19. Cancer

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Summary

A sedentary lifestyle and overweight causes 25 per cent of all new cancer cases in the world. Increased knowledge of the impact of overweight and physical inactivity on prevention, treatment and rehabilitation of cancer diseases is therefore important. Cancer develops in a complex interaction between genetics, environment and lifestyle, in which a number of biological mechanisms affect one another. Physical activity affects a series of biological mechanisms, such as metabolism of energy, levels of sex hormones, insulin resistance, leptin, prostaglandins and C-reactive protein, and immune function. It also enables DNA repair. Increased knowledge of these effects on concrete biological mechanisms has laid the groundwork for understanding the observed relations between physical activity and individual cancer diseases, and made it possible to recommend physical activity as a protective factor against cancer.

We know today that regular physical activity is one of the key factors that a person is able to influence to prevent becoming ill with cancer. Existing knowledge shows that, depending on the frequency, intensity and duration, regular activity at work or as recreation can reduce cancer of the colon by 20–60 per cent. Corresponding knowledge on physical activity in relation to breast cancer, shows that 4 hours of activity per week, at an intensity corresponding to 6 METs (MET = metabolic equivalent, i.e. the uptake of oxygen at rest; 6 METs corresponds to a light jog), reduces breast cancer by 30–50 per cent. Physical activity also protects against uterine cancer and may also be significant with respect to prostate and lung cancer.

As a result of the growing incidence of cancer as well as increased survival of patients, an increasing number of people are living longer with cancer. In recent years, research has shown that physical activity not only protects against a number of types of cancers, but is also valuable for patients undergoing cancer treatment and during the rehabilitation phase, as well as for improving function and quality of life. Regular physical activity is an effective way to reduce the side-effects of cancer, resulting in part from physical inactivity and in part from the disease itself. Too much rest can lead to a decrease in aerobic fitness, strength, mobility and unwanted weight gain in the patient.

With respect to physical activity as treatment and rehabilitation for cancer diseases, an effort should be made to include at least 15–60 minutes of daily activities that involve the large muscle groups, such as walking, cycling or skiing, at moderate to high intensity adapted to the particular individual. Avoid heavy loading.

Incidence, causes and risk factors

Historically speaking, cancer has always existed. It was a more uncommon disease in our forefathers who lived as hunters and gatherers some 10,000 years ago (1), however, both because average life expectancy was lower and because the disease itself was less common. Since then, our ways of life have undergone dramatic change, while our genetic make-up has changed by only 0.003 per cent (2). Thus, our modern living habits characterised by physical inactivity subject human cells and biological processes to much more strain than in the past.

The word "cancer" comes from the Greek *karkinos* (carcinoma), meaning crab. Cancer can manifest as a solid growth or "tumour", or as non-tumorous cancers such as leukaemia. "Cancer" is a collective term used to describe over 100 different cancerous diseases that can attack all types of cells in the body. Each cell type can produce completely different forms of cancer, and several different cancer diseases can develop from the same cell type.

Although there are many different types of cancer, they share a number of common characteristics, for example, an uncontrollable cell proliferation (cell division), cell growth and cell death, as well as interaction with other cells and the spread of growth into other organs.

