

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Deaths and major biographical events: A study of all cancer deaths in Germany from 1995 to 2009
AUTHORS	Medenwald, Daniel; Kuss, Oliver

VERSION 1 - REVIEW

REVIEWER	Mitsuru Shimizu Southern Illinois University Edwardsville, USA
REVIEW RETURNED	22-Dec-2013

GENERAL COMMENTS	<p>It was great pressure that I reviewed the manuscript entitled "Cancer Deaths and Major Biographical Events: The German Experience 1995-2009." I think the authors present some interesting findings. However, I have to say that the paper has several sections that are vague and in place that may help strengthen the paper.</p> <ol style="list-style-type: none"> 1. In the Introduction, the authors did not clearly discuss why cancer patients could postpone their death until important events by focusing on some psychological or behavioral mechanisms, such as the will to live (which is mentioned in the Article Summary, though). Rather, they just focused on the general effects of events by focusing on stress, depression, etc., which is mainly relevant to the hastening effect. I think it is important for them to address why people, especially those with cancer could who the postponement as well as hastening effects. 2. Although the authors briefly discussed the importance of considering the age effect for birthdays (p. 3), they did not clarify why this study looked at several moderators (i.e., gender, age group, marital status, religiosity) on the postponement/hastening effects of all three ceremonial events. 3. The hastening effect of Christmas is only observed in women. But was the interaction effect significant? More importantly, however, why is this the case? As related to the point above, the authors needed to provide explanations about this effect. In addition, why the effect was not found for Easter? 4. In the Discussion, the authors described that the hastening effect of Christmas they found might be related to reduced social support or distress. However, if this is the case, why the effect was only observed in unmarried people (who usually have less social network than married people). Similarly, why this is the case for atheists? The authors also provided some potential explanations (e.g., pathological affections) regarding the hastening effect, but they were unclear and did not address the moderation effects. 5. Relatedly, why was the hastening effect not observed in 2-week window? 6. Also, the authors described that cancer patients should be more sensitive to the postponement effect. Nevertheless, they showed the
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	<p>only hastening effect for Christmas. I think it is important to address the reason.</p> <p>More generally, I would suggest authors should state their hypotheses more clearly based on several potential theories (for the postponement and hastening effects). I understand that the importance and nature of descriptive study like this, but the present article simply described findings without clear explanations, which limits overall significance of the study.</p>
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REVIEWER	<p>Thomas Wise MD Inova Fairfax Hospital Johns Hopkins University School of Medicine USA</p>
REVIEW RETURNED	28-Jan-2014

GENERAL COMMENTS	This is a topic long considered in "folklore". It also overlaps with anniversary issues in an unusual manner. Should be published
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VERSION 1 – AUTHOR RESPONSE

Reviewer Name Mitsuru Shimizu

Institution and Country Southern Illinois University Edwardsville, USA

Please state any competing interests or state 'None declared': None declared

It was great pressure that I reviewed the manuscript entitled "Cancer Deaths and Major Biographical Events: The German Experience 1995-2009." I think the authors present some interesting findings. However, I have to say that the paper has several sections that are vague and in place that may help strengthen the paper.

1. In the Introduction, the authors did not clearly discuss why cancer patients could postpone their death until important events by focusing on some psychological or behavioral mechanisms, such as the will to live (which is mentioned in the Article Summary, though). Rather, they just focused on the general effects of events by focusing on stress, depression, etc., which is mainly relevant to the hastening effect. I think it is important for them to address why people, especially those with cancer could who the postponement as well as hastening effects.

The review raises a relevant point. Our main focus to include cancer patients was to avoid any distortion of the results due to cardio-vascular diseases. To make the postponement effect in cancer patients clearer, we added a more comprehensive account on this phenomenon to the introduction of the text. A short-time release from the burden associated with cancer disease might be the main underlying mechanism for a potential postponement of death. Such an effect would in consequence lead to an apparent virtual "intentional" prolongation of live. Such reasoning might also hold for the found effects in unmarried individuals: A higher general stress due to low social support might cause a much stronger release from the tumour associated distress. In this context the hypothalamic-pituitary-adrenal axis stands in the focus of interest. We added the following:

An increased distress-induced activity of the hypothalamic-pituitary-axis (HPA) leads to a reduced NK cell activity and thus tumour control^{2 7}. In head and neck cancer poorer psychosocial functioning (including depressive symptoms, perceived stress, anxiety, social support) was associated with a greater expression of vascular endothelial growth factor (VEGF), which itself triggers tumour growth by inducing angiogenesis⁸. However, demographic parameters such marital status, age and sex were

not associated with VEGF expression.

