2 Sports & Exercise Training in Cancer

In the following chapter, the impact of sports and exercise training as a potential therapy on prevention and risk reduction of cancer is surveyed in detail as well as the palliative care for the 24 most common and deadliest cancer types in women and men worldwide. The order of cancer types was made by listing the cancer with the highest mortality rate of 2012 downwards to the cancer with the lowest mortality rate of 2012 worldwide.

2.1 Lung Cancer

Lung cancer represents the cancer with the highest mortality rate with 1,589,925 cancer deaths in 2012 worldwide by being the most common and deadliest cancer in 2012 among men resp. the 3rd most common and 2nd deadliest cancer in 2012 among women with an incidence rate of 1,241,601 new cases as well as a mortality rate of 1,098,702 deaths in 2012 among men resp. an incidence rate of 583,100 new cases as well as a mortality rate of 491,223 deaths in 2012 among women.² "The relative 5-year survival for patients with this disease is 14%, and has remained largely unchanged for years".¹⁹ 85% - 90% are present as non-small cell lung cancers being subdivided into 25% - 30% of squamous cell carcinoma, 40% of adenocarcinoma and 10% - 15% of large cell carcinoma whereas 10% - 15% are present as small cell lung cancer.²⁰ Between 80% - 90% of lung cancer is attributable to smoking being unequivocally represented as the major risk factor, but risk factors appearing inde-
pendently from smoking such as environmental tobacco smoke, cooking fumes, ionizing radiation, radon gas, asbestos, inherited genetic susceptibility, occupational exposures to carcinogens or pre-existing lung diseases accounting for ca. 10% - 15% of all lung cancers have also been confirmed as potential risk factors for lung cancer. The risk of lung cancer in never-smokers is considered higher in women. Important symptoms in patients with lung cancer are cough, dyspnea, hemoptysis, chest discomfort, phrenic nerve paralysis accompanied by bone pain, dysphagia, fever or clubbing.

2.1.1 Sports & Exercise Training on Lung Cancer Incidence

A lack of physical activity can be associated with a higher risk owing to available data suggesting “moderate to high levels of leisure-time physical activity were associated with a 13% - 30% reduction in lung cancer”. A study accompanying 38,000 men from 1974 - 2003 ranging in age from 20 - 84 years and consisting of smokers and non-smokers evaluated a treadmill test. The people were assigned to low fit, moderately fit and high fit groups. The study illustrated that people with higher and moderate cardiorespiratory fitness levels may reduce the risk of getting lung cancer in comparison with those individuals with lower cardiorespiratory fitness levels. The afore-noted outcome was also encouraged by a meta-analysis taking together the results of 7 different studies that also “indicate that moderate or high levels of leisure time physical activity are associated with reduced risk of developing lung cancer among smokers”. “Contrary to studies in smokers, … data showed no evidence of inverse associations with higher BMI and increased physical activity” in never-smokers. The correlation between physical activity and lung cancer risk in non-smokers in 230 cases and 648 controls was
scrutinized in another study whereby physical activity of more than 24 MET-hours/week obtained the best results in never-smokers and ex-smokers.\textsuperscript{28} 1 MET (metabolic equivalent) is the rate of energy expenditure at rest whereby intensities of physical activities under 3 METs are considered to be as light, between 3 and 6 METs as moderate resp. above 6 METs as vigorous. MET-hours are calculated by METs times minutes of physical activities divided by 60. The generation of reactive oxygen species (ROS) by oxidative stress working mutagenic can be well regulated by sports and exercise training to prevent oxidative damage and mechanisms of carcinogenesis transiently increasing ROS production, but in the long term, reducing the systemic ROS levels.\textsuperscript{29} 30 Because of cancer cells producing energy by aerobic glycolysis resulting in high lactic acid levels, sports and exercise training combined with reduced carbohydrate availability contribute to increase the level of the tumor suppressor protein p53 that may benefit by a decrease of the glycolysis, a regulation of oxidative stress in the mitochondria as well as a protection against metabolic stress.\textsuperscript{31} 32 Another study included 8 active male subjects performing a high-intensity endurance training with high or low carbohydrate availability whereby the maximal oxygen uptake (VO\textsubscript{2max}) was settled at preliminary testing on the treadmill by 3-min. stages at 10, 12, 14 and 16 km/h and 2% inclination changes after the completion of 16 km/h until exhaustion. In the morning of the experimental trials being separated by a minimum of 7 days, the subjects performed a 50 min. bout of running on the treadmill being constituted of alternate 6 x 3 min. at 90% and 50% of the maximal oxygen uptake (VO\textsubscript{2max}) whereat the warm-up and cool down lasted 7 min. at 70% of the VO\textsubscript{2max} whereas the groups received CHO diets of 8g/kg (high) resp. 3g/kg (low) in the 24h before the experimental trials and a high-CHO breakfast comprising 2g/kg (high) as well as 8ml/kg resp. 3ml/kg of CHO beverages 10 min.
before and during recovery periods 2 and 5. Increases in p53 between pre- and post-exercise as well as between post-exercise and 3 hours after the interval training was shown while no increases were determined in the group with high CHO availability.\textsuperscript{32}

