

Project Details	
Project Code	MRCPHS24Ba Campbell
Title	Investigating how physical activity prevents cancers in humans: harnessing 'big' data to understand the genomic profile of human cancers that are preventable by physical activity.
Research Theme	Population Health Sciences
Summary	How physical activity prevents cancers is unknown. It has been proposed that physical activity may do this by augmenting immune function to reduce the outgrowth of immunogenic cancers. To test this theory, this PhD will analyse cancer genomic and population health datasets to determine whether tumour mutational burden – a biomarker indicative of cancer immunogenicity – is a defining feature of the cancers that are preventable by physical activity.
Description	<p>BACKGROUND: Physical activity is associated with the reduced incidence of many cancers. For example, a landmark pooled analysis of 1.44 million adults enrolled in prospective cohort studies in the US and Europe demonstrated that a high physical activity level was associated with the reduced incidence of thirteen different cancers [PMID: 27183032]. These effects withstood adjustment for other lifestyle-related measurements including smoking, diet, alcohol and body mass index, thus indicating that the mechanism-of-action of physical activity is independent of many well-established cancer risk factors. However, the mechanism-of-action responsible for the reduced incidence of cancers in physically active individuals remains unknown. We have recently proposed that the anti-cancer effects of physical activity are ultimately driven by augmented anti-cancer immune function – specifically to T cells – in those who are physically active [PMID: 35359426]. To test this overarching theory, we will investigate whether the cancers that exhibit reduced incidence in highly active people have a genomic profile that renders these cancers more immunogenic, and therefore susceptible to the anti-cancer effects of physical activity. For example, this PhD will determine whether physical activity prevents cancers which typically have a higher tumour mutational burden (TMB). TMB regulates the expression of neoantigens that strongly determine tumour cell immunogenicity to T cells. Thus, TMB is used clinically to predict the immunogenicity of tumour cells to T cells, so that T cell immunotherapies (e.g., checkpoint inhibitors) can be deployed in the most immunogenic cancers. If T cell immunogenicity is integral to the anti-cancer mechanism-of-action of physical activity, we postulate that TMB can also be used to estimate the potential efficacy of physical activity in preventing different cancers. KEY QUESTION/OBJECTIVE: To determine whether the genomic profile (e.g., TMB, and other features) of different cancers is associated with the incident risk reduction of those different cancers in physically active vs physically inactive people. PROJECT OVERVIEW: To address the above objective, the student will firstly analyse existing cohort study datasets (available to the research team) on physical activity level and the incidence of different cancer types in >1,000,000 people from the USA and Europe [PMID: 27183032]. These data will then be profiled against cancer genomic data, obtained from (i) Genomics England, which has tumour mutational burden profiles on 42,922 cancer genomes from 17,000 participants; (ii) The Cancer</p>

	<p>Genome Atlas Program (TCGA) conducted by the NIH in the US on 20,000 cancer genomes spanning 33 cancer types. Using these data, the student will determine whether the magnitude of cancer risk reduction (hazard ratio) from high versus low physical activity for different cancer subtypes is associated with the established TMB of those different cancer subtypes. The student can also pursue many other research questions using these data. STUDENT OWNERSHIP OF PROJECT The student will be the cornerstone of a new supervisory collaboration between Bath and Bristol, responsible for combining expertise in different areas (e.g., cancer, immunology, genetics, epidemiology) to advance knowledge. The student will take ownership and steer numerous aspects of this project, which is flexible in design. From the outset, the student will liaise with collaborating sites (e.g., the NIH in the USA) to decide which data and outcomes to interrogate in this project, and to enable identification of any additional research questions that could be answered using the available datasets. IMPACT: Understanding the anti-cancer mechanism-of-action of physical activity is important from a population health perspective, because it will permit physical activity to be prescribed optimally to reduce the burden of cancer.</p>
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