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Comment on: 'Trends in the lifetime risk of developing cancer in great Britain: comparison of risk for those born from 1930 to 1960'—cancer predictions need more context

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Sir,

Projections of lifetime risk and cancer incidence for the next 25 years reported by Ahmad *et al* (2015) are alarming but probably realistic. In the last 30 years, the incidence of all cancers in the United Kingdom has risen from 293 cases per 100 000 persons in 1975 to 396 per 100 000 in 2011 (Cancer Research UK, 2012), a rise of 35%. We were, however, surprised to such limited discussion or analysis of cancer mortality trends over the equivalent time period, which has fallen 21% since 1971 (Cancer Research UK, 2012).

There has been a steady and linear increase over time in cancer incidence (Figure 1, solid black line). Extrapolating this trend forward (black dotted line) using simple linear regression produces incidence rates that generate lifetime and cumulative risks that are broadly in line with Ahmad *et al*'s more sophisticated approach. Using the same method to extrapolate the trend in all-cancer mortality (solid grey line) suggests that all-cancer mortality will continue to decline (grey dashed line). In short, extrapolating current trends forward sends incidence and mortality in different directions, and this suggests a future in which cancer becomes more common but at the same time more benign.

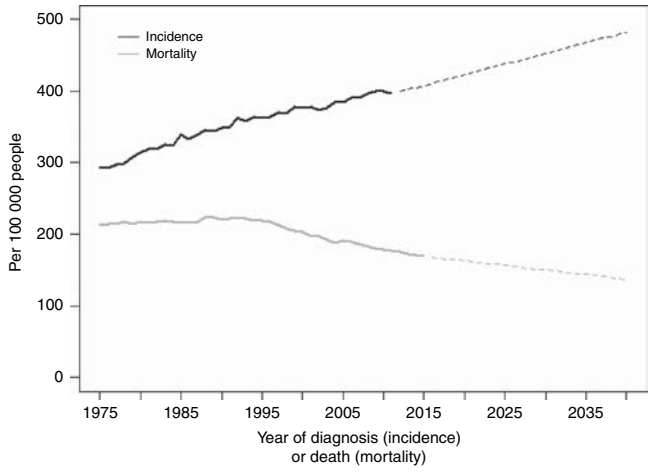

Figure 1. All-cancer incidence and mortality in the United Kingdom from 1975 to 2011(solid lines) and projected incidence and mortality (dashed lines).

One explanation for detecting increasing levels of cancer on the scale suggested by Ahmad *et al* without a concomitant increase in mortality is the detection of disease that will not go on to cause symptoms or death: 'overdiagnosis' (Welch and Black, 2010). This was acknowledged as contributory to the increased incidence in prostate cancer in relation to PSA testing, yet similar trends can be seen for thyroid, kidney, melanoma and breast cancer. Although it is methodologically challenging to take into account the impact of over-diagnosis and its underlying causes, diagnostic drift, increasing test sensitivity and changing competing mortality risks, these are important considerations to note when interpreting incidence data (Carter *et al*, 2015).

We call on the authors to publish their projected mortality rates to provide greater context to these worrying figures. The public deserve clear information about the drivers behind them, especially given the cumulative risk of over-diagnosis in an ageing population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Comment on 'Dexamethasone exerts profound immunologic interference on treatment efficacy for recurrent glioblastoma'

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Sir,

In this manuscript, Dr Wong and colleagues observed that patients with recurrent glioblastoma who underwent therapy with tumor treating alternating electrical fields and were on higher doses of dexamethasone had lower T-lymphocyte counts and shorter survival (Wong *et al*, 2015). The investigators attributed these outcomes entirely to 'global immunosuppression by dexamethasone'. In fact, this patient population receives three therapies that are highly toxic to lymphocytes – glucocorticoids, radiation, and temozolomide. Recent studies have demonstrated that 40% of patients with newly diagnosed glioblastoma develop grade III and IV lymphopenia with CD4 counts <200 cells mm^{-3} 2 months after beginning radiation and temozolomide (Grossman *et al*, 2011). This profound lymphopenia lasts for over 1 year and on multivariate analysis is independently associated with inferior survival. Treatment-induced lymphopenia has also been studied in other solid tumors that are not treated with dexamethasone or temozolomide; data from these studies strongly point to radiation as the primary causative factor in treatment-induced lymphopenia. These studies reported rates of lymphopenia that were very similar to those seen in glioblastoma and again identified an association between treatment-induced lymphopenia and survival in patients with pancreatic cancer, non-small cell lung cancer, and breast cancer. (Balmanoukian *et al*, 2012; Campian *et al*, 2013; Wild *et al*, 2013; Tang *et al*, 2014; Afghahi *et al*, 2015) Two hypotheses have been advanced to explain this phenomenon. The first relates to the inadvertent radiation of circulating lymphocytes (MacLennan and Kay, 1978; Yovino *et al*, 2013). The second stems from observations that IL-7 levels are inappropriately low in irradiated patients with severe treatment-related lymphopenia (Ellsworth *et al*, 2014). We agree that immune status is an important prognostic factor in patients with recurrent glioblastoma.