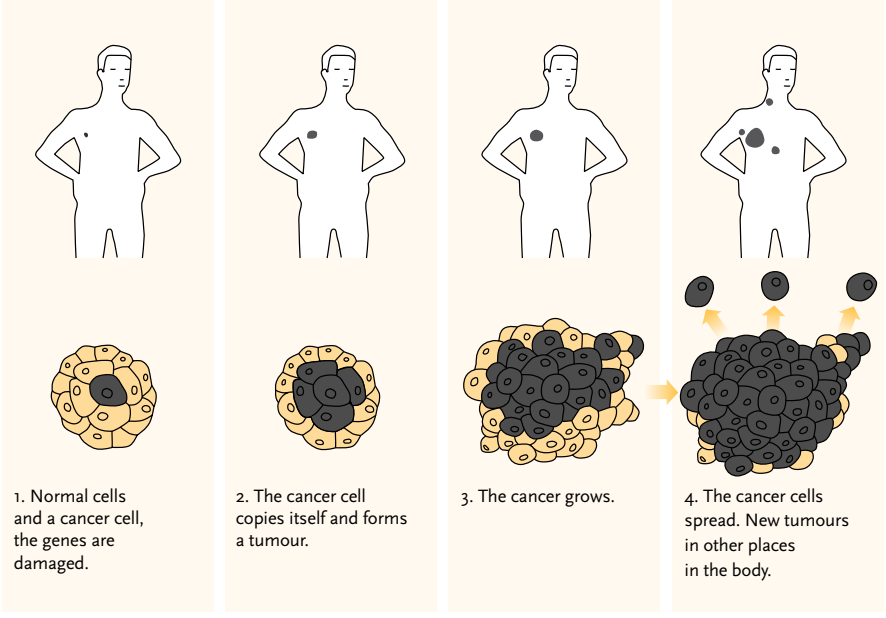

Figure 1. Development of cancer from a normal cell to a cancerous growth (1–20 years).

Cancer develops in a complex interaction between genetics, environment and lifestyle, in which a number of biological mechanisms influence one another. The time from when an uncontrolled process begins until the cancer can be diagnosed varies greatly and it can take up to 20 years from initial development of a cancer cell until a tumour is able to be detected in an organ. Who gets cancer and whether it can be prevented is dependent on whether the preventive factor or the factor to be used in treatment specific to the cancer in question, for example, physical activity, is able to affect the interaction between all the biological mechanisms involved.

