Reply to the letter to the editor ‘Albumin to globulin ratio, a predictor or a misleader?’ by Alkan et al.

We appreciate the letter to the editor by Alkan et al. [1] in response to our recently published article [2]. Alkan et al. bring up some potentially valid points about our study. They suggest that some rheumatic diseases should have been excluded from the study population, as these conditions are ‘important causatives for chronic inflammation.’ They also suggest the inclusion of elderly subjects older than 60, comprising 24.2% of the study population, as these subjects are ‘prone to malnutrition and also hypoalbuminemia.’

In order to address these suggestions, we have investigated the association of low albumin-to-globulin ratio (AGR) with cancer after having further excluded (in addition to the exclusion criteria originally implemented in our study) elderly subjects older than 60, as well as subjects with previous history of major rheumatic diseases, including rheumatic arthritis (ICD-10 M05), systemic lupus erythematosus (M32), ankylosing spondylitis (M45), systemic sclerosis (M34), dermatopolymyositis (M33), other connective tissue disease (M35–M36), as well as Crohn’s disease (K50), and ulcerative colitis (K51). The study population thus decreased from 26 974 to 20 695 subjects.

The results are shown in Table 1. As expected, event numbers have significantly decreased (~70%) but the overall trend is shown to be apparently intact, with adjusted hazard ratios remaining similar in general throughout all AGR groups.

Overall, the association between low AGR and cancer is a legitimate observation, although its clinical application remains undetermined, deserving elucidation by future studies.

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disclosure

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references


Table 1. Cox proportional hazards models for mortality and cancer incidence before and after revision in study population

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>Event no.</td>
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<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
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<tr>
<td>AGR ≥1.5</td>
<td>12 356 (45.8)</td>
<td>81</td>
</tr>
<tr>
<td>1.5 &gt; AGR ≥1.2</td>
<td>12 599 (46.7)</td>
<td>175</td>
</tr>
<tr>
<td>1.2 &gt; AGR ≥1.1</td>
<td>1519 (5.6)</td>
<td>34</td>
</tr>
<tr>
<td>1.1 &gt; AGR ≥1.0</td>
<td>395 (1.5)</td>
<td>15</td>
</tr>
<tr>
<td>1.0 &gt; AGR</td>
<td>105 (0.4)</td>
<td>11</td>
</tr>
</tbody>
</table>

Cancer mortality

| AGR ≥1.5            | 12 356 (45.8) | 44 | 0.77 | 1 | 9918 (47.9) | 23 | 0.49 |
| 1.5 > AGR ≥1.2      | 12 599 (46.7) | 87 | 1.12 | 1.24 (0.86–1.80) | 1.26 (0.74–2.13) | 9407 (45.5) | 40 | 0.68 |
| 1.2 > AGR ≥1.1      | 1519 (5.6) | 17 | 1.52 | 1.49 (0.84–2.64) | 1.72 (0.72–4.10) | 1038 (5.0) | 7 | 0.90 |
| 1.1 > AGR ≥1.0      | 395 (1.5) | 9 | 3.05 | 2.95 (1.42–6.11) | 4.49 (1.67–12.03) | 265 (1.3) | 5 | 2.49 |
| 1.0 > AGR           | 105 (0.4) | 4 | 5.55 | 4.38 (1.57–12.25) | 3.33 (0.45–24.82) | 67 (0.3) | 1 | 2.08 |

Cancer incidence

| AGR ≥1.5            | 12 356 (45.8) | 158 | 2.77 | 1 | 9918 (47.9) | 101 | 2.18 |
| 1.5 > AGR ≥1.2      | 12 599 (46.7) | 244 | 3.15 | 1.07 (0.87–1.31) | 1.12 (0.87–1.46) | 9407 (45.5) | 152 | 2.58 |
| 1.2 > AGR ≥1.1      | 1519 (5.6) | 42 | 3.77 | 1.21 (0.85–1.72) | 1.20 (0.74–1.94) | 1038 (5.0) | 21 | 2.70 |
| 1.1 > AGR ≥1.0      | 395 (1.5) | 19 | 6.52 | 2.07 (1.28–3.36) | 2.53 (1.37–4.65) | 265 (1.3) | 12 | 6.08 |
| 1.0 > AGR           | 105 (0.4) | 10 | 14.21 | 3.99 (2.10–7.58) | 2.48 (0.78–7.86) | 67 (0.3) | 3 | 6.33 |

*aRate per 1000 person-year.

*bMultivariable Cox proportional hazards models adjusted for age, sex, current smoking, body mass index, and previous history of chronic liver disease.
Obesity and cancer: links with survival differ from those with incidence

The letter from Bifulco in the *Annals of Oncology* [1], prompted by the recently published data from the POSH study [2], gives a refreshing update on the link between obesity and cancer, and emphasises the need for continued research to understand the underpinning molecular mechanisms in a cancer-specific framework. However, for the readership unfamiliar with the field of ‘adiponcasis’, one might mistakenly think that the negative impacts of obesity on cancer risk are paralleled by adverse influences of obesity on treatment outcome.

There is a large volume of epidemiological data that excess weight [commonly approximated as body mass index (BMI)] is associated with increased incident risk for several common adult cancer types. Given the consistency, strengths, and specificities of associations; the sufficiently long latency times between BMI measurements and cancer occurrence (typically >8 years); and reversibility 10 years and more after bariatric surgery; many of these associations are probably causal. For 2012, the estimated attributable risk due to high BMI worldwide was 3.6% of all incident cancers, or almost half a million new cancers [3]—in other words, this is globally a substantial public health problem.

In contrast, the evidence that excess weight, either at the time of cancer diagnosis or in the survivorship period sometime after cancer diagnosis, influences either overall or cancer-specific survivals is far from clear. For breast cancer, the tumour type with the greatest volume of evidence, the World Cancer Research Fund (WCRF) recently undertook a comprehensive review of this question, including up to 49 studies totally 16 000 deaths (varied by analysis type) [4]. The report emphasized that, while there are many studies reporting an adverse impact of excess weight on survival, interpretation of the majority of studies is limited by biases and confounding. In relation to breast cancer mortality, the report concluded that ‘the evidence suggesting that greater body fatness before, or less than 12 months after a diagnosis of postmenopausal primary breast cancer increases risk is limited’. The POSH study [2], published since the WCRF report, which shows that excess peri-diagnosis BMI is associated with a poorer survival in young women with ER-positive breast cancer, does not materially alter the WCRF conclusions. My research team have arrived at similar conclusions for colorectal cancer [5]; and after secondary analyses of randomised trial data (where patients receive standardised allocated treatments and therefore reduces biases), arrived at similar interpretations for endometrial cancer [6], a malignancy where risk is strongly linked with obesity.

By extension, there are two clinical lessons here. First, there is an important epidemiological principle: that an established link between an exposure (here, body fatness) and increased incident cancer risk, does not necessarily translate into an inferior outcome following treatment of that cancer. Second, if a lifestyle factor is not causally linked with prognosis, it is unlikely that its modification during survivorship will impact significantly on oncological outcomes.

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