However, as radiation-associated lymphopenia is common and long-lasting in patients with glioblastoma, as well as in patients with pancreatic, lung, and breast cancer, where dexamethasone is not an integral part of therapy, it is likely that the immunosuppression described by Dr Wong *et al* was due to prior radiation exposure, rather than to dexamethasone treatment. At a minimum, this issue should be formally addressed in this manuscript and in subsequent work regarding this important topic.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Response to: Comment on 'Dexamethasone exerts profound immunologic interference on treatment efficacy for recurrent glioblastoma'

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Sir,

We would like to thank you for an opportunity to respond to the comments from Drs Ellsworth and Grossman in their letter to the editor concerning our recent paper, 'Dexamethasone Exerts Profound Immunologic Interference on Treatment Efficacy for Recurrent Glioblastoma', by Wong *et al* (2015).

Contrary to the assertion by the authors, our paper did not claim that the effects of dexamethasone were mediated via steroid-induced lymphopenia. It is widely accepted that dexamethasone exerts pleotropic effects on the immune system that lead to the suppression of multiple effector systems required for therapy-induced tumor rejection (Fauci, 1976; Benedetti *et al*, 2003). Within our single institution patient cohort, we aggressively weaned dexamethasone doses and we found that patient outcome correlated with T-cell counts. T-cell count was used as a marker of potential immunological competency to test if it correlated with outcome, as suggested by our initial observation in the phase III trial that high dexamethasone dose was correlated with a poorer survival. As pointed out by Drs Ellsworth and Grossman, the observed lymphocyte counts in our single institution cohort were probably related to patient treatment history, intrinsic immune state or both, but not necessarily to corticosteroid usage. Furthermore, overall survival as a function of the effect of dexamethasone in each of the two arms in the phase III trial was very likely independent of the T-lymphocyte counts of patients entering the trial, as supported by our single institution patient cohort where no correlation was observed between dexamethasone dose and T-lymphocyte count.

The authors also cited their work on the immunosuppressive effect of radiation and temozolomide when given to patients with newly diagnosed glioblastomas (Grossman *et al*, 2011). They found that 40% of patients had <200 CD4 cells mm^{-3} 2 months after initiation of treatment and this was associated with a poorer survival when compared with those with $\geqslant 200$ CD4 cells mm^{-3}. Given that corticosteroid use was not a controlled variable, it is possible that dexamethasone may have contributed to the poor survival outcome in this study. Regardless, the overall conclusion of their study was also consistent with our utilisation of T-lymphocyte counts as a marker of poor outcome. Furthermore, an earlier study by Hughes *et al* (2005) investigated the phenomenon of lymphopenia in the pre-temozolomide chemo-irradiation era and found that 24% of the cohort had <200 CD4 cells mm^{-3} whereas 76% had $\geqslant 200$ CD4 cells mm^{-3}. Therefore, it is possible that the addition of temozolomide to dexamethasone plus radiotherapy increased the proportion of patients who developed poor outcome and low CD4 lymphocyte count (from 24 to 40%). Taken together, it may be important to re-examine the potential role of dexamethasone in these two studies.

Lastly, the authors also cited that treatment-related lymphopenia is a marker of poor outcome in pancreatic and non-small cell lung cancers (Balmanoukian *et al*, 2012; Campian *et al*, 2013; Tang *et al*, 2014; Wild *et al*, 2015). Our data are consistent with this contention, but do not address the cause of the low T-lymphocyte counts in our patients. It is notable that patients in these studies also received concurrent emetogenic chemotherapies, such as taxol/carboplatin, gemcitabine or gemcitabine/carboplatin, and dexamethasone was likely an important antiemetic in the premedication regimen and may therefore confound the outcome analysis.

Although it is hard to absolutely devolve the contribution of dexamethasone from prior radiation and chemotherapy effects in patients with recurrent glioblastoma, the NovoTTF-100A monotherapy arm in the phase III trial nevertheless offered us a unique opportunity to evaluate the sole effect of dexamethasone dosage because the influence of prior radiation and chemotherapy was randomized and balanced. In contrast to commonly used chemotherapeutic regimens (Grossman *et al*, 2011), NovoTTF-100A does not exert such deleterious effects on the immune system. Given these conditions, we were able to determine that subjects who received a dexamethasone dose of $\geqslant 4.1$ mg day^{-1} had a significantly shorter survival than those who took <4.1 mg day^{-1}. Therefore, one of the obvious implications of our work is that future clinical trials in the glioblastoma population may need to control for the confounding dexamethasone effect in outcome. Furthermore, it may be worthwhile to re-examine treatment outcomes of prior clinical trials based on dexamethasone stratification.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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