# Investigating the impact of exercise on T and NK cells in skin cancer: a systematic review

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## ABSTRACT

*Skin cancer has the highest incidence of all cancers, and their incidence are increasing in both melanoma and non-melanoma skin cancers. Alternative adjuvant treatment strategies appropriate for their management are needed. Modifiable lifestyle factors influence disease outcomes, either improving or worsening outcomes. Exercise is an example of a modifiable lifestyle factor, and can be prescribed as an adjuvant therapy in other cancer types to improve immune function and overall clinical outcomes.*

*The initial aim of the review was to investigate the T-cell specific mechanisms of exercise which affect clinical/disease outcomes in skin cancer. Study quality was assessed by a modified Covidence quality assessment template with animal-model study specific criteria. A total of 10 articles were included; all articles were murine model studies investigating melanoma. Eight studies (n=8) employed a randomised controlled trial design, with two bio-informatics studies, and one study using human data which could solidify a link to human health.*

*While the review focussed initially on T-cells, many studies reported significant changes in NK cells, and as they share the same haematopoietic lineage/ common lymphoid progenitor as T cells, the data was included in the analyses. Most studies indicated that exercise reduced melanoma tumour burden. Exercising prior to melanoma inoculation was most effective for delaying carcinogenesis and reducing tumour burden. Synergism was a topic identified in studies; PD-1/PD-L1 treatment, and exercise were not synergistic. Conversely, exercise and mental stimulation were synergistic, and the temperature at which exercise was conducted significantly reduced tumour burden.*

*Several murine studies reported that exercise improved clinical outcomes in melanoma, and that long-term exercise was more effective in reducing tumour burden. Further studies are required to investigate this relationship in humans, and in other types of skin cancer.*

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## INTRODUCTION

Of all cancers, skin cancer has the highest incidence in jurisdictions with mostly white populations. Skin cancer, including both melanoma and non-melanoma skin cancer (NMSC), is one of the most prevalent and burdensome diseases globally [52, 62]. NMSC is an umbrella term describing all other cutaneous malignancies outside of melanoma, and the most common NMSCs are known as keratinocyte cancers (KC), forming around 97% of NMSC presentations [50]. Worldwide, 90% of all skin cancer cases are a KC, and their global absolute mortality rate surpasses melanoma [16, 50, 62].

Immune function is important to both the development and treatment of skin cancer. T cells are an integral immune cell involved in skin health and can originate and/or act dermally or systemically. Resident and circulating T cells have separate roles, but work and influence each other synergistically [32]. T cell composition appears to be different in the skin compared to the systemic circulation, and ~90% of dermal resident T cells are memory T cells (Tm) cells [32]. These cells are associated with immunosurveillance; however, it is unclear how their number and function change in the context of cutaneous malignancies [31]. There is a three times greater incidence of CD4+ Tm cells than CD8+Tm cells within the epidermis. The CD4+Tm population increases with age, indicating a pro-inflammatory phenotype, but it is unclear how this change may be influential in the development of KC, that are often seen in older adult, or in other NMSCs cases [33, 54].

When immune function is compromised, individuals are more likely to develop cutaneous malignancies, including the KC sub-types of basal cell carcinoma (BCC), and cutaneous squamous cell carcinoma (cSCC) [38, 50]. Individuals can become immunocompromised via UV radiation, viral illness, age-associated immunosenescence, and immunosuppressive drugs especially in the context of solid organ transplants [30, 38]. In the general population, the ratio of BCC cases to cSCC cases is 4:1; this ratio is reversed in immunocompromised cohorts [49]. Individuals are up to 100 times more likely, depending on the transplanted organ, to develop invasive cSCC [30, 49]. Immunosuppression is an established prognostic factor for determining the invasiveness of disease. Metastatic

risk for cSCC can be as low as 0.1% but as high as 13.7% in immunocompromised individuals [25].

There are many under-recognised burdens associated with a KC diagnosis that impact health and quality of life [19]. Only limited systemic treatment options and highly invasive surgery are typically offered as a treatment solution for complex, high-risk and/or re-occurring lesions [16, 22]. Surgical operations might cause lifelong structural and functional alterations, especially in the head and neck impacting the patients' quality of life [22]. Individual burden is further compounded by the fact that almost 75% of individuals diagnosed with a KC will have multiple primary carcinomas [8, 34]. Disability-adjusted life years (DALYs) data clearly highlight the significant global burden of KC [52]. KCs have a higher DALY rate across all global regions and age ranges than melanoma [52]. The limited treatment options have resulted in a gradual shift in the classification of KCs to a chronic illness, which acknowledges their severity and burden. Further research into appropriate treatment strategies, and development of adjuvant therapies and rehabilitation programs for individuals living with KC is required [18, 48] .

Modifiable risk factors including lifestyle choices and habits such as alcohol consumption and tobacco use, poor diet and physical inactivity can influence initiation, incidence and outcomes of various diseases including cancer. In the United States, ~42% of all cancer cases are associated with a modifiable risk factor [9]. Sun exposure is one of the better-described modifiable risk factors for development of skin cancer [23]. Other studies investigating modifiable factors such as diet, obesity and exercise have informed the Centre for Diseases Control and Prevention (CDC) and World Health Organisation (WHO) guidelines for general cancer prevention. Their exercise recommendation for cancer prevention is a combination of resistance exercises focusing on all major muscle groups, in conjunction with either 75-150 min of vigorous intensity aerobic exercise or 150-300 min of moderate-intensity aerobic exercise per week [7, 13]. There is a perception that exercise may be skin cancer-provoking, but this arises from studies that either did not conduct exercise in sun-safe manners or indoors, and/or failed to examine the direct effect of exercise or physical activity. Several studies only investigated body mass index (BMI) and prematurely concluded that exercise increased the risk of skin cancer [57, 59]. Investigating the direct effect of exercise on underlying biological mechanisms such as the immunological response to exercise would better assess whether exercise is an appropriate and effective adjuvant therapy for skin cancer.

Exercise improves a multitude of cancer and cancer treatment-related symptoms such as fatigue, more effectively than some pharmaceutical interventions [20]. Progressive increases in the intensity of resistance exercise can reduce lymphedema flares in breast cancer [24, 44, 45]. Exercise can also improve psychological parameters in cancer, reducing depression and anxiety to improve the overall quality of life [5, 7, 11]. Exercise has been recommended across the entire cancer care continuum to improve cancer outcomes, in both haematological and solid malignancies [7, 21, 58].

