

## Cancer and physical activity



### INTRODUCTION

Mere word, “cancer” to a common man is terrifying irrespective of their socioeconomic and educational background. In 2012, cancer incidence in India was 1.01 million, which is projected to increase to 1.4 million by 2025.<sup>[1]</sup> In men, lung, esophagus, prostate, stomach, oral and pharyngeal cancers predominate, while in women, cervical and breast cancers predominate followed by oral, stomach and esophageal cancers.<sup>[2]</sup>

Although advanced treatment modalities have led to improved cancer survival rate, more focus is required on posttreatment care to manage adverse short- and long-term effects of cancer and its treatment.<sup>[3]</sup> The cancer management modalities constitute surgery, chemotherapy, immunotherapy and radiotherapy which are considered to be having certain serious side effects with morbidity, some risk of relapse and development of metastasis. They are cytotoxic even to normal cells, leading to adverse effect on health and quality of life adding physical agony to psychological trauma.<sup>[2]</sup> Such adverse effects constitute nausea, vomiting, diarrhea, anorexia, mucositis, alopecia, constipation, alteration in taste, sleep disturbance, headache, anemia, dry skin, fatigue, anxiety, depression, immunosuppression and reduced physical

fitness leading to compromised quality of life in cancer survivors along with socioeconomic issues.<sup>[1-3]</sup>

The side effects of cancer immune therapy occur due to immune mechanisms leading to T-cell hyperactivation with reactivity directed against normal tissue. Cytokines cause diffuse effects due to nonspecific T-cell reactivity while checkpoint protein inhibitors, adoptive cell therapies and vaccines cause specific organ damage due to more specific T-cell activation.<sup>[4]</sup>

### EXERCISE AND CANCER IMMUNITY

Several studies have reported reduced risk of the development of colorectal, breast and prostate malignancies associated with exercise.<sup>[3,5,6]</sup> It is also reported to be associated with improved survival and lower risk of cancer relapse.<sup>[7]</sup> Although exact mechanism mediating such effect is not yet understood, factors which have been suggested include weight control, improvement in immune function and better control of endogenous hormone levels.<sup>[3]</sup> The role of physical activity and exercise in rehabilitation phase of cancer survivor is gaining importance as it is believed to modulate immunity and inflammation.

According to “Inverted J hypothesis,” regular moderate exercise enhances immune function lowering susceptibility to cancer while sedentariness and repeated

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exhaustive exercise suppress immune function increasing susceptibility to cancer. Long-term, regular exercise is suggested to have anti-inflammatory effect, providing protection against chronic inflammation-associated diseases. The anti-inflammatory effect is due to reduction in body fat, release of catecholamines, anti-inflammatory cytokines by muscles and inhibition of pro-inflammatory cytokine production.<sup>[3]</sup> The serum levels of inflammatory cytokines such as tumor necrosis factor alpha (TNF $\alpha$ ), interleukin (IL)-6 and C-reactive protein are found to be reduced in persons who are on low-calorie diet and are physically active. IL-6 and TNF $\alpha$  are formed by adipose tissue, and their levels are higher in obese persons. Hence, exercise could reduce inflammation by reduction of body fat. Studies have reported the association of exercise with reduced levels of C-reactive protein in postmenopausal women and prostate cancer survivors.<sup>[8]</sup>

### NATURAL KILLER CELLS

The body's immune surveillance system is responsible for identifying and eliminating transformed cells. Potential immunologic biomarkers in cancer research include number of polymorphonuclear leukocytes (PMNs), natural killer (NK) cells, T-lymphocytes and their regulating cytokines. Both the innate and acquired immune defense against tumor cells involves PMNs, lymphocytes, monocytes and NK cytotoxic activity.<sup>[3]</sup> NK cells are known to have role in the first line of defense against pathogens and also in cancer immunosurveillance.<sup>[9]</sup> They have been implicated in immune elimination of tumor cells since the time they were described first in 1975.<sup>[10]</sup> They are subpopulation of lymphocytes having capacity to kill tumor cells without prior sensitization.<sup>[7,10]</sup>