2.1.2 Sports & Exercise Training on Lung Cancer Progression

The oxidative status of 16 lung cancer patients during a 14-week sports and exercise training period being comprised of 3 sessions per week was explored in a study and detected increases in urinary measures in postsurgical non-small cell lung cancer being able to promote cancer progression. “In week 1, exercise intensity was initially set at 60\% of baseline peak workload for a duration of 15 to 20 minutes. Duration and/or intensity were then subsequently increased throughout weeks 2 to 4 up to 30 minutes at 65\% peak workload. In weeks 5 and 6, exercise intensity varied between 60\% - 65\% of peak workload for a duration of 30 to 45 minutes for 2 sessions; in the remaining session patients cycled for 20 - 25 minutes at ventilatory threshold determined by a systematic increase in the VE/VO\textsubscript{2} ratio, while VE/VCO\textsubscript{2} remained constant. From the 7th week onwards, patients performed 2 sessions at 60\% to 70\% peak workload with one threshold workout for 20 - 30 minutes. Finally, in weeks 10 to 14, patients performed 2 sessions at 60\% to 70\% peak workload with one interval session. Interval workouts consisted of 30 sec. at peak workload followed by 60 s of active recovery for 10 - 15 intervals”.\textsuperscript{30} Higher levels of red cell distribution width (RDW) are also associated with advanced lung cancer stages, advanced age, more white blood cells, lower hemoglobin and higher levels of tumor markers.\textsuperscript{33} Therefore 118 patients with chronic heart failure were supervised whereby the exercise group consisted of 71 patients resp. the control group of
47 patients. The exercise group completed a 6-month endurance training program of 3 weekly sessions of 60 min. each including an intensity of 90% of the heart rate at the anaerobic threshold (HR_AT), which was evaluated by cardiopulmonary testing on the treadmill being composed of a starting load of 20 or 40 W and incremental increases of 10 or 20 W every minute. The outcome indicates that high-intensity endurance training is associated with a decrease in RDW.34

2.1.3 Sports & Exercise Training on Lung Cancer Mortality

Relevant to the subject of performing sports and exercise training before lung cancer resection to improve pre-operative functional capacities and to decrease post-operative respiratory morbidity, 24 patients were randomly allocated into a group performing strength and endurance training (PR) and a group performing breathing exercises (CPT) for a period of 4 weeks and 20 sessions. The PR group performed a shoulder flexion with a minimum rate of 15 repetitions per min. resp. a treadmill run of 10 min. in week 1, 20 min. in week 2 and 30 min. in weeks 3 and 4 with the intensity of 80% of the maximum load that was determined by a test before and achieved better results compared to the CPT group performing 30 min. of inspiratory muscle training.35
2.1.4 Sports & Exercise Training on Palliative Care of Lung Cancer

Generally speaking, “exercise capacity is decreased due to lower peripheral muscle strength and pulmonary functions and increased dyspnea severity and anxiety and depression levels in patients with advanced-stage (stages III-IV) NSCLC and hence the quality of life of these patients is impaired much more in relation to reduced exercise capacity compared to patients with early-stage (stages I-II) NSCLC”. Therefore, articles of sports and exercise training prior to resp. post surgical resection were reviewed and occasioned results of endurance training lasting 30 or more min. per session performed three - five times per week at moderate intensity of a 50% - 70% of the heart rate reserve (HR_{res}) being calculated by maximal heart rate minus resting heart rate may have a positive impact on sports and exercise training tolerance, the quality of life and fatigue of early-stage lung cancer.