Studies indicate that exercise can modulate the immune system. Exercise and physical activity are recognised as adjuvant therapy strategies for a variety of cancers, including chronic lymphocytic leukemia and non-Hodgkins lymphoma [36, 61]. An acute 45-60 minute bout of treadmill exercise, at an intensity equivalent to 70% of heart rate reserve can modulate T-cell frequencies, T regulatory (Treg) count, while CD4+, CD25+ and FOXP3+ cells are decreased in number , and T helper 17 (Th17) , Interleukin 6 (IL6) and transforming growth factor beta increased after exercise [36]. In individuals with non-Hodgkins lymphoma, a single acute bout of cycle ergometry exercise at a moderate intensity for 30 minutes, increases the concentration of IL-6 and macrophage migration inhibitory factor, and induces epigenetic modification of natural killer (NK) cells [61].

Improving immune function through immunotherapies has been successful in skin cancers as a whole, likely as a function of these malignancies being characteristically 'immunogenic' [56]. In addition to immunotherapies, exercise is an adjuvant therapy and can potentially enhance immune function, including immunosurveillance and T cell function in cancer [15]. While exercise has been used as an adjuvant therapy in other cancers, there is no clinical evidence to support its use in skin cancer thus far. Preliminary evidence has been complicated by the confounding effects of sun exposure and body mass index [57, 59]. Characterising immune cells involved in skin cancer is needed to identify relationships between exercise, immune function, and skin cancer. Investigating the direct effect of exercise on the immunological response to exercise would better assess whether exercise is an appropriate and effective adjuvant therapy for individuals with locally advanced or metastatic skin cancer. The aim of this review was to investigate the effect of exercise on NK and T-cell specific mechanisms to describe disease outcomes in all types of skin cancer.

## METHODS

**Search strategy**

Four databases were searched: Science Direct, Web of Science, Medline via EBSCO host and Scopus. The search string/terms used in the search were as follows: (Physical activity OR sport OR exercise), (melanoma OR non-melanoma skin cancer OR skin cancer) and (immune OR "T cell" OR CD8 OR CD4 OR CD25 OR CD3 OR CD45 OR lymphocyte OR PD-1). Articles were searched by title, abstract and keyword textual contents where available. The searches were finalised in September 2023.

**Eligibility Criteria and study selection**

The protocol for this systematic review was registered with PROSPERO (PROSPERO registration: CRD42023397176). All skin cancer types including melanoma and non-melanoma skin cancers, of all stages of disease; pre-malignant non-melanoma skin cancers, melanoma in-situ, early and late stage skin cancer were included. In addition, all stages of treatment were included; pre, during and post treatment. Studies had to have a focus on exercise or physical activity and measure T cells or PD-1. Initial searches indicated very limited research in humans, and consequently we included both human and animal model studies, from any publication date and any

experimental research article type; bioinformatics/in-silico, animals and human models. The only caveats were that articles had to be published in English, and that other review articles; systematic reviews, narrative reviews, study protocols, case studies or articles submitted in other formats such as posters, presentations, commentaries, editorials, opinion articles or abstract-only journal entries were excluded.

We used the Covidence platform (https://www.covidence.org/) which adheres to the PRISMA checklist and tracks study selection to automatically populate a PRISMA flowchart. Figure 1 presents a graphically altered PRISMA flowchart that includes all relevant information of study selection in a simple visual form. Articles were screened independently by (HB) and (CG) with any conflicts resolved by discussion, or involvement of a third assessor (DP).

**Data extraction**

ExtrExtraction was completed using the Covidence extraction template 2.0 [10]. Multiple measures were extracted from the eligible studies and separated into 3 main categories: general article information, characteristics included in the study, and outcomes. The measures extracted in the general article information were; study ID/ DOI, title, lead authors contact details, the country in which the study was conducted, and other study notes. The information extracted from the 'characteristics included in the study' category included: the aim of the study, study design, source of funding, research methods, mice type, cancer type, inclusion criteria of participants, exclusion criteria, the total number of participants, intervention and comparisons/ groups and controls, exercise type, other environment condition information, immune cells analysed, and other measures. Lastly, the outcomes extracted included changes in immune cell NK and T cell percentage, counts, frequencies, or involvement of immune related genes or their expressions and non-immune-related measures. A simplified representation of this data is presented in table 1