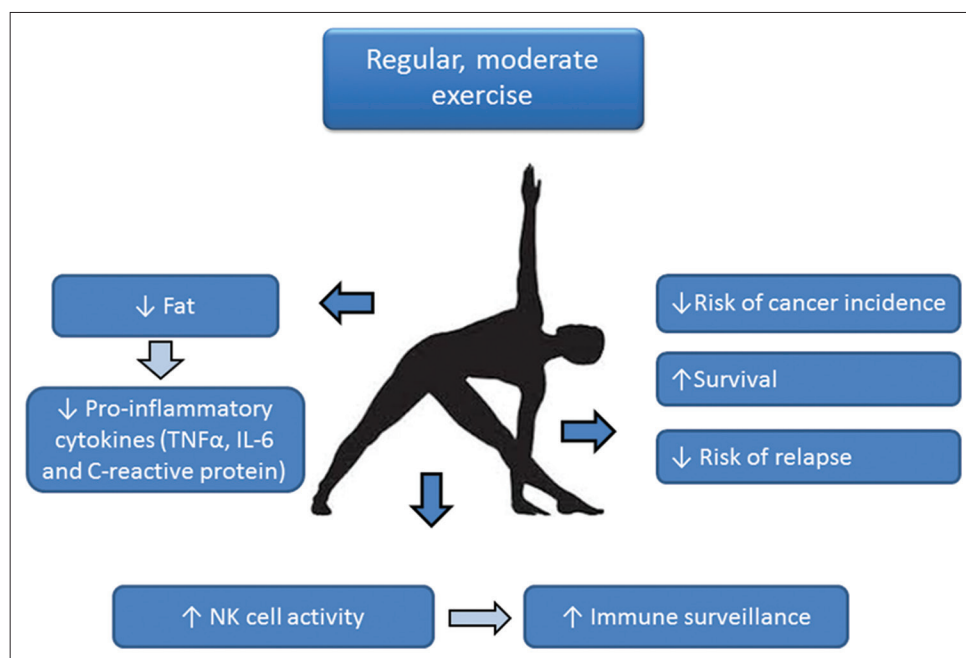
NK cells constitute 5%–15% of lymphocyte population at rest, out of which 90% are involved in cytotoxic and 10% in immunoregulatory function. NK cells can distinguish between healthy and tumor cells by way of interaction between its surface inhibitory and activating receptors, and the ligands present on host cells. Destruction of healthy cells by NK cells is prevented by expression of inhibitory killer cell immunoglobulin-like receptors on NK cells, which interact with Human Leukocyte Antigen (HLA) and other ligands on host cells.<sup>[7]</sup> Recognition of target cells by NK cells is regulated by balance between activating and inhibitory signals.<sup>[9]</sup> Malignant cells become target for NK cells due to downregulation of HLA and upregulation of ligands for activating receptors on them.<sup>[7]</sup> NK cells induce apoptosis of tumor cells by either perforin/granzyme pathway or by way of death receptor ligands.<sup>[9]</sup> NK cells

and cytotoxic T-lymphocytes destroy tumor cells by granule exocytosis pathway which involves releasing granules containing perforin and granzymes into immunological synapse. Perforin induces pore formation which helps granzymes to get into cells and induce apoptosis by cleaving of intracellular substrates. Hence, NK cells infiltration in tumor is associated with prolonged survival and increased cytotoxic activity of NK cells with reduced risk of cancer.<sup>[11]</sup>

### NATURAL KILLER CELLS AND EXERCISE

There is evidence that NK cell activity increases as a result of chronic exercise; number of leukocytes, lymphocytes and neutrophils increase as a result of acute exercise. Studies report increase in number of granulocytes, lymphocyte proliferation and phagocytic activity of monocytes due to exercise. There is also evidence that after exercise, there is increase in cytotoxicity of NK cells while the number of NK cells, T-lymphocytes and cytokine profile remains unchanged. Relation between acute exercise and increase in number of NK cells and its cytotoxicity has been studied in healthy individuals, while in cancer patients, the studies have been done only in relation to chronic exercise interventions.<sup>[3]</sup> Regular exercise is suggested to be beneficial for cancer survival by enhancing NK cell function though certain studies found no effect of exercise on NK cell count or function.<sup>[7]</sup> However, most of these studies are done *in vitro* on cultured malignant cell lines and not on patients own tumor cells.

