**Supplementary Materials**

**Supplementary Table S1:** Summary of potential effects of exercise on cancer and its therapy retrieved from the literature

| **Knowledge item** | **Evidence** | **Reference** |
| --- | --- | --- |
| **Effects of exercise on risk of developing cancer, survival rates, and wellbeing of patients and survivors** |   |   |
| Prolonged sedentary behavior increases the risk of several common types of cancers including endometrial, colorectal, breast, and lung cancers.  | Meta-analysis of prospective studies conducted in humans | [[1](#_ENREF_1)] |
| Physical activity reduces risk of certain types of cancer.  | Meta-analysis and systematic review of studies conducted in humans |  [[2](#_ENREF_2)] |
| Exercise reduces recurrence of certain types of cancer.  | Systematic review of epidemiological and randomized controlled trials conducted in humans | [[3](#_ENREF_3)]  |
| Exercise improves survival rates among patients with certain types of cancers.  | Meta-analysis and systematic review of studies conducted in humans |  [[4](#_ENREF_4)] |
| Exercise reduces tumor size, growth, and metastasis in animal models.  | Meta-analysis and systematic review of preclinical data conducted in animal models, notably rodents  | [[5](#_ENREF_5), [6](#_ENREF_6)]  |
| Exercise has positive effects on objective physiologic measures related to physical function, body composition, and cardio-pulmonary fitness of cancer patients and survivors.   | Meta-analysis and systematic reviews of studies conducted in humans |  [[7-11](#_ENREF_7)] |
| Engaging cancer patients and survivors in exercise might promote their adherence to healthy lifestyle including healthy diet and physical activity.   | Meta-analysis and systematic reviews of studies conducted in humans, an integrative data analysis, and review of studies conducted in humans | [[12-14](#_ENREF_12)]  |
| **The effects of exercise on metastasis of cancer** |   |   |
| Exercise improves the systemic pro-inflammatory profile in cancer patients and survivors and might consequently improve the immunological responses.  | Meta-analysis and systematic reviews of studies conducted in humans, animal models, and *in vitro* mechanistic studies  | [[5](#_ENREF_5), [15-19](#_ENREF_15)]  |
| Exercise induces molecular factors that might be capable of interfering with tumor formation. | Reviews of animal and *in vitro* mechanistic studies  | [[18](#_ENREF_18), [20](#_ENREF_20)]  |
| Exercise stimulates the release of catecholamines that activate the Hippo and YAP signaling pathway which is implicated in tumor formation.  | Mechanistic studies using human exercise–conditioned serum from patients and other *in vitro* studies |  [[18](#_ENREF_18), [21-23](#_ENREF_21)] |
| **The effects of habitual exercise on metabolism within tumors** |   |   |
| Tumors favor aerobic glycolysis to support high energy demands within a rapidly proliferative environments of the tumor. Exercise might target the Warburg-type highly glycolytic metabolism within tumor cells and inhibit glycolysis. |  Review of studies conducted in animal models | [[24-26](#_ENREF_24)]  |
| Tumors are susceptible to increased energy stress during habitual exercise.  |  Reviews of animal and *in vitro* mechanistic studies | [[24-26](#_ENREF_24)] |
| Exercise regulates metabolism within tumors probably through inhibiting the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (PKB (Akt))/mammalian target of rapamycin (mTOR) (PI3K-Akt-mTOR) signaling pathway. | Reviews of *in vitro* mechanistic studies | [[22](#_ENREF_22)]  |
| **The effects of exercise on the functions of immune system and exposure to carcinogens** |   |   |
| Exercise increases the number of natural killer cell and their cytotoxic activity.  | Systematic reviews of studies in humans and mechanistic *in vitro* studies |  [[27-32](#_ENREF_27)] |