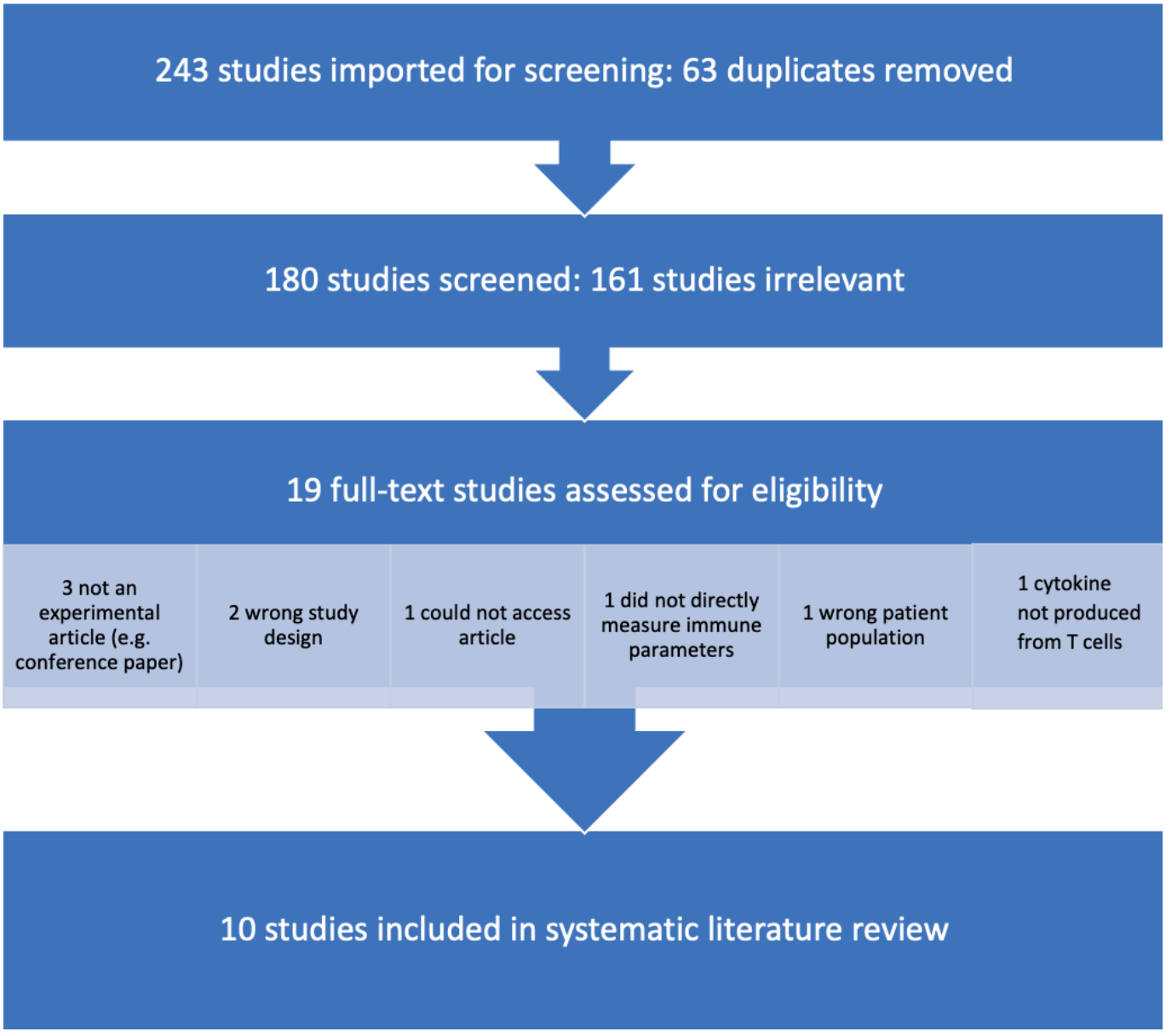


**Figure 1.** PRISMA flowchart for effects of exercise on immune parameters in animal models of skin cancer.

**Table 1:** Extracted study outcomes investigating general measures and changes in immune cells after exercise in murine models of skin cancer.

| Title | Changes in immune cells | | | Other disease measures |
|---|---|---|---|---|
| | **No change/other results** | **Decrease/Downregulated** | **Increase/Upregulated** | |
| [29] (Lee, 2019) | •CD4+T cell no. and differentiation of CD4+T cells | | • CD8+ T cells producing IFNγ by 1.5x in circulation<br>•IFNγ+ CD8+ T cells frequency by 3x in spleen of thermoneutral mice<br>•CD8+ T cells, effector memory CD8+T cells, γδT cells, NKT and NK cells sig. in thermoneutral group. | • Min. tumour growth, ↓ tumour mass in thermoneutral group vs. body temperature and control groups |
| [35] (Pedersen, 2016) | | | •NK, dendritic, NK1.1+, CD4+, CD8+ and CD3+ T (+gamma delta and NKT cells) after exercise<br>•NK frequency, cell cytotoxicity/function and promoted epinephrine-dependant mobilisation of IL-6 sensitive NK cells to tumours.<br>•NK cell no. and infiltration was inversely correlated with tumour burden | • Pre-exercise mice had greatest ↓ in tumour growth (61%) and tumour volume (67%), followed by the exercise group.<br>• All exercising groups significantly ↓ no. of metastases<br>• 66% ↓ in tumour burden in T cell-depleted mice, indicating NK cells activity<br>• Tumour growth was ↑ in NK-depleted athymic mice. |
| [60] (Zhu, 2021) | •3 major pathways; NF-kappa B, chemokine signalling and immune responses<br>• 6 hub genes; genes relevant to T cell functioning included : WDFY4 (CD8+ T cells, alpha beta T cell activation) and ITGAM (macrophages). These genes were weakly associated with overall and disease-free survival.<br>• Exercise related hub genes were dysregulated in melanoma, and verified using melanoma and healthy tissue data from the TCGA database. | •Itgam expression in human melanoma, stages 1-4, differed dependent on disease stage showing stage 2 had the lowest Itgam expression.<br>•Wdfy4 expression in human melanoma stages 1-4, didn't differ depended on disease stage | | • 1627 DEGs were identified; 1285 upregulated genes and 342 downregulated genes in response to voluntary exercise |

| Title | Changes in immune cells | | | Other disease measures |
|---|---|---|---|---|
| | No change/other results | Decrease/Downregulated | Increase/Upregulated | |
| [55] (Xia, 2020) | •3 main group of DEG functionality identified s; molecular function (MF), cellular component (CC) and biological process (BP). BP group associated with immune and inflammatory responses, MF group prominently enriched in chemokine and cytokine activity. | • 5 BP genes were downregulated and 3 MF genes were downregulated.<br>• Immune-related hub genes were: C3, Fgg, Pf4, Orm1 all involved in ↓ immune function | • 209 BP related genes were upregulated and 42 MF genes were upregulated. | • 315 DEGs were identified, 294 upregulated genes, and 21 downregulated genes. |
| [42] (MomessodosSantos, 2019) | • IL-4, IL-10, IL-17 and IL-6 secretions unchanged in mice with/without melanoma on any treatment. | • IL-2, IFN-gamma and TFN alpha in high fat+ exercising cohorts | • Lymphocyte proliferation in mice with melanoma +exercise vs. mice without melanoma or sedentary groups on any diet | • High fat diet ↑ tumour growth<br>• High fat diet + exercise had slower tumour growth |
| [2] (Bay, 2020) | | | •Spleen weight after PD-1 treatment, indicating immune cell expansion, associated with ↑ PBMC killing capacity: 17% in sedentary mice, 23% mice of PD-1 treatment, 15% exercised mice, 17% exercise and PD-1 treatment. | •Wheel running sig. ↓ tumour growth (72%)<br>•Wheel running+PD-L1 treatment reduced tumour size (83%).<br>•Treatments separately were effective<br>•No synergistic effect |
| [3] (Buss, 2021) | • T cell, CD3+ T cells and NK infiltration in any group | •CD8 T cell no. in exercise +antiPD-1<br>•CD8+T cell % in CD3+T cell population, indicating immunosuppressive phenotype shift | •NK cell no. in mice with antiPD-1<br>•FoxP3+ T cells no. in mice with antiPD-1 but not sig.<br>•FoxP3+CD3+ cell % in tumour immune cell hotspots | •Exercise had no effect on tumour growth rate, tumour cell proliferation or mice survival<br>•Exercise did not affect perfusion of vessels, vessel density or hypoxic state of tumour |

