

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Breast cancer survival and season of surgery: an ecological, open cohort study
AUTHORS	Dorthe Teilum, Karsten D Bjerre, Anne M Tjønneland and Niels Kroman

VERSION 1 - REVIEW

REVIEWER	MMA Tilanus-Linthorst MD, PhD Erasmus University Medical Centre Department of Surgical Oncology Rotterdam The Netherlands
REVIEW RETURNED	19/10/2011

THE STUDY	<p>Method's: Direct measurement of 25(OH)D would have been better. The authors have described the limitation of their using season as an indirect measure of vit D level and there is sufficient evidence that their indirect measure is relevant. They correctly have conclusions only on the influence of season on survival not of 25(OH)D.</p> <p>Please update: The following 2 articles on this subject with direct vit D measurements appeared possibly too short before their submission, but at least the first should be referred and discussed</p> <p>1. Breast Cancer Res. 2011 Jul 26;13(4):R74. Serum 25-hydroxyvitamin D and postmenopausal breast cancer survival: a prospective patient cohort study. Vrieling A, Hein R, Abbas S, Schneeweiss A, Flesch-Janys D, Chang-Claude J.</p> <p>and 2. Ann Surg Oncol. 2011 Jul;18(7):1830-6. Vitamin D deficiency is correlated with poor outcomes in patients with luminal-type breast cancer. Kim HJ, Lee YM, Ko BS, Lee JW, Yu JH, Son BH, Gong GY, Kim SB, Ahn SH.</p>
RESULTS & CONCLUSIONS	In the above mentioned article by Vrieling as in other articles worse tumor stage, positive axillary nodes, high grade tumors and ER-/Pr-status are all associated with lower 25(OH) D level and they predict usually poorer outcome. This study does correct for all these factors, but does therefore correct for factors influencing not only the main outcome, "survival", but also the investigated topic "vit D level "for which season is only a surrogate measure.
GENERAL COMMENTS	<p>1. Mortality of breast cancer has gradually decreased over the years 1978-2010 Please give in Table 1 also the proportion of women treated in each season per time of treatment cohorts. E.g. 1978-1999 / 1990-2000 / 2000-2010</p> <p>2. Adjuvant therapy has significant influence on survival. There are data on adjuvant systemic treatment in the registry of the Danish Breast Cancer Cooperative Group (DBCG). Please give in Table 1 also the data of adjuv chemoth + vs - and endocrine adj ther + vs -/</p> <p>3. Can a power calculation be added to the statistical paragraph</p>

REVIEWER	Prof John Boyages Director and Professor of Breast Oncology Macquarie University Cancer Institute The Australian School of Advanced Medicine
REVIEW RETURNED	31/10/2011