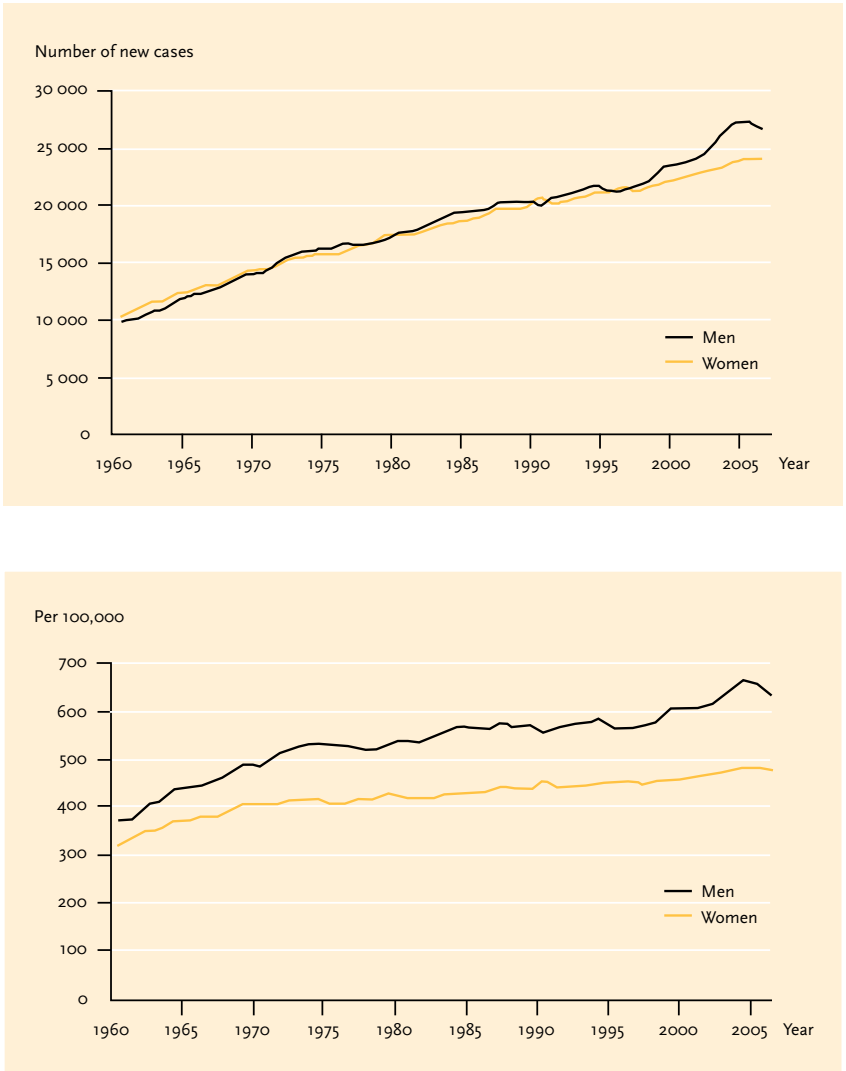

Figure 2. Cancer development in Sweden. Source: Swedish National Board of Health and Welfare, 2006 (4).

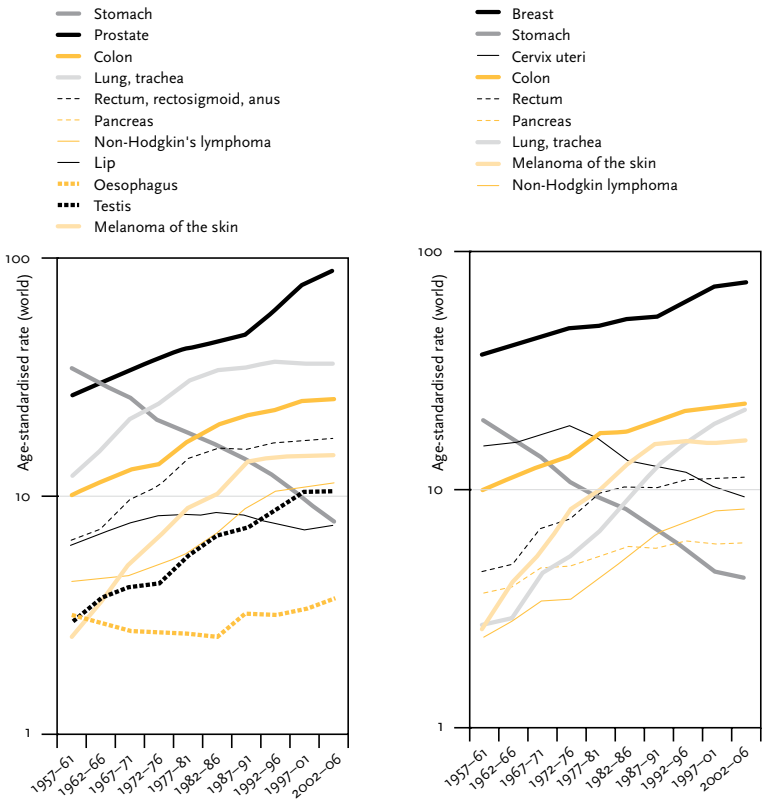

Figure 3. Cancer development in Norway. Source: Cancer Registry, Norway, 2007 (3).

The number of new cancer cases in the world has grown considerably. In Sweden and Norway, an increase of an entire 80 per cent has been noted over the past 50 years (3, 4). In the past few decades, the number of cancer cases has increased at an annual average of 1.7 per cent in men and 1.1 per cent in women. Prostate cancer is the most common type of cancer in men, while breast cancer dominates in women. The fact that we are living longer is partly responsible for the increase, but there is also an actual increase in the number of cancer cases. The chances of survival now are virtually double what they were 40 years ago. The survival rate has increased steadily since the 1950s. The reason for this is earlier diagnosis and better surgical treatment in the large diagnosis groups. Today's cytotoxins, radiation and hormone treatments have also helped. Of those who get breast cancer, 84 per cent now live longer than 5 years with the disease. Even the survival rate for patients with colorectal cancers has continually increased in recent years. In the late 1980s, three of ten patients with rectal cancer suffered a relapse, while the corresponding figure at the turn of the millennium was one in ten (3, 4).

Physical activity – biological mechanisms

Both the increased incidence of cancer and the increased percentage of people living with the disease are connected to our sedentary lifestyles. A growing number of studies show a relationship between physical activity and several types of cancer and there is discussion of whether physical activity may also have a role to play in treatment and rehabilitation (1, 5).