| Title | Changes in immune cells | | | Other disease measures |
|---|---|---|---|---|
| | **No change/other results** | **Decrease/Downregulated** | **Increase/Upregulated** | |
| [4] (Cao, 2010) | • In tumour burden in running only mice, but had an enhanced immune response<br>• Improved clinical outcomes achieved in enriched in environment indicated synergism between mental and physical stimulation | • IGF-1 in running only mice, similar to enriched mice | •NK cytotoxicity and CD8 T cell functionality in enriched environment (started prior to melanoma inoculation) | •Delayed carcinogenesis: 17% of enriched environment mice did not develop macroscopically visible tumours. All control mice developed tumours.<br>•Enriched environment mice had 77.2% lower tumour burden vs. control. They had ↓ tumour cell proliferation |
| [14] (Fei, 2020) | | | •NK cell tumour infiltration in all swimming treatments. Effect increased with increasing intensity<br>•NK cells no. in the pre-free swimming group | • Continuous swimming ↓ tumour mass, detraining ↑ tumour growth<br>•Thymus weight ↑ in pre-free swimming |
| [43] (Savage, 2023) | • CD4+ T, CD3+ or FoxP3 T reg cells in YUMMER<br>• FoxP3 T cells in B16F10<br>• CD8+ T cell no. or presentation of CD69 activation marker and PD1 expression in B16F10<br>• Efficacy of anti-PD1 treatment in YUMMER | •CD3+ and CD4+ T cells no in B16F10 | •VCAM1 expression in tumour vessels, but unchanged in normal vessels indicating exercise differentially affecting cancer/normal tissue<br>•CD8+ T cell abundance and no. presenting CD69 activation marker and PD1 expression in YUMMER<br>• CD8+ T cell mobilisation to tumour | •Exercise sig. ↓ tumour size in YUMMER but not B16F10 tumours<br>•Exercise significantly improved vasculature in both tumour models<br>•Exercise ↓ hypoxia in YUMMER cells only. |

**Quality assessment**

The Covidence quality assessment template was modified as it was clear at the point of extraction all included articles were conducted in animals. Therefore, the quality assessment needed to be appropriate and relevant for this type of study. The Covidence quality assessment template was modified using animal study-specific criteria [28]. An explanation of the criteria and assessment strategy are detailed in Table 2 using the descriptors of 'high', 'low', or 'unsure'.

## RESULTS

One article was identified and added to the Covidence platform through manual searching [29]. This article was deemed to be appropriate and suitable for inclusion in this systematic review. In total, 10 articles were extracted. All articles had a focus on melanoma, and no studies investigated the immune-modulating effects of exercise in animals with any other skin cancer types. Despite this investigation being open to both human and animal studies, only animal studies met the specified inclusion criteria.

General information on each study is presented in Table

**Table 2:** Quality assessment characteristics and descriptions used in assessing all studies

| Quality assessment characteristic | Description |
|---|---|
| Treatment allocation/randomization | Did this study describe how humans/mice were randomized to treatment type? If so were treatments allocated as the method indicated?<br>High= the study detailed that treatment allocation was randomized |
| Blinding of personnel | Did the researchers/ assistance know which mice/humans were on certain treatments?<br>High= high quality and adequately blinded |
| Sample size | Does the paper clearly indicate the sample size, and was the sample size adequate?<br>High=article clearly indicated what the resulting sample size was, and the sample size appeared to be adequate |
| Explanation of statistical analysis/what models were used | Did the paper indicate what statistical models were used/ why they were used?<br>High= high quality explanation/explanation was present |
| Whether all animals were accounted for/ incomplete outcomes | Were all animals accounted for throughout the study and at the conclusion of the study/ in the results?<br>High= yes all animals were accounted for. |
| Descriptions of animals used | Study had clear descriptive of animals e.g. mouse type, age.<br>High= Detailed descriptions of animals were included |
| Statement of compliance with any regulatory requirements | Have the authors clearly stated that the study was conducted in compliance with any regulatory requirements<br>High=yes, article clearly stated the study was conducted in accordance with regulatory requirements, and referred to any codes/ registrations |
| Conflicts of interest reported | All conflicts of interest were acknowledged and reported<br>High=yes |
| Other sources of bias | Were other sources of bias acknowledged within the article/ discussion?<br>High=yes |
| Selective reporting | Does the article discuss all results or only pay attention to one aspect of the study?<br>High=no selective reporting |

Studies were marked as 'unsure 'when the article was ambiguous, or when some elements were included but did not meet include the entire criteria to be assessed as 'high' or 'low'.

**Table 3:** Simplified table of extracted article information and study characteristics

| Title | Study design | Population description and cancer type | N= | Intervention and Comparisons/ groups and controls: | Exercise type And other environment conditions | Immune cells analysed | Measures |
|---|---|---|---|---|---|---|---|
| [29] (Lee, 2019) | Randomised controlled trial | C57BL/6 (B6) mice, 7 weeks old<br><br>B16F10 murine melanoma cells | n=27 (n=9 mice per group) | Housed/control: no exercise<br>TT: Thermoneutral temperature 29°C<br>BT: Body temperature 36°C | Swimming in either 29°C water OR 36°C for 30 minutes, 6 days a week., for 3 weeks. | NK cells, γδT cells, NKT cells, and cytotoxic CD8+ T cells | Rectal body temp.<br>Tumour volume<br>Conc. of immune cells<br>Detection of soluble γc receptor |
| [35] (Pedersen, 2016) | Randomised controlled trial | C57BL/6 mice, female mice. 3 months old and 18 month old. Tg(Grm1)EPv transgenic male mice<br><br>B16F10 murine melanoma cells | Unclear but n ≈11 for the separate groups in each study | PBS: sedentary<br>EX: control exercising<br>aPD-L1: aPD-L1 sedentary<br>aPD- L1 þ EX: aPD-L1 treated exercising | Voluntary wheel running for 4-6 weeks. Average distance per mouse was 4.1km/day. | NK cells, T cells, cytokines: IL1 alpha, iNOS, dendritic cells, NKT cells gamma delta T cells, B cells | Tumour volume<br>Lung tumours (mets.)<br>Microarray analysis on B16 tumours<br>Immune cell frequencies<br>NK cell cytotoxicity |
| [55] (Xia, 2020) | Bio-informatics study | Data from Pedersen 2016 | Data from Pedersen 2016 | Data from Pedersen 2016 | Data from Pedersen 2016 | Genes associated with immune function: C3, Fgg (T-cell associated), Pf4 ( T cell function), Orm1 (associated with decreased immune function) | Identifying hub genes<br>Signalling pathways/ pathway analysis<br>Gene expression levels<br>Identification of DEG's<br>Functional enrichment of DEG's (to investigate their biological functioning) |
| [60] (Zhu, 2021) | Bioinformatics study | Data from Pedersen 2016 | Data from Pedersen 2016 | Data from Pedersen 2016 | Data from Pedersen 2016 | Genes associated with the functioning of: WDFY4 (CD8+ T cells, alpha beta T cell activation) ITGAM (macrophages). NK cells. | Measures/ type of analysis:<br>Gene Ontology (GO) analysis.<br>Pathway enrichment analysis<br>Identification of DEG's |