GENERAL COMMENTS	<p>This paper presents an interesting hypothesis that breast cancer survival is related to season of surgery and vitamin D. The large sample size, prognostic nature of the study and ability to control for tumour characteristics make this a worthwhile study.</p> <p>The title implies that vitamin D is a major variable in the study however the authors have been unable to account for individual vitamin D levels, which they acknowledge is a weakness of their study. Instead, they rely on season of surgery as a surrogate for vitamin D on breast cancer survival. The latter may reflect a more accurate title.</p> <p>The introduction describes the theory that vitamin D may influence prognosis for breast cancer and provides relevant evidence both in support and in opposition to this theory. The authors then mention that breast cancer prognosis varies with season of diagnosis, which they are attempting to validate in this study. The authors then link the evidence that there is a seasonal variation in vitamin D levels in Denmark. They then propose that the aim of this study is to compare the prognostic outcome for breast cancer patients diagnosed and operated at different seasons of the year.</p> <p>However, it should be explained that season is being used as a proxy marker for vitamin D status as this is not made explicit. In addition an explanation is required regarding the production of vitamin D from sunlight exposure.</p> <p>It is a giant leap to state that vitamin D is or is not related to survival when not measuring vitamin D directly as there are numerous other factors that will affect vitamin D level, therefore it is important to make mention of such other factors.</p> <p>The conclusion that this study does not provide support to that statement that vitamin D at the time of surgery influences prognosis is not justified as vitamin D was not measured. Additionally, the authors state in the conclusion that no evidence of a seasonal variation in survival, when in the results they quote (marginally) significant results. This needs clarifying.</p> <p>Overall the paper is worth publishing but I would recommend - changing the title (by omitting Vitamin D) and aligning the conclusion in the abstract with that in the main discussion.</p> <p>General Comments The paper is reasonably well written however there is an overuse of commas and there are several technical and grammatical errors which makes it difficult to understand in certain places. I suggest revision by an English editor. The paper is not technically well written, for instance the use of the words "blood levels of vitamin D" should be referred to as "serum"; "produce" vitamin D in the skin referred to as "synthesise", and "the amount of vitamin D in the</p>
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	<p>blood" referred to as "vitamin D status."</p> <p>Specific comments</p> <p>Page 2: Line 22 and 25 - no full stop required</p> <p>Page 3: Delete commas in line 6, 18, 22, 37, 53 (after patients), delete full stop line 23 (after found); add full stop line 53 (after year)</p> <p>Line 8 – Assumes the reader is aware that sunlight is the primary source of vitamin D</p> <p>Line 15 – refer to 25(OH)D also as vitamin D as this will describe what fraction of vitamin D you are referring to</p> <p>Line 8 – it should be mentioned that vitamin D refers to 25(OH)D, and that 25(OH)D is the form of vitamin D used as an indicator of vitamin D status.</p> <p>Line 27 /29 – season should be provided for each month as in the southern hemisphere these months would reflect different seasons.</p> <p>Page 7: is 3 significant places required?</p> <p>Page 8: Line 6: this is not a multivariable analysis but rather a multivariate analysis.</p> <p>Line 39, the comment about the comparison between males and females is seemingly irrelevant.</p> <p>Page 9: Line 8: delete space; Line 18 the statement: " If the level of vitamin D at the time of surgery should influence prognosis, the mechanism must be differences in peri-operative resistance to cancer dissemination" is speculative and rules out other causes; Line 23 add corner after dissemination.</p> <p>Page 15: Table 2: show significant results in bold text.</p>
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VERSION 1 – AUTHOR RESPONSE

Thank you for positive and inspiring comments. We have revised the manuscript accordingly.

VERSION 2 – REVIEW

REVIEWER	<p>MMA Tilanus-Linthorst MD, PhD Erasmus University Medical Centre Department of Surgical Oncology Rotterdam The Netherlands</p> <p>I have no competing interests</p>
REVIEW RETURNED	27/11/2011

THE STUDY	<p>In the abstract, the results and conclusions are less balanced than in the previous version.</p> <p>The last sentence of the abstract should be left out in the abstract, as it concerns vit D status, that was not measured in this study. It is sufficient to make this statement of caution in the manuscript.</p> <p>The 0-1 year result is more correctly described as: " Only after adjustment for prognostic factors that may be influenced by vit D, like tumor stage, one year survival was close to significantly associated with season of surgery.</p> <p>The mentioning of improved or decreased survival in addition to the Hazard Ratio in the manuscript is useful.</p>
GENERAL COMMENTS	<p>This is an informative study of nearly 80.000 Danish breast cancer patients on the influence of season as a proxy for vit D level, on survival, with survival data with a median follow-up of 10 years and</p>

	<p>very complete data on nearly all other prognostic factors like age at diagnosis, tumor stage and histology and on treatment. No significant association could be demonstrated. The authors correctly state that this does not exclude a longterm influence of sun exposure and vit D on survival of breast cancer patients. The one year result of worse survival in summer that can only be demonstrated after adjustment for even those factors, that might be influenced by the women's vit D level, like tumor stage and histolog, does not belong in the abstract. This result is possibly caused by multiple testing, gets otherwise too much emphasis. Nor is it a finding in line with the cited literature, that overall is well discussed.</p> <p>I hope the abstract can still be adapted before publication. The mentioning of improved or decreased survival in addition to the Hazard Ratio in the manuscript is useful.</p>
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