Physical activity is an important factor for good physical health and its positive relation to things such as intestinal function, immune status, energy balance and reduced menstrual pain have been known for several hundred years (6). Physical activity also affects a number of biological mechanisms than in turn affect cancer development and the risk of reoccurrence.

Demonstrating the effects of physical activity on concrete biological mechanisms of importance in cancer development has established the plausibility of the connection observed between physical inactivity and certain cancer diseases (7). We also know that cancer develops through an interplay of genetic predisposition/vulnerability and environment and lifestyle.

Early studies on the importance of physical activity in cancer development addressed energy metabolism (6, 8), sex hormone levels (6, 9), and animal studies the ability to influence DNA repair (1, 5). Other biological processes and factors have since been studied, for example, hyperinsulinemia, insulin resistance and other hormones (leptin), prostaglandins and C-reactive protein. Physical activity and energy balance have been shown, separately and in interaction, to influence these potentially cancer-related factors.

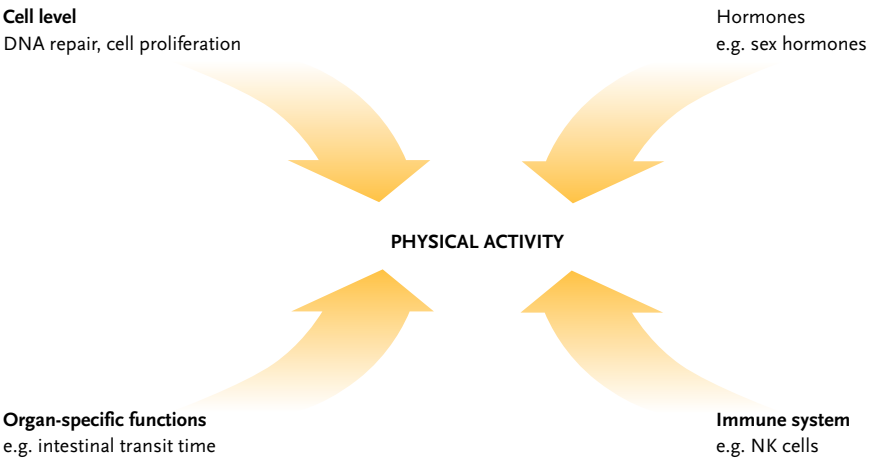

Figure 4. Physical activity and biological mechanisms.

The impact of physical activity on the metabolism of sex hormones is one of the factors that has been shown to have the strongest association to the protective effect against cancer in women. Women with elevated levels of oestrogen and androgen have an increased risk

of developing breast cancer, and anti-oestrogens are used both preventively and in treatment (1, 5). Elevated levels of oestrogen also increase the risk of uterine cancer.

Anti-androgen therapy is used to treat prostate cancer and has also been shown to prevent its development (5). Physical activity reduces the cumulative oestrogen dose that women are subjected to throughout life in a number of ways: it increases the age of menstrual onset, leads to changes in the hormonal environment of each menstrual cycle, and reduces levels of oestrogen and binding proteins in postmenopausal women. It has also been clearly demonstrated that physical activity affects testosterone levels in men, which has a potential effect on prostate cancer.

There are also other hormones related to variations in physical activity, for example, insulin. Physical activity affects insulin sensitivity and glucose uptake, shown in recent years to be linked to various types of cancer, for example, cancer of the colon, breast, uterus, prostate, pancreas and stomach. Insulin stimulates cell proliferation (cell division), inhibits apoptosis (cell death), and impacts the synthesis and availability of sex hormones.

An insulin-like growth factor, IGF-1, and its binding proteins, are believed to be associated with a higher risk for several forms of cancers, and variations in physical activity have been shown to affect the levels of this hormone.

The close relationship between physical activity and energy balance thus shows that physical activity levels are related to weight development in a population, and weight gain constitutes a risk factor for a number of cancer diseases (of the colon, breast, kidney, uterus). Physical activity also affects the availability of energy, which again plays a role in the overall ability to repair and control cells.