| Exercise increases monocytes and macrophages in number and function. This include increasing their anti-tumor cytotoxic activity and their ability to produce cytokines that suppress cancerous cells.  | Systematic reviews of studies conducted in humans, animals, and other *in vitro* mechanistic studies |  [[5](#_ENREF_5), [31](#_ENREF_31), [33-36](#_ENREF_33)] |
| Exercise decreases the number and function of pro-inflammatory monocytes and pro-inflammatory cytokines.  | Systematic and narrative reviews of studies conducted in humans, animals, and other *in vitro* studies |  [[20](#_ENREF_20), [31](#_ENREF_31), [34](#_ENREF_34), [37-42](#_ENREF_37)] |
| Exercise enhances T-cell priming and antigen presenting by increasing expression of dendritic cells, IL-4, and IFN-γ expressing T-cells. | Systematic reviews of studies conducted in humans, animals, and other *in vitro* studies | [[10](#_ENREF_10), [25](#_ENREF_25), [43-47](#_ENREF_43)]  |
| Exercise improves adaptive immunity by increasing the number of naïve CD8+ T-cells, decreasing the number of senescent/exhausted CD4+ and CD8+ T-cells.  | Systematic reviews of studies conducted in humans, animals, and other *in vitro* studies | [[34](#_ENREF_34), [43](#_ENREF_43), [47-50](#_ENREF_47)]  |
| Exercise mobilizes and redistributes cytotoxic immune cells. | Reviews of studies conducted in humans, animals, and other *in vitro* studies | [[5](#_ENREF_5), [50-53](#_ENREF_50)]  |
| Exercise increases the levels of chemokines attracting immune cells, natural killer cell-activating receptor ligands, and ligands that reduce blockade check-points of immune cells.  | Reviews of studies conducted in humans, animals, and other *in vitro* studies | [[34](#_ENREF_34), [54-58](#_ENREF_54)]   |
| Exercise increases the number of neutrophils and their production of antitumor peroxides and free radicals.  | Reviews of studies conducted in humans, animals, and other *in vitro* studies | [[5](#_ENREF_5), [33](#_ENREF_33), [59](#_ENREF_59), [60](#_ENREF_60)]  |
| Exercise increase interferon levels and cytotoxic NK and T cells infiltration of tumors.  | Reviews of studies conducted in humans, animals, and other *in vitro* studies | [[10](#_ENREF_10), [27](#_ENREF_27), [47](#_ENREF_47), [61-63](#_ENREF_61)] |
| Exercise decreases levels of lactate resulted from high aerobic glycolysis and thus, reduce suppressive effects of lactate on the functions of cytotoxic immune cells like T cells.  | Reviews of studies conducted in humans, animals, and other *in vitro* studies | [[24](#_ENREF_24), [64-66](#_ENREF_64)]  |
| Exercise increases mobilization of cytotoxic immune cells through different mechanisms that involve shear stress induced by blood flow and adrenergic signaling. These immobilized cytotoxic immune cells might identify and eradicate cancerous cells. | Reviews of studies conducted in humans, animals, and other *in vitro* studies | [[18](#_ENREF_18), [27](#_ENREF_27), [67](#_ENREF_67), [68](#_ENREF_68)]  |
| Exercise might induce hyperthermia which can regulate and delay growth of tumors and increase infiltration of tumors by natural killer cells by increasing the diameter of blood vessels within the tumor.  | Meta-analysis and systematic reviews of studies in humans  | [[46](#_ENREF_46), [69-71](#_ENREF_69)]  |
| Exercise increases body temperature which in turn induces IL-6 trans-signaling and subsequently make blood vessels more permissible to cytotoxic T cells within the tumor. | Meta-analysis and systematic reviews of studies in humans  | [[10](#_ENREF_10), [20](#_ENREF_20), [39](#_ENREF_39), [72](#_ENREF_72)]  |
| There is an inverse association between exercise and colon cancer in men and women. | Meta-analysis and systematic reviews of studies in humans  | [[73-76](#_ENREF_73)] |
| Exercise alters fecal pH and modify the intestinal flora, thus reduce formation of carcinogens. | Reviews of studies conducted in humans, animals, and other *in vitro* studies | [[76-79](#_ENREF_76)]  |