Several studies have implicated link between regular physical exercise and health.<sup>[12]</sup> NK cells are found to increase in number up to five folds in circulating blood after exercise.<sup>[9]</sup> This remarkable sensitivity of NK cells to exercise stress indicates that these cells may be implicated as link between regular physical activity and overall health.<sup>[12]</sup> Irrespective of whether exercise is aerobic or anaerobic in nature NK cells mostly cytotoxic are quickly mobilized into peripheral circulation which is linked to enhanced immune surveillance with transient increase in NK cell cytotoxic activity. It has been reported that NK cell cytotoxic activity is increased during recovery from acute exercise in both healthy and cancer patients.<sup>[7,12]</sup> However, it has been noted that very prolonged, strenuous exercise leads to drop in NK cell count to preexercise level or still lower, possibly due to their entry into sites of muscle damage, thereby reducing number of circulating NK cells.<sup>[12]</sup> It is also been reported in certain studies that exercise and aerobic capacity has no correlation with NK cell cytotoxic activity.<sup>[7]</sup> Such conflicting reports may be due to diverse methodology and study population.



**Figure 1:** Role of exercise in cancer immunity

### RECOMMENDATIONS FOR PHYSICAL ACTIVITY IN CANCER SURVIVORS

The American Cancer Society has given certain guidelines on nutrition and physical activity for the prevention of cancer. It recommends maintaining healthy weight, active lifestyle, healthy diet and to avoid/limit tobacco and alcohol consumption.<sup>[13]</sup> Studies suggest that mild physical exercise is practicable and safe during cancer therapy and also improves quality of life during and posttreatment. Certain studies have even reported faster rate of completion of chemotherapy with physical exercise. However, when to start and how to maintain such physical activity must be customized to patients' needs and condition. The goal of the exercise program should be to maintain the physical activity as much as possible at low intensity and for shorter duration during treatment and increase the levels after completion of treatment. In some cases, it may be necessary to wait to determine extent of adverse effects of chemotherapy before beginning exercise. Although exercise may be beneficial to cancer survivors, issues such as increased risk of exercise-related injuries call for certain precautions. Judicious exercise is shown to reduce fatigue, anxiety, improves self-esteem, strength and cardiovascular fitness.<sup>[14]</sup> The role of exercise in cancer immunity is depicted in Figure 1.

Effect of yoga has also been studied in various intervention trials in breast cancer patients. A meta-analysis reported yoga to improve psychological health outcomes, reducing anxiety, depression and distress.<sup>[4]</sup> Studies have found positive influence of yoga on quality of life in cancer

patients with few studies reporting significant improvement in inflammatory markers IL-6 and IL-1β.<sup>[8]</sup> Yoga is reported to trigger neurohormonal mechanism by suppression of sympathetic activity and improve autonomic function along with reducing anxiety, stress, insomnia, fatigue and mood disturbances, thereby may be beneficial for cancer patients' physical as well as psychological health. There are many studies reporting potential psychological benefits of yoga while studies on its physical benefits are scarce. Furthermore, most of these studies are done on breast cancer patients, which need it to be tested in other type of malignancies too. Yoga, though is not totally risk-free, is a safe form of exercise provided practiced under qualified supervision. As many of the cancer patients undergo lot of psychological trauma along with physical pain, yoga may be helpful in managing psychological stress, thereby even improving physical healing as both are closely related.<sup>[15]</sup>

### FUTURE RESEARCH

With advanced cancer therapies, cancer survivorship is an emerging public health concern. Although exercise is recognized as an integral part of cancer intervention in improving the immunity of cancer survivors in many developed countries, it has not got much of attention in Indian cancer research.<sup>[10]</sup> Despite having National Cancer Control Program since 1975, research on exercise intervention in cancer survivors is still in initial stages in India. The reason for this could be lack of importance to exercise intervention at the policy level, leading to reduced awareness among treatment providers as well as patients.<sup>[11]</sup>

It is required to have trained professionals to guide cancer survivors in this area of cancer intervention. The study of immunological effects of exercise in humans is a growing area of research. It will be more pertinent to try to establish intensity and duration of exercise required so as to develop a customized training protocol for each patient for optimal anti-inflammatory effect.

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