Variation in physical activity is associated with systemic inflammation, which in turn is related to a number of chronic diseases, including cancer. Pro-inflammatory factors such as C-reactive protein, serum amyloid A, interleukin-1 and TNF-alpha (tumour necrotic factor), and anti-inflammatory factors like adiponectin, are associated with cancer risk and prognosis. The importance of physical activity for these factors in relation to cancer risk is not clear.

The direct effect of physical activity on DNA repair and normal cell growth is studied as physical activity appears to affect a cell's ability to grow normally, for example, in the intestinal epithelium.

The immune system plays a role in the development of cancer with respect to identifying and eliminating unknown components. People with inherited immune diseases and/or congenital immune defects have a higher risk of cancer. Physical activity can both improve the quality and number of specific components in the immune system, for example, natural killer (NK) cells. An increase in physical activity results, in addition, in an increase to a number of immune system components (monocytes, neutrophils), followed by a reduction of these same factors to below-initial levels that lasts from 1–3 hours. In the case of continuous physical activity, there is a reverse dose-response relationship between these factors in the immune system and physical activity. The actual importance of physical activity and its effect on the immune system in relation to cancer development has, however, not been established.

There is great variation between individuals with respect to how long it takes food to pass through the intestine. Physical activity reduces this transit time and thus also the time that intestinal cells are subjected to potentially carcinogenic substances. One randomised controlled intervention study shows that physical activity reduces cell proliferation (cell division) in the colon (10). Physical activity can also affect the secretion of bile salts.

Physical activity also affects lung function, and improved lung capacity reduces the time that lung cells are in contact with carcinogenic elements in the air.

Table 1. Biological mechanisms – physical activity and cancer (prevention and prognosis).

Mechanisms	Effect	Type of cancer
Energy metabolism	Fat deposits that store/metabolise carcinogenic elements are reduced, carcinogens are reduced.	All types of cancer
Blood flow	Local and general blood flow increase and carcinogenic elements are reduced.	All types of cancer
Mechanical transit time stomach-intestine	Passage time for food and potentially carcinogenic elements is shortened.	Stomach-intestinal cancer
Respiration	Potential particle deposition in the lungs is reduced.	Lung cancer
Heat/trauma	Cell division/regeneration can increase.	All types of cancer
Sex hormones	Reduction of the cumulative levels of hormones that affect the growth of all cell types.	Breast, uterine and prostate cancer
Insulin and glucose	Insulin levels are reduced, sensitivity to insulin is improved.	Colon, breast, pancreatic, oesophageal, kidney, thyroid and uterine cancer
Inflammation	Reduces the ability of cells to repair themselves.	All types of cancer
Immune function	Optimisation of the number and activity of macrophages and lymphokine-activated NK cells.	All types of cancer

Measuring physical activity in relation to cancer

Different methods are used to measure physical activity in studies relating to cancer (1, 11, 12), which can make comparison difficult. Self-reported measurements like questionnaires and recorded data are often used, though in recent years direct observation and more objective measurements such as heart rate and fitness tests have also been used (1). This data is often linked to validation associated to energy metabolism and metabolic profile, and researchers have later attempted to gain knowledge of the total daily physical activity.

The most accurate self-reported measures of physical activity provide information about the type, intensity, frequency, duration and reason for the activity (e.g. cycling to work). Physical activity is thus quantified as minutes per day or metabolic equivalent (MET), or MET minutes per day (11). Calculations like these are important in order to study the dose-response relationship, a critical value related to specific cancer risk and survival. Another important factor is that the level of physical activity differs in different phases of life and varies over time, which appears to be significant for specific types of cancer.

Unfortunately there is no consensus on what level of activity constitutes "inactivity". These levels vary between studies and are therefore often related to country, social group, age and gender. Often studies use a percentage of the study sample (e.g. one quarter) as the definition of "most inactive". The levels of physical activity that form the basis for who is classified as inactive therefore vary between studies.