| Exercise might reduce the conversion of steroids to more potent carcinogens. | Reviews of *in vitro* studies | [[24](#_ENREF_24), [80](#_ENREF_80)]  |
| **The role of myokines release induced by habitual exercise**  |   |   |
| Exercise stimulates skeletal muscles to release myokines. The released myokines like Oncostatin M, Irisin, and SPARC have the potential to inhibit cancer cells *in vitro*.  |  Reviews of *in vitro* studies | [[18](#_ENREF_18), [81](#_ENREF_81)]  |
| Myokines released during habitual exercise stimulate the release of cytokines, which in turn, induce the release of interleukins. Interleukins (for example IL-6) are known to promote proliferation, differentiation, and maturation of natural killer and T cells.  |  Reviews of *in vitro* studies |  [[18](#_ENREF_18), [20](#_ENREF_20), [82](#_ENREF_82), [83](#_ENREF_83)] |
| **The effects of habitual exercise on anticancer therapies** |   |   |
| Exercise have the potential to reduce tumor-induced muscle mass loss. | Reviews of studies conducted in humans | [[10](#_ENREF_10), [84](#_ENREF_84), [85](#_ENREF_85)] |
| Exercise might help reduce intramuscular protein degradation associated with chemotherapeutic agents.  | Reviews of studies conducted in humans | [[24](#_ENREF_24), [86](#_ENREF_86)]  |
| Exercise might induce the hormone ghrelin which induces appetite and reduces anorexia. | Reviews of studies conducted in humans and animal models | [[87-91](#_ENREF_87)]  |
| Exercise have the potential to stimulate the release of anti-inflammatory cytokines and reduce the levels of pro-inflammatory factors in cancer states. | Systematic and narrative reviews of studies conducted in humans, animals, and other *in vitro* studies |  [[20](#_ENREF_20), [31](#_ENREF_31), [34](#_ENREF_34), [37-42](#_ENREF_37)] |
| Exercise have the potential to reduce body fats and cardiovascular risk factors in cancer states. |  Meta-analyses of clinical trials and systematic reviews | [[92-94](#_ENREF_92)]  |
| Exercise has the potential to reduce the symptoms of anxiety, depression, and cognitive problems associated with cancer itself and anticancer therapies. Symptoms of depression were seen when kynurenine, which is a metabolite of tryptophan, crossed the blood-brain barrier. During exercise, PGC-1α transcription factor was upregulated which subsequently increased metabolism of kynurenine into kynurenic acid that cannot cross the blood-brain barrier.  | Meta-analyses of randomized controlled trials and systematic reviews | [[9](#_ENREF_9), [67](#_ENREF_67), [95](#_ENREF_95), [96](#_ENREF_96)] |
| Exercise improves muscle strength which is powerful predictor of patient survival after surgery for cancers. |  Reviews of studies conducted in humans and other mechanistic studies | [[18](#_ENREF_18), [81](#_ENREF_81)]  |
| Exercise has the potential to improve the potency and efficacy of anticancer drugs. | Meta-analysis and systematic reviews of studies in humans | [[10](#_ENREF_10), [67](#_ENREF_67), [93](#_ENREF_93), [97](#_ENREF_97), [98](#_ENREF_98)]  |
| Exercise has the potential to reduce the toxicity of anticancer drugs. | Meta-analysis and systematic reviews of studies in humans |  [[93](#_ENREF_93), [99](#_ENREF_99), [100](#_ENREF_100)] |
| Exercise improves blood flow, this might improve delivery of adequate concentrations of anticancer agents to tumors.  | Meta-analysis and systematic reviews of studies in humans | [[71](#_ENREF_71), [93](#_ENREF_93)]  |
| Exercise improves recovery and reduce postoperative complications in patients undergoing surgery for solid tumors. | Meta-analysis and systematic reviews of studies in humans |  [[101-103](#_ENREF_101)] |
| Exercise can protect patients with and survivors of cancer from co-morbidities.  | Meta-analysis and systematic reviews of studies in humans | [[3](#_ENREF_3), [10](#_ENREF_10), [84](#_ENREF_84)]  |

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