| Title | Study design | Population description and cancer type | N= | Intervention and Comparisons/ groups and controls: | Exercise type And other environment conditions | Immune cells analysed | Measures |
|---|---|---|---|---|---|---|---|
| [42] (Momessod osSantos, 2019) | Randomised controlled trial | C57BL/6 mice, female 6 weeks old<br><br>B16F10 murine melanoma cells | N=80 | 1) normolipidic (N) control<br>2) N + melanoma (NM)<br>3) high-fat (H) control<br>4) H + melanoma HM)<br>5) N control + physical exercise (NE)<br>6) N melanoma + physical exercise (NEM)<br>7) H + physical exercise (HE), and<br>8) H melanoma + physical exercise (HEM). | Moderate treadmill running 10 weeks, 3 times a week, 10 minutes each day<br><br>Normolipidic diet: diet composed of 10% of energy from fat/lipids sources<br>High fat diet: 60% energy from lipid fat sources. | T-helper 1 cells, M1 macrophages T-reg cells. Th-17 cells | Serum leptin levels Lymphocyte concentration<br>Treg and Th17 cell counts.<br>Cytokine production by stimulation of lymphocytes.<br>•Lymphocyte proliferation.<br>•Melanoma growth |
| [2] (Bay, 2020) | Randomised controlled trial | C57Bl/6NTac or NMRI-Foxn1nu mice, female, 8-16 weeks old<br><br>Murine B16F10 melanoma cells | n=14 (however, 6 mice were sacrificed prematurely) | PBS: sedentary<br>EX: control exercising<br>aPD-L1: aPD-L1 sedentary<br>aPD- L1 þ EX: aPD-L1 treated exercising | Voluntary running wheel exercise (5 weeks prior to melanoma inoculation)<br><br>Half the participants were treated with aPD-L1 | PD-L1, PBMC's | Tumour weight<br>Tumour volume<br>Spleen size<br>Spleen volume |
| [3]<br><br>(Buss, 2021) | Randomised controlled trial | C57BL/6 mice Female mice. Aged 6-10 weeks<br><br>B16F10 murine melanoma cells | n=24 Some were prematurely euthanised due to ulceration of tumours (n=4) | Mice were randomly assigned to either the exercise OR no exercise group | Voluntary wheel running for 2-5 weeks (this was dependant on tumour size).<br>Mice ran on average 8km/day | NK cells, T cells: Treg, cytotoxic T cells | Tumour volume Conc. of intratumoural T cells, NK cells and infiltrating NK cells.<br>Spatial infiltration of T cells within tumour |

| Title | Study design | Population description and cancer type | N= | Intervention and Comparisons/ groups and controls: | Exercise type And other environment conditions | Immune cells analysed | Measures |
|---|---|---|---|---|---|---|---|
| [4] (Cao, 2010) | Randomised controlled trial | C57BL/6 mice, 3 week old. Males<br><br>B16 melanoma cells | n=18-20 | Control/grouped housing, EE (enriched environment), grouped housing, and a sub study with voluntary running mice only | EE had free access to running wheel and other stimuli. Running mice had free access to running wheel .<br>EE group ran an average of 0.64km/day and running mice ran 2km average per day | Splenic lymphocytes<br>NK cells<br>CD 8 T cell<br>IGF-1 | Tumour size<br>Tumour volume<br>Cellular proliferation<br>Apoptosis. |
| [14] (Fei, 2020) | Randomised controlled trial | C57BL/6 mice Male mice. Aged 6-8 weeks<br><br>B16F10 murine melanoma cells | n=50 | Free swim (FS)<br>Exhausted swim (ES)<br>T con: 4 wks rest, melanoma injection, after 2 wks.<br>F group: FS 4 wks, melanoma injection, FS 2 wks, analysed.<br>E group: 4 wks ES, melanoma injection, 2 wks ES, analysed.<br>F pre: 4 wks FS, melanoma injection, 2 wks rest, analysed<br>E pre: 4 wks ES, melanoma injection, 2 wks rest, analysed. | 6 week intervention. Free swimming, without load and exhausted swimming, mice are load-bearing. | T lymphocytes, NK cells | Tumour weight Thymus and spleen weight<br>Proliferation of splenic T lymphocytes<br>NK cell tumour infiltration |
| [43] (Savage, 2023) | Randomised controlled trial | C57Bl/6 WT male mice, 8-12 weeks old for most of the study (mixed gender for ERK5 S496A knock-out study)<br><br>YUMMER 1.7 and B16F10 murine melanoma cells | N=52? | Control: sedentary mice<br><br>Exercised mice with YUMMER cells (inoculated 5-6 days prior to exercise)<br><br>Exercised mice with B16F10 cells (inoculated 7 days prior to exercise) | Aerobic exercise (treadmill exercise) 45 minutes per/day, 12-14 consecutive days | CD8+ T, CD3+ T cells, CD4+ T cells and FoxP3+ regulatory T cells, myeloid-derived suppressor cells (MDSC), myeloid cells (TAM1, TAM2, and Mono DCs), and lymphocytes (NK, CD4T, CD8, and Cycling CD8T | Tumor vessel hyperpermeability and perfusion assays, VCAM1 expression in tumor vasculature |

