase necessarily makes this eye more susceptible to CNV. Conversely, a reduction in drusen area in eyes with an already large area may not reduce an eye’s risk of conversion. This would be the case if an eye’s drusen area falls within the region of the curve where the slope is zero. Furthermore, our results also indicate that in eyes whose fellow eye is affected (dashed line in our curve), the slope may even turn negative, so a greater drusen area might possibly reduce risk.

Our Prophylactic Treatment of Age-Related Macular Degeneration (PTAMD) subjects had more drusen to start with than AREDS subjects. The criticism regarding small numbers is valid as we so stated. However, we also pointed out that we used multiple models, and we found rather consistent results across

Figure. (A) Plot of CNV versus the number of large drusen from the table provided by Dr. Ying. His data are extracted from the AREDS. Note that the slope is initially steep and then levels off, indicating that the effect of increasing drusen area on the CNV event rate is diminishing. (B) Plot of the probability of a CNV event versus total drusen area based on our drusen area measurements for AREDS subjects at our center. The region of regard was the central 3000 micrometers of the macula. The dotted line plots eyes of subjects where the fellow eye had not been affected by a CNV event at baseline. The slope is initially steep and then flattens out when a drusen area of about 0.80 mm² is reached.
almost all of them. We also separated our PTAMD subjects and presented those results alone in Figure 1 in our paper. Dr Ying makes an overt declaration that the minimum number of events per risk factor needed to produce valid statistical results is 10. We found significance, nevertheless, and generally refute the assumption that a magic number of events somehow exists independent of how an analysis is conducted.

Dr Ying implies that our statistics must have been flawed for us to reach our supported conclusions, and he suggests that we conduct a survival analysis. He also suggests that our follow-up was insufficient. Addressing his concerns, we conducted a survival analysis of our data (using a frailty model to account for both eyes) and also completed a separate analysis after removing subjects who had less than 200 days of follow-up. These results confirmed our original results that drusen area, as a continuous variable, was not a significant risk factor for the development of CNV in our cohort. We stand by our conclusions and welcome further inquiry into this important topic.

References

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