Positive expectations towards approaching holidays/biographically important events might be associated with a relief from the chronic distress in cancer patients leading to a reduction in HPA activity. As chronic maladies are more easily affected by social and psychological factors than acute diseases, cancer related deaths have the potential to draw reliable conclusions of possible postponement effects. Assuming that cancer patients are under continuous (dis)stress two mechanisms, acting in opposite directions, might be working:

- (1) A reduction of distress prior to an event leading to more deaths after the event.
- (2) An augmentation of distress before an event reflected by more deaths before the event.

2. Although the authors briefly discussed the importance of considering the age effect for birthdays (p. 3), they did not clarify why this study looked at several moderators (i.e., gender, age group, marital status, religiosity) on the postponement/hastening effects of all three ceremonial events.

The effects related to the mentioned mechanisms of inflammation and tumour progression are very complex. Social support and family background are important points (Aizer et al. 2013) that require clarification in a study intending to examine postponements effects. Sociological differences are important in Germany, especially due to their different socio-historical background after the Second World War and reunification. This makes an intensive examination of age effect essential. Religiosity is important, as we would expect the largest effect to be present in religious people compared to atheists. However, the reviewer is right that we should point out these aspects more clearly. Thus we wrote in the maintext:

The authors discussed an interaction of psychological mood and immune function⁴. Male and female cancer patients perceive disease related distress differently^{5 6}.

...

More generally, social support was related to tumour survival; the lack of a partner was associated with a reduced quality of life⁹ and a worse prognosis¹⁰. However, in breast cancer patients Kornblith et al.¹¹ revealed that social support has to be very high to cause an improvement of distress.

In terms of cancer treatment, patients with helpless attitudes might receive less health care than they require to experience a maximum survival and this aspect might be influenced by major holidays due to e.g. staff shortage¹². As shown recently, married people receive better treatment than their unmarried counterparts and thus have a better prognosis¹³.

...

(9) Taking previous findings into account, the analysis of socio-demographic characteristics such as marital status, age, sex, religious affiliation are important to consider as they might affect hastening/postponement effects.

3. The hastening effect of Christmas is only observed in women. But was the interaction effect significant? More importantly, however, why is this the case? As related to the point above, the authors needed to provide explanations about this effect. In addition, why the effect was not found for Easter?

The hastening effect was actually observed in men and women; however it was not statistically significant in men. The reviewer is correct that the interaction should be taken into account. This was not statistically significant, which makes it not possible to speak of a sex difference in the hastening effect. Thus, we would refrain from interpreting an effect only observed in females. We added this aspect to the discussion section by pointing out that there was no interaction in the data:

The similarity in effect sizes between sexes is reflected by a non-significant interaction ($p=0.332$) indicating comparable hastening effects in men and women.

The reviewer's remark regarding Easter is very relevant, we think the best explanation is the low importance of this holiday as compared to Christmas. This was added to the discussion section:

The weak effects observed for Easter might be mainly due to lower importance of this holiday

compared to Christmas in Germany.

4. In the Discussion, the authors described that the hastening effect of Christmas they found might be related to reduced social support or distress. However, if this is the case, why the effect was only observed in unmarried people (who usually have less social network than married people). Similarly, why this is the case for atheists? The authors also provided some potential explanations (e.g., pathological affections) regarding the hastening effect, but they were unclear and did not address the moderation effects.

The effect observed in singles might be mainly due to a special relief from distress due to the establishment and renewal of social relations prior to Christmas; however the interaction was again not significant. We respected this reasoning in the discussion section by writing:

Surprisingly, singles did not show a hastening of death as it was the case for the majority of subgroups, which was similarly found by Byers et al.¹⁹. For singles, Christmas might be a time to develop and renew social relations weakening a relative social isolation⁴², giving pleasure⁴³, and possibly culminating in a relief of cancer-related distress.