**Table 4:** Assessment of study quality

| Study ID | Treatment allocation | Blinding of personnel | Sample size | Explanation of statistical analysis/ models used | All animals accounted for/ incomplete outcomes | Details of animals used | Statement of regulatory compliance | Conflicts of interest reported | Other sources of bias | Selective reporting | Overall quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| [29] Lee 2019 | Unsure | Unsure | Low | Low | High | High | High | High | Unsure | High | Moderate |
| [35] Pedersen 2016 | High | Unsure | Low | High | Low | High | High | High | Unsure | High | High |
| [60] Zhu 2021 | High | Low | High | High | Unsure | Low | Low | High | Unsure | High | Moderate |
| [55] Xia 2020 | High | Unsure | High | High | High | High | Low | Low | High | High | High |
| [42] MomessodosSantos 2019 | Low | Unsure | Unsure | High | High | High | High | High | Unsure | High | High |
| [2] Bay 2020 | High | Unsure | Low | High | Low | High | High | High | Unsure | High | High |
| [3] Buss 2021 | High | Unsure | High | High | High | High | High | Low | Unsure | High | High |
| [4] Cao 2010 | High | Unsure | Low | Low | Low | High | High | Unsure | Unsure | High | Low |
| [14] Fei 2020 | High | Unsure | High | Low | High | High | High | High | Unsure | High | High |
| [43] Savage, 2023 | Low | Low | Low | High | Low | High | High | High | High | High | High |

3. All but two studies employed a randomised controlled trial design, with the remaining two studies evaluating omics, mostly genomics data from animal-based studies. Most studies used the same cancer type - B16/B16F10 murine melanoma cells to inoculate mice, but one study used another murine melanoma cancer cell line, YUMMER 1.7, which produced markedly different results [43]. Most studies used the same murine model - C57BL/6 mice - with the exception of one study [35]. However, there was apparent variation in mouse characteristics, including gender and age, which fluctuated between the studies.

The studies were of moderate to high quality (Table 4), but there were categories in which most studies scored either 'low' or 'unsure'. These categories were blinding of personnel and a discussion or statement explaining any other sources of bias. Overall article quality was determined by counting the number of 'high' scores received compared to number of 'low' or 'unsure' scores. If the number of 'high' scores, were less than the number of 'low'/'unsure' then the article was deemed as a low-quality article. If they were equal, then the article was of moderate quality and if there were more 'high' scores then the articles was rated as high quality.

Substantial heterogeneity in experimental design and selection of immune measures between the studies was identified, so a meta-analysis was deemed not appropriate. Moreover, an array of exercise prescription and types of exercise employed in the studies for the mice was found, varying from wheel running, treadmill running to swimming. Nevertheless, a key experimental aspect these studies shared was they all examples evaluated the effects of aerobic exercise.

While the effect of exercise on T cells was a priority, many of the included studies also investigated the effect of exercise on natural killer (NK) cells. We decided to include NK cells as they share the same haematopoietic lineage/ common lymphoid progenitor as T cells. Additionally, one study [43] explored myeloid cells. This information was beyond the scope of this review, so the myeloid-specific results were not reported.

Describing the effect of exercise was investigated on T cell subsets and NK cells provided additional context to disease outcome measures. CD4+ T cells, FoxP3+Treg cells and CD8+ T cells were the most notable T cell subsets identified. Mixed results were observed in the effect of exercise on CD4+ T cells, where one 3-week swimming study observed no change [29]. Another shorter 12-14 day treadmill intervention observed a decrease in CD 4+ T cell numbers [43]. However, the longest of all studies that recorded CD4+ T cell changes observed an increase in their numbers in their 4-6 week wheel running intervention [35].

FoxP3 Treg cell results were also inconclusive and only explored in two studies; one study observed a non-significant increase in FoxP3 T cell numbers in their exercise and anti-PD1 treatment group [3]. The same study also observed that FoxP3+CD3+T cell percentage was increased in immune cell 'hot-spots' within tumours [3]. The second study found no change in FoxP3+T cell numbers in either their YUMMER or B16F10 melanoma model [43]. These studies were 2-5 weeks and 12-14 days in length respectively [3, 43].

CD8+T cell results number and function were investigated in more studies. Of the five studies that documented change in CD8 T cells, 4 out of 5 studies reported an increase in their number, abundance, function [4, 29, 35, 43]. The only caveat was that one of these studies completed the same experiments in another melanoma model (B16F10, as opposed to YUMMER) and reported no change in CD8+ T cells numbers nor presentation of CD69 activation marker and PD1 expression in the B16F10 model [43]. The final opposing study reported a decrease in the percentage of CD3+CD8+T cell population in the exercise and anti-PD-1 treatment group[3].

A more conclusive effect was also observed in NK cells, potentially due to the larger number of studies exploring them. A majority of studies (4/5) studies that documented NK cells reported that exercise increased the number, frequency, cytotoxicity and infiltration of cells into tumours [4, 14, 29, 35]. Exercise appeared to have the greatest effect on NK cell number, function, and mobilisation to tumours, to potentially elicit the observed disease outcomes such as reduced tumour burden. This effect was evident in athymic mice, where a significant reduction in tumour burden was still achieved through exercise, mediated by NK cells [35]. The one study that opposed these results reported no change in NK infiltration in tumours, but observed an increase in NK numbers in the exercise and anti-PD-1 treatment group [3].

Many studies tested various factors, varying from diet to temperature, and synergism between other treatments, while other treatments, yielded a wide variety of changes in immune parameters and animal well-being. Nevertheless, exercise generally improved cancer outcomes. Diet was explored in a moderate intensity treadmill intervention. The diet comprised of 60% of the dietary energy sourced from lipids, and the prescribed exercise regimen was 10 minutes per day, 3 time a week over 10 weeks. Mice with melanoma on a high fat diet had tumour volumes of approximately 2000mm3 compared to 800mm3 for mice on the same melanoma on a high fat diet [42].

Several studies investigated the importance and effectiveness of exercise before melanoma development, and four studies investigated exercise in combination with other factors such as PD-1 immunotherapy [2, 3, 43], mental stimulation [4], and ambient temperature [29]. Three studies investigated the effect of PD-1 treatment in combination with exercise. Studies came to the same conclusion that exercise and PD-1 immunotherapy worked well independently of each other, but not synergistically [2, 3, 43]. A modest increase in CD8+T cell abundance [43] was not observed in the other studies [2, 3]. The incongruence in outcomes may relate to starting the immunotherapy at different times during the exercise intervention. However, these studies indicate that exercise and anti-PD1 therapy in a murine melanoma model done concurrently may not be synergistic, and other exercise/ immunotherapy regimens may elicit different results.