Primary prevention factors

Colorectal cancers

The relationship between physical activity and the risk for colorectal cancers has been investigated in many observation studies, epidemiological studies in several countries, in both men and women of different ages and ethnic groups. In healthy men and women who engage in regular physical exercise, the risk of colon cancer is reduced by 10–70 per cent (1, 5, 13–15). A threshold value for physical activity has not been able to be established, but studies indicate that the dose-response relationship is such that the longer the duration and the higher the intensity of physical activity, the higher the protective effect found for colon cancer. Men and women who reported high intensity during three periods of life, and men who burned more than 2500 kcal per week in high intensity physical activity, were shown to be able to cut their risk of developing colon cancer later in life by half (5).

Important biological mechanisms that reduce intestinal transit time, insulin sensitivity and cell proliferation in the intestinal epithelium have been studied and support the connection between physical activity and colon cancer (1, 5).

It has, however, not been established whether physical activity protects against rectal cancer. Even here, many studies have been conducted but have not yielded a similarly uniform picture. The existing biological mechanisms are not as convincing for rectal cancer either (1, 5).

Breast cancer

Oestrogen and progesterone levels are important factors in the development of breast cancer, and physical activity affects the production, metabolism and excretion of these hormones. It was thus not surprising that Frisch and colleagues reported early on, in 1985, that physical activity among college students in the US protected against later development of breast cancer (9). A number of studies and reports conclude that 4 hours of physical activity per week, at work and during leisure time, at an intensity corresponding to 6 METs (i.e. 6 times the oxygen uptake at rest, corresponding to a light jog), yields a 30–50 per cent reduction of breast cancer in postmenopausal women (16–18). Physical activity also protects younger, premenopausal women, but in this case genetic factors play a larger role than lifestyle and the protective effect is lower and can be associated to specific subgroups, for example, women with a particular genetic predisposition.

A study of women who carry the inherited BRCA1 and BRCA2 genes showed much earlier development of breast cancer in women who were not physically active compared to physically active women who carried the BRCA1/BRCA2 gene (19). This emphasises

the importance of the interaction between heredity and environment in the prevention of cancer, and that a factor such as physical activity can also be important for people with a congenital vulnerability to developing different types of cancer.

Another important aspect of physical activity as a protective factor against breast cancer is that it appears to have a particular effect during so-called "sensitive" periods, when the breast is especially susceptible to carcinogenic agents, for example, during puberty (1, 5, 18).

Uterine cancer

Due to its biological effect on energy balance, sex hormones and insulin sensitivity, physical activity may be of importance in cancer of the uterus. A number of studies have shown that physical activity gives a 20–40 per cent reduction in uterine cancer (1, 5, 20). Researchers have, however, been unable to identify especially critical periods or thresholds for physical activity.

Prostate cancer

Even if prostate cancer is a common and increasing form of cancer in men, we know very little about the underlying mechanisms for developing prostate cancer. Few of the risk factors are known. Physical activity as a potential effect on endogenous hormone levels, like testosterone and insulin, is equally important to consider. A series of studies have investigated the link between physical activity and prostate cancer (1, 21). Most of these studies, especially those that looked at the most aggressive and advanced types, have found that physical activity protects against prostate cancer (1, 5).

Lung cancer

Because physical activity can affect the time that potential carcinogenic agents are in contact with lung cells, both through improved lung capacity and overall blood flow, it is of interest to note that the majority of published studies (1, 22, 23) in this field show that physical activity protects against lung cancer. The problem of adjusting for so strong a risk factor as smoking, however, makes it difficult to draw final conclusions (1, 5).

Other types of cancer

A number of studies have been done on ovarian and testicular cancer, cancer of the kidneys and lymph nodes, etc. (though the number of studies in each individual disease group is limited). However, researchers have not arrived at a uniform picture of the importance of physical activity in these diseases.