Additionally we provided some deeper explanation of the effect of distress in cancer patients from previous studies. In short, they found a substantial involvement of the hypothalamic-pituitary-axis and VEGF inducing angiogenesis. However, we are of course not able to determine a certain cause for the hastening of death before Christmas. Coming to apparent hastening of death in cases with no religious affiliation it is most probable that atheists attribute a similar meaning to Christmas as religious people. This is mainly because Christmas has lost its original religious meaning in Germany and has become a “family celebration”. To the introduction we added the following:

Coming back to the mechanisms presented in the discussion, we found evidence of negative influences such as increased distress to be present before Christmas surpassing possible positive aspects of this holiday, which might in turn advance tumour progressive effects of the HPA2 7 or growth factors⁸. Nevertheless, we cannot attribute a certain cause (immunological, social) underlying these changes. Hillard et al.³⁵ revealed that there was no data based increase in acute psychological disorders on and before Christmas, which weakens a psychological explanation. However, there are tendencies for a depressed mental status during the Christmas period, mainly due to concerns such as loneliness and absence of family³⁶, which supports our findings and leads to a possible interaction of social support and distress.

...

Coming to the behavioural component it might be possible that nutrition and physical activity of cancer patients worsens before Christmas; however, data supporting this statement are not sufficiently available. It was reported that Christmas is a difficult time for obese to stick to a certain diet regime⁴⁵ and that artificial and palliative nutrition procedures may be adapted for patients' needs around Christmas^{46 47}. Thus, a loser nutrition concept might worsen survival leading to more deaths before Christmas, however, the evidence is weak. Similarly, physical activity might decrease before Christmas; but the seasonal effect of winter time is difficult to distinguish from an actual “Christmas effect”.

Regarding the effect in atheists we added this aspect to the main text by writing:

In terms of religiosity, similar hastening effects in religious people and atheists might reflect a similarly attributed meaning to Christmas and a change from a primarily religious feast to a secular holiday in Germany.

5. Relatedly, why was the hastening effect not observed in 2-week window?

Taking the day by day pattern into account (Figure 5) the peak of death was observed six to four days before Christmas, while deaths earlier before Christmas or later after were evenly distributed. It is difficult to speculate about the reasons; however an early onset of the reason for the hastening of death might be likely such as distress starting before Christmas and culminating six to four days

before Christmas. We included this aspect in the discussion section:

In terms of the time window of four weeks, effect estimates were weaker indicating the short term effect of the hastening, which is also supported by the day by day pattern (Figure 5) with a maximum six days before Christmas. As the number of deaths peaks several days before Christmas when considerable stuff shortages are not to be expected the distress hypothesis seems indeed to be more plausible, while the key role of the HPA was emphasized by previous studies^{2 7}. In consequence, the process of growing distress might start even earlier and just cumulate few days before Christmas.

6. Also, the authors described that cancer patients should be more sensitive to the postponement effect. Nevertheless, they showed the only hastening effect for Christmas. I think it is important to address the reason.

The reviewer is very right, and thus we tried to explain the reason for this effect a bit more in detail. The most probable explanation is again an apparent hastening of deaths due to distress. A postponement of death might be caused by a decrease of distress before Christmas. Nevertheless, as previous studies revealed such a decrease is difficult to accomplish (Kornblith et al. 2001). This was included in the main text:

A postponement of death (reduction of distress) was not observed. Indeed, taking the study by Kornblith et al.¹¹ into account (social support affecting peoples' emotional state needs to be very high to reduce distress) the small effect sizes in our study make it difficult to observe a distress reduction (which might only be achieved for a minority) over all observed cancer deaths.

This is a considerable point: Adverse effects prior to Christmas seem to dominate in cancer patients, while approaching holidays do not seem to decrease chronic distress. Cancer patients are sensitive to a possible postponement because they suffer from a chronic disease and thus distractions due to acute causes of death (heart attack) are unlikely and again they have the pressure of chronic distress making a postponement due to a relief at least possible; however not in our data. We additionally wrote in the introduction:

See point 1.

More generally, I would suggest authors should state their hypotheses more clearly based on several potential theories (for the postponement and hastening effects). I understand that the importance and nature of descriptive study like this, but the present article simply described findings without clear explanations, which limits overall significance of the study.

Indeed, this might clarify the general purpose of our study and also facilitate the readability. Thus we incorporated the following to the introduction section:

Assuming that cancer patients are under continuous (dis)stress two mechanisms, acting in opposite directions, might be working:

- (1) A reduction of distress prior to an event leading to more deaths after the event.
- (2) An augmentation of distress before an event reflected by more deaths before the event.

Reviewer Name Thomas Wise MD

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Please state any competing interests or state 'None declared': None declared

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