In contrast, the combination of mental stimulation and exercise appeared to have a synergistic effect in an animal model. The effect may have been mediated through improvements in CD8+ T cell and NK cell function [4]. Ambient temperature in which the mice swam was also identified as an important factor

in immune function and skin cancer. Swimming in thermoneutral water (29°C) or colder water, compared to body temperature water (36°C), increased the number of effector CD8+ T cells, and improved their function with a 1.5-fold increase in CD8+ T cells producing IFNy compared to other groups [29]. Temperature may be a factor that works synergistically with exercise to modulate immune cell frequencies and function to reduce tumour burden in melanoma [29].

Two omics studies were also identified [55, 60]that used the same main data set [35]. One of the studies also used data from The Cancer Genome Atlas to investigate whether their findings from animal data had biological relevance to human melanoma [60]. Despite using the same main dataset, the studies reported different outcomes; the earlier study investigated biological functioning, and the functional enrichment of differentially expressed genes (DEG's) to identify 3 main groups: molecular function , cellular component and biological process [55]. The biological processes group exhibited enriched immune and inflammatory responses, and genes in this category were specific to immune system function, inflammation, and immune response. The molecular function group was prominently enriched in chemokine and cytokine activity.10 top nodes/ hub genes were reported, C3, Fgg, Pf4, and Orm1 were immune-related genes, and generally are associated with decreased immune function (Xia et al., 2020). Conversely the later study identified six different hub genes, with two specific to immune/ T cell function, Wdfy4 (CD8+ T cells, alpha-beta T cell activation) and Itgam (macrophages). The exercise-related genes identified from the animal data were dysfunctional in human melanoma samples, and only weakly associated with disease-free and overall survival [60]. Wdfy4 had decreased expression in melanoma stages 1-4, but did not differ depending on the stage of the disease. Decreased expression of Wdfy4 was not seen in normal tissue [60]. Itgam expression was also decreased in melanoma, stages 1-4, and differed depending on the stage, showing that stage 2 was the most decreased. Moreover, Itgam was not observed to be downregulated in normal tissue [60].

In general, exercise reduced the number of metastases/ tumour burden and delayed carcinogenesis, through different immunological mechanisms. The improved outcomes may have been mediated by the identified exercise-induced T-cell and NK cell modulations. However, results were magnified with increased exercise intensity [14] and in a continuous exercise regimen commenced 3-6 weeks prior to melanoma inoculation. Starting exercise prior to melanoma inoculation delayed carcinogenesis [4] and reduced tumour burden [14, 35]. This effect was mediated by improving the function of CD8+T cells [4] and NK cells. NK cell function was improved characterised by increased cytotoxicity [4] and their ability to mobilise and infiltrate tumours [14, 35]. Collectively these responses would likely to prepare and bolster the immune system against melanoma carcinogenesis [4, 14, 35].

## DISCUSSION

The studies evaluated in this review were limited to murine models of melanoma skin cancer. Studies were relatively heterogenous in design, methods and immune measures, as different types of exercise were investigated. Synergism was also investigated various studies involving PD-1 immunotherapy [2, 3, 43], mental stimulation [4], and/or temperature [29]. Overall, it appears that exercise increased immune cell numbers in a melanoma murine model, in particular T cells and NK cells. Exercise was shown to improve immune cellular function with the effects magnified when exercise was started prior to melanoma inoculation.

When exercise was started 3-6 weeks prior to melanoma inoculation, CD8+T cell [4] and NK cell function was improved [4]. While other immune cell changes were within systemic circulation and may potentiate anti-cancer effects and tumour infiltrating potential downstream, cells CD 8+ T cells and in particular NK cells, were observed to migrate and infiltrate tumours. This sequence of events exemplifies a tumour-specific targeted response to exercise [14, 35, 43]. Longer adherence to these exercise regimens, or exercising prior to development of a melanoma appeared to elicit better clinical outcomes in experimental settings. The results are congruent with recommendations made by the Centre for Disease Control and Prevention (CDC) and the World Health Organisation (WHO), who recommend exercise for the prevention of cancer [7, 13]. Exercise may 'prime' the immune system, improving immune function and allowing the immune system and its surveillance capabilities to better combat melanoma development [4, 35].

Unlike the recommendations made by WHO and CDC, these studies did not incorporate or investigate anaerobic/strength training type exercises. All studies were representations of aerobic exercise primarily treadmill, wheel running and swimming. Most authors did not investigate whether aerobic exercise had any effective, causative or even direct or indirect association (or causation) with the outcome that may lead to further discussion or future investigations. The exception was in a study of soleus muscle citrate synthase activity, which identified that moderate aerobic exercise increased citrate synthase activity and mitochondrial activity [42]. Taken together these results indicate that moderate physical activity is a positive stressor on cells/ cellular function, preserves mitochondrial function and integrity, and combats a range of dysfunctions that may lead to cancer development. However, to contrast the effects of aerobic exercise with strength (resistance) training, or high intensity interval training, would provide a better understanding of how the type of exercise affects outcomes. Comparative studies would also improve mechanistic knowledge, as they may highlight cellular or molecular pathways that differ between exercise types and may help identify a causative effect. This approach would bring a deeper understanding of associations between exercise, immune function, disease progression and clinical outcomes, and downstream guide what types of exercise might be most beneficial in human participants. On the basis of the initial studies evaluated here that the duration of animal exercise studies that was most effective was 3-6 weeks, preferably begun prior to melanoma inoculation. The general consensus was that moderate intensity exercise was effective [42] but there were opposing opinions and results [14,55].

It appears that exercise may have had the greatest impact on CD8+ T cells and NK cells in murine melanoma models, by improving their function to potentially improve disease outcome measures. This outcome was not unique to this study; NK cells in particular respond well to both acute and chronic exercise interventions, and their functions are improved in the context of cancer [27, 46]. NK cells are a topic of interest in cancer therapy research, as improving NK cell function is understood to improve the effectiveness of immunotherapies [6, 46]. Therefore, an intervention or activity to improve their function, like exercise, would be an ideal adjuvant therapy, potentially for use in locally advanced or metastatic KC's.

