Author’s response to reviews

Title: Association Between Dietary Fat and Skin Cancer in an Australian Population Using Case-Control and Cohort Study Designs

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Author’s response to reviews: see over
Response to Reviewer #1 (Andre Nkondjock)

Major Points

1a) The odds ratios to which the reviewer refers are reported in the text. To have added these to Table 2 would have necessitated a further column in what is already a substantial table.

1b) We have added the following sentence to the conclusion of the abstract:

“Instead, our results suggest a risk reduction for high fat intake.”

2) We have data for Clark’s level for 236 of the 242 CMM cases, and on lesion thickness for 149 of them, but no staging information is available for NMSC cases. Clark’s level (r=0.04) and thickness (r=0.09) were very weakly correlated with the fat score. Dichotomising the CMM cases into n=148 with lesions of Clark’s level I or II and n=88 with lesions of Clark’s level III, IV or V, the results were:

<table>
<thead>
<tr>
<th>Fat score*</th>
<th>Both sexes</th>
<th>CMM Clark’s I/II</th>
<th>CMM Clarks III/IV/V</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N†</td>
<td>OR(95%CI)‡</td>
<td>N†</td>
</tr>
<tr>
<td>1–21 points</td>
<td>126</td>
<td>55 1.00</td>
<td>25 1.00</td>
</tr>
<tr>
<td>22–28 points</td>
<td>174</td>
<td>51 0.71(0.45–1.13)</td>
<td>40 1.15(0.66–2.02)</td>
</tr>
<tr>
<td>29–51 points</td>
<td>171</td>
<td>42 0.58(0.36–0.93)</td>
<td>23 0.72(0.38–1.35)</td>
</tr>
<tr>
<td>Trend</td>
<td></td>
<td>p=0.03</td>
<td>p=0.28</td>
</tr>
</tbody>
</table>

Owing to the small differences found, for brevity we chose not to report these data. We stand ready to add these results to the text if required.

3) In response to the reviewer’s request for more details on measurement of sun exposure, skin phenotype and sun sensitivity, we have added the following to the Measures section of Methods.

“Sun exposure in childhood, teenage years and recent adult life were assessed by questions about the numbers of hours usually spent in the sun during weekends and holidays, along with the frequency of activities outside at those times. Natural hair colour at those time points was also reported. Self-assessed skin sensitivity was determined by questions on tendency to burn and inability to tan. Cutaneous melanin density at the upper inner arm was assessed from measurements of skin reflectance made using a handheld Minolta 508 spectrophotometer (19). The interviewer also counted naevi on the left arm and back of subjects, and graded each subject’s skin colour, eye colour and freckling.”
4) We have added the following sentence to the Measures section:

“The questionnaire was not designed to assess energy intake.”

5) The reviewer points out that we did not report the sex-adjusted mean dietary fat intake scores. We have now replaced the sentence in question (Results, para 1) with the following:

“Despite being similar in body size, the controls had higher sex-adjusted mean values (25.9, standard error SE=0.5) for dietary fat intake than did CMM cases (24.5, SE=0.5, \( p<0.01 \)), BCC cases (24.9, SE=0.5, \( p=0.07 \)) and SCC cases (24.3, SE=0.05, \( p<0.01 \)).”

6) We thank the reviewer for bringing this to our attention. We have revised the results with the fat scores re-classified so that, as closely as is possible, one third of all subjects fall in each category. The odds ratios are strengthened by so doing.

7) We have included further information about the measurements of sun exposure in response to the reviewer’s earlier point 3.

8) We have added the following phrase to provide information on the association between BCC and waist-to-hip ratio (WHR):

“…for which the age- and sex-adjusted odds ratio was OR=0.83 (95% CI: 0.69–0.98) for each 0.1 increase in waist-to-hip ratio units.”

9) We have replaced the sentence, which was also queried by another reviewer (Teresa Fung, Major Point 2) with the following:

“The results from the follow-up of cases suggest reduced risk for higher fat intake.”

10) We reported the correlations with socioeconomic status and sports participation in Results (para 2), but neglected to provide information on how sport participation was measured. We have now rectified this by adding the following sentence to Methods:

“The questionnaire also sought information on frequency of participation in a checklist of recreational and sporting activities.”

11) We did not measure total energy intake, and cannot shed further light on this. This is explained as a limitation to our study as per Teresa Fung’s query (major point 1).

12) To state more clearly our finding, we have added to the following sentence to the final paragraph of the conclusion:

“Instead, our results suggest a risk reduction for high fat intake.”
Minor Points

1) Some eligible cases and controls did not respond for a variety of reasons. That so many of them did participate (89% of cases, 81% of controls) gives us added confidence about the findings of this study.

2) The reviewer questions the initiating date of cases for the follow-up study, which was set at 90 days post-diagnosis of the initial lesion. To some extent, the 90 day rule is arbitrary, but clearly we need to leave some gap after the occurrence of the first lesion because it is common for persons diagnosed with a NMSC to have other NMSC lesions removed within days, weeks or a month or two of the first. The view we have taken is that these additional lesions are manifestations of the same disease process that gave rise to the initial lesion. We and others refer to these nearly-concurrent events as “synchronous lesions”. In relation to stage of disease, we do not have this for NMSC cases.
Response to Reviewer #2 (Teresa Fung)

Major Points

1) The following has been inserted into the Discussion section:

“A further limitation of our analyses was the inability to adjust for total energy consumption, which was not measured by our dietary questionnaire. We are unable to demonstrate that the effect of fat intake is independent of total caloric intake [24]. Further, we cannot dismiss the possibility that the higher fat intake of those subjects at lowest risk of skin cancer constituted a smaller proportion of their total energy intake, although their similar body sizes mitigates against this possibility. It is also reassuring to note that total energy intake has not previously been shown to predict risk of NMSC.”

An additional publication [24] was introduced to support this statement.

2) This has been addressed in response to Reviewer #1, Major Point 9.

Minor Points

1) A sentence in the Abstract was modified to read:

“We then followed all subjects for 56-80 months until 31 August, 2004 for a new NMSC using record linkage with both the TCR and the Births, Deaths, and Marriages registry.”

2) The second last sentence of the final paragraph of the Statistical Analyses subsection was altered to read:

“Confounding by factors including age, sex, socioeconomic status, sun exposure and skin phenotype were assessed by the change-in-parameter-estimate approach.”

3) To reassure this reviewer, the correlations have been re-calculated from the ranks of the data and, as requested, p-values have been added. In addition, the following phrase has been added to the Statistical Analyses section of Methods:

“…and Spearman correlations were calculated from the ranks of the data.”

4) Summary data for age, skin phenotype assessed as the density of melanin in the skin of the upper inner arm, sport participation and socioeconomic status have been added to Table 1.
Response to Reviewer #3 (Sarah McNaughton)

Major Points
None

Minor Points

1) Information already added as per request of Reviewer 2.