Physical activity as treatment and rehabilitation in cancer disease

There used to be a perception that cancer was difficult to prevent and that patients treated for cancer should rest and reduce their physical activity. This is partly true in that physical activity can lead to pain, heart palpitations and breathing difficulties. Research has shown, however, that physical activity not only protects against a number of cancer diseases, but

is also valuable during both the treatment and rehabilitation phases (5, 24, 25). Physical activity also improves cancer patients' quality of life (25–27). Regular physical activity is an effective way of reducing side-effects resulting in part from the inactivity (13, 28) and in part from the disease itself. Inactivity leads to a loss of fitness, strength and mobility, unfavourable weight gain (29–31) and insulin sensitivity (32) in the patient. It is also known from a number of smaller and larger studies that cancer patients generally reduce their level of activity when the disease breaks out. Physical activity is therefore being recommended for more and more patients.

In recent years, there have also been a number of studies that looked at the relation between physical activity and survival, above all regarding breast cancer and colon cancer (33). After renewed review of the existing literature, international specialist groups nevertheless conclude that it is too early to determine whether physical activity can affect the survival of cancer patients (5, 24).

Possible benefits of regular physical activity

- Maintained and improved fitness
- Better balance and reduced risk of falls and broken bones
- Reduced risk of heart disease
- Prevents osteoporosis
- Improves blood flow and prevents blood clots
- Improves ability to manage on one's own and reduces dependence on others
- Better self-esteem
- Reduced anxiety and depression
- Reduced nausea
- Increased ability to maintain social network
- Reduced fatigue
- Better ability to maintain a stable weight
- Better quality of life
- Encourages a healthy and varied diet
- Possible improved survival

A person's level of physical activity is impacted by the ongoing treatment, the time that has passed since the previous treatment, medications, and the patient's fitness and stress levels. On the other hand, we know that physical activity in itself strengthens the muscles, improves fitness and the ability to tolerate medicines, and increases the chances of recovery. Physical activity can also lead to improved self-esteem and self-control. It is, however, important to seek the advice of the responsible physician and physiotherapist, so that the level of physical activity can be adapted to the individual's needs. In cases where the patient has no pain, 30–60 minutes of daily physical activity, adapted to the patient's situation and previous experience, is recommended.

Goals for physical activity

- Maintain good physical and social function
- Optimise the ability to provide an individually adapted treatment
- Reduce symptoms, with respect to nausea and fatigue in particular
- Attain an optimal weight and avoid unfavourable weight gain or weight loss

It is important to be aware that different types of cancer in themselves, as well as intensive treatment in the form of chemotherapy and radiation therapy, can produce very different pain symptoms. If a patient experiences pronounced fatigue after a difficult operation or intensive chemotherapy, it can be hard to motivate them to be physically active. Intensive radiation therapy can result in stomach problems in the form of powerful bowel movements, which may make activity impossible.

Type of activity, frequency, intensity and duration

Type of activity
Activities that involve large muscle groups, for example, walking, cycling and skiing. Avoid heavy loading.

Frequency
Daily

Intensity
Moderate to high intensity adapted to the particular individual

Duration
A minimum of 15–60 minutes

The time must be adapted to the individual's situation, age and previous experience of physical activity and exercise.

Other considerations

During ongoing treatment it is important that the physical activity be discussed with the responsible physician, preferably in cooperation with the physiotherapist, and adjusted as necessary. It is important to remember that the cancer disease, ongoing treatment and blood profile, for example, low haemoglobin levels, affect the type of activity that should and can be performed. During ongoing treatment, the following special precautionary measures should be taken:

- Always consult the physician responsible for treatment before beginning an activity. This is of particular importance if the patient is taking special medications or has some form of heart or lung disease.

- Avoid activities that:
  - require high intensity in patients with low haemoglobin levels, < 8.0 g/dl
  - entail an increased risk for bacterial infection in patients with a low white blood cell count, < 0.5 x 10^9/l
  - can lead to an increased risk of bleeding in cases where thrombocyte levels are < 50 x 10^9, such as contact sports.
- In the case of shortness of breath – investigate cause, activity and tolerance.
- In the case of leg pain – avoid activities that can lead to increased risk of fracture, such as contact sports.
- In the case of pronounced fatigue – plan daily activities of a low to moderate level, preferably outdoors, balanced with rest.

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