The effect of exercise on T cells have been widely studied in the context of healthy adults, showing phenotypic T-cell changes, resulting in longer-lasting improved outcomes associated with immunosenescence and functional changes resulting in increased cytotoxicity [46, 51, 53]. More recently, the effects of exercise on CD8+T cells in the context of cancer are now being explored, highlighting that exercise plays an immunomodulatory role towards CD8+T cells to enhance disease outcomes [17, 27].

The results for CD4+ T cells and FoxP3+T cells evaluated in animal studies, were uncertain, possibly a consequence of disparities in the duration of exercise interventions. FoxP3 T cell results were inconclusive in interventions that were comparatively shorter, and a longer intervention may uncover the effect of exercise on Fox3+ T cells in melanoma models. A similar discrepancy was seen with the results of the CD4+ T cells. No clear outcome could be concluded as the results were highly varied with exercise intervention durations ranging from 3-6 weeks.

Another point of methodological variation between studies was the use of different murine melanoma models. In the slowly developing mouse model Tg(Grm1)Epv, exercise was equally effective in reducing tumour burden regardless whether commenced before or after melanoma inoculation [35]. Furthermore, exercise differentially effected the outcome in YUMMER 1.7 murine melanoma model, which exhibited an increase in CD8+ T cells presenting with their activation marker CD69 - these cells also expressed PD1. The increase in CD8+T cell abundance relates to mobilisation through the increased Vascular Cell Adhesion Molecule 1 expression, and decreased levels of tumour hypoxia seen only in the YUMMER model. These processes in turn increase the effectiveness of immune cell function and reduced tumour size in the YUMMER model, and not in the B16F10 cells [43]. Exercise may differentially impact various cancer types, such as the case for the slower growing Tg(Grm1)Epv, which may be likened to other slower growing skin cancers such as KCs. Acute exercise may promote immune function in other skin cancers underpinning its utility as a clinical/lifestyle intervention for skin cancer management. These lifestyle factors and clinical interventions are important to investigate in both isolation and combination as they may be associated with developing a cancer, and more reflective of an accurate 'picture' of the behaviours seen in humans [42].

Diet also appears to play in role in cancer management, in particular the effects of a high-fat diet on melanoma in mice who exercise [42]. Leptin may increase pro-inflammatory and potentially pro-carcinogenic factors in T-helper 1 cells and M1 macrophages. Reduced serum leptin levels, and decreased production of pro-inflammatory cytokines, are associated with chronic sustained low-grade inflammation that accompanies both obesity and carcinogenesis [42]. Several studies investigating the relationship between diet and skin cancer in humans have been conducted [41, 47]. It would be beneficial to extend this knowledge as this high-fat content study has done and identify how exercise and nutrition are best managed in clinical and community settings. Studies also investigated synergism of therapeutic and lifestyle approaches in skin cancer management in a murine model. Whether exercise and anti-PD1 therapy is synergistic or not in cSCC is unclear, as cSCC has an even better response rate to immunotherapies than melanoma [56]. Further studies investigating synergism between exercise and immunotherapies are indicated as improving the response rate and reducing drug tolerance/resistance is a common goal in immunotherapy research [1]. Improving the clinical and mechanistic understanding of immune function is required to make advancements in immunotherapy.

Mental stimulation used in combination with exercise was also investigated. The objective of investigating mental stimulation or cerebral health in relation to its synergism with exercise in combating cancer development was to investigate how the macroenvironment interacts with cancer development [4]. Only a limited number of studies in humans that test the effects of both cognitive training and exercise in cancer patients. Exercise in many cancer types improves cognition and other mental symptoms such as depression and brain fog [26, 39]. A single study has investigated whether there was a synergistic effect between cognitive and physical training in humans [37]. This study found no synergistic effect, and did not investigate whether there was any modulation in underlying immunological mechanisms, cells or function. This is a promising area to expand research efforts.

Swimming water temperature was another identified potential synergistic factor with exercise. Swimming in different temperatures is an already established and utilised rehabilitation strategy, but there is limited understanding its effects on the immune system. Identifying temperature-induced modifications that enhance effectiveness of immune regulation may be of great benefit. Cold swimming water improved CD8+ T cell number and function to reduce tumour burden [14]. However, these outcomes contrasts with the area of hyperthermia medicine; stemming from Dr. William Coley's observation made over 100 years ago, of patients with cancers who experienced high fevers were more likely to experience remission [40]. Heat or fevers may enhance immune function to improve clinical outcomes associated with cancer through changing the tumour microenvironment by a multitude of mechanisms; heat increases CD8+ T cell trafficking into immune organs and to the tumour, and can improve macrophage and dendritic cell function and NK cell cytotoxicity [12, 40]. Exercising temperature is a factor that should be investigated further, as this could improve clinical outcomes in combination with skin cancer immunotherapy.

While the results identified in this review were based in murine melanoma models, genomic sequencing/ omics studies take a whole genome approach that allows investigators to

expand research efforts into areas which warrant further study, especially when coupled with human data. One of these omics studies used The Cancer Genome Atlas to identify prognostic genes relevant to human melanoma [60]. The study utilised this resource and additional data, to contextualise the results for the human health 'picture'. However, the value of animal models should not be discounted, as they are the foundation of the drug discovery and development pipeline, and lead to solutions relevant to human health. Outcomes of animal studies provide a mechanistic framework for evaluating the effects of exercise on skin cancer in humans as a potential lifestyle intervention in a broader cancer management strategy. A combination of experimental studies in both human and animal models coupled with omics studies utilising human data is recommended. Further studies of how T cells, NK cells, and other immune parameters are implicated in the management of keratinocyte cancer, using exercise alone or in combination with therapeutic approaches, are warranted.

## CONCLUSION

We identified multiple potential multiple immunomodulatory mechanisms of aerobic exercise specific to T and NK cells in relation for improving disease outcomes in murine models. CD 8+ T cells and NK cells can directly migrate to and infiltrate tumours to reduce tumour burden, particularly when exercise was begun prior to melanoma inoculation and continued for3-6 weeks Other factors that improved clinical outcomes and worked synergistically with exercise were lower swimming water temperature and increased mental stimulation. More foundational animal models and bioinformatics studies will inform the planning and execution of future mechanistic or bio-informatics research utilising human data. Studies are needed to determine whether the results from animal studies are observed in humans in relation to both keratinocyte cancer and melanoma. In conjunction with human interventions, these results have the potential to uncover the value of exercise as an adjuvant treatment for humans with skin cancer, a cancer with a high prevalence and burden in the community.

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