Exercise Window Trial in Newly Diagnosed Breast Cancer - Letter

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We read with great interest the article by Ligibel and colleagues [1], of the Pre-Operative Health and Body (PreHAB) study looking at the molecular effects of exercise on breast tumours between diagnosis and surgery. The reported up-regulation of pathways related to inflammation and immunity is consistent with the expected role of the tumour microenvironment in response to exercise [2]. Sequentially-sampled window studies have great potential to inform by minimising patient-patient variation, but are a very challenging way to examine the effects of treatment or other interventions. Assessment of proliferation is a natural endpoint for response, but measurement of Ki67 is notoriously unreliable.

There are many different gene expression analysis approaches and numerous breast cancer signatures [3]. The current drive for reproducible research has led to expectations that datasets and analysis software are made freely available. With this in mind and our desire to perform similar studies, we reanalysed the PreHAB study gene expression data (GSE129508) using the GeneFu package [4] to calculate estimations of the established genomic grade index, PAM50 and Mammaprint risk of relapse prognosis prediction algorithms of the samples taken at diagnosis and excision from patients randomised to the exercise and control groups.

The majority of exercising patients (12/16) had significantly reduced predicted PAM50 risk of relapse scores ($p=0.03$), whereas half of the control group had smaller non-significant ($p=0.81$) reductions in predicted risk of relapse. Trends ($p=0.08$, $p=0.09$) for reductions in genomic grade index and Mammaprint scores in most exercising patients were not evident in controls (Figure 1). These prognostic signatures were derived from different analytical approaches and represent different facets of breast tumour biology including proliferation, immune response and oestrogen signalling.

Whole tumour gene expression profiling captures information on all cell types, whereas deconvolution approaches can generate *in silico* predictions of the proportions of immune cell types present in samples. As above, we used the ImSig package [5] to assess changes in immune cell content changes in the PreHAB data. Increases in several immune cell types were observed including macrophages and B-cells, alongside a reduction in proliferation, but these changes were not statistically significant.

Our analysis highlights different analysis approaches and supports the findings of the original study. We strongly encourage further studies in this area to examine the biological consequences of exercise on tumours along with assessments of the feasibility of introducing optimal and tolerable exercise regimens into routine clinical care for cancer patients.

References

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Figure 1 Pre-surgical exercise improves predicted prognosis for breast cancer patients Reductions in molecular signature scores are shown in blue and increases in red.