2.2 Liver Cancer

Liver cancer represents the cancer with the 2\textsuperscript{nd} highest mortality rate with 745.533 cancer deaths in 2012 worldwide by being the 5\textsuperscript{th} most common and 2\textsuperscript{nd} deadliest cancer in 2012 among men resp. the 9\textsuperscript{th} most common and 6\textsuperscript{th} deadliest cancer in 2012 among women with an incidence rate of 554.369 new cases as well as a mortality rate of 521.041 deaths in 2012 among men resp. an incidence rate of 228.082 new cases as well as a mortality rate of 224.492 deaths in 2012 among women. “The most common histological type of liver malignant neoplasm is hepatocellular carcinoma (HCC). Other forms include: childhood hepatoblastoma, and childhood cholangiocarcinoma (originating from
the intrahepatic biliary ducts) and angiosarcoma (from the intrahepatic blood vessels). The established risk factors for HCC include Hepatitis B or C viruses (HBV and HCV) infection, alcohol drinking, tobacco smoking, and aflatoxin. The suspected risk factors for liver cancer include diet, obesity, diabetes and insulin resistance, use of oral contraceptives, iron overload". The major symptoms of liver cancer include drastic weight loss without any obvious explanation, swelling of the abdomen caused by growing cancer or a build up of fluid called ascites and jaundice as well as other symptoms like feeling full or bloated even after a small meal or loss of appetite over a few weeks or sudden health problems in people with chronic hepatitis or liver cirrhosis.

2.2.1 Sports & Exercise Training on Liver Cancer Incidence

“Body mass index in both boys and girls during school age is positively associated with the risk of liver cancer in adulthood”. In addition, diabetes mellitus, an important component of metabolic syndrome and risk factor for non-alcoholic fatty liver disease (NAFLD), has recently been associated with hepatocellular carcinoma (HCC) in patients with chronic liver diseases”. Physical activity levels of 6.093 participants at high risk of liver cancer were investigated by using accelerometers to measure frequency and intensity of regular physical activity (<100 counts/min./day = sedentary; 100 - 2.019 counts/min./day = light; 2.020 - 5.999 counts/min./day = moderate; > 6.000 counts/min./day = vigorous) with the final outcome that patients with a diagnosis of NAFLD, diabetes and metabolic syndrome have significantly reduced physical activity levels. However, a resistance training of 3 weekly sessions of 60 min.
at 8 - 12 maximum repetitions each as well as consisting of 10 whole-body exercises (leg press, leg extension, leg curl, chest press, lat pull-down, seated row, biceps curl, triceps extension, push-ups and sit-ups) shows significant improvement in insulin sensitivity as compared with an aerobic exercise of 3 weekly sessions of 40 min. at 50% of the maximal oxygen uptake at the point of voluntary stopping (VO\textsubscript{2peak}) in week 1 and 60 min. at 60% - 75% of the maximal oxygen uptake at the point of voluntary stopping (VO\textsubscript{2peak}) by week 2 whereas health issues associated with metabolic syndrome seem to be predominantly improved by endurance training of running about 12 miles or 120 min. per week at 65% - 80% of the maximal oxygen uptake at the point of voluntary stopping (VO\textsubscript{2peak}) as against resistance training of 3 weekly sessions of 3 daily sets of 4 upper body and 4 lower body major muscle exercises of 8 - 12 maximum repetitions per set whereby performing the resistance training in addition to the afore-noted endurance training brings along further benefits.\textsuperscript{62,63} Another study examined 19,921 NAFLD patients by performing an at least moderate-intensity sports and exercise training of 3,0 - 6,0 METs more than three times per week for at least 30 min. and for an overall duration of at least 3 months, and reached the result that subjects who exercised regularly had a lower risk of having NAFLD and were less insulin resistant.\textsuperscript{64} 1 MET (metabolic equivalent) is the rate of energy expenditure at rest whereby intensities of physical activities under 3 METs are considered to be as light, between 3 and 6 METs as moderate resp. above 6 METs as vigorous. MET-hours are calculated by METs times minutes of physical activities divided by 60. On the other hand, short-term endurance training of 60 min. per session at 80% - 85% of the maximal heart rate (HR\textsubscript{max}) and performed for 7 consecutive days also contribute to risk reduction of NAFLD and the following nonalcoholic steatohepatitis (NASH).\textsuperscript{65} But “... whether NAFLD is a causative factor for HCC remains unclear” although “NAFLD should be taken as a risk factor for HCC”.\textsuperscript{66} Concerning a correlation between sports and
exercise training and hepatobiliary cancer also including liver cancer, a study contained 507,897 participants aged 50 - 71 by completing a baseline questionnaire of how often physical activity that increases respiration, heart rate or perspiration is done during a typical month whereby never (1), rarely (2), 1 to 3 times per month (3), 1 to 2 times per week (4), 3 to 4 times per week (5) and 5 or more times per week (6) were the options listed with the final result that the highest level of physical activity was significantly associated with a 36% risk reduction in total liver cancer as against physically inactive participants although in turn, HCC had a stronger association regarding reduction of liver cancer risk as compared with no significant associations in other liver cancer. A number of studies “suggest that targeting insulin resistance and lipogenesis can reduce HCC risk over the long term” as well as “to prevent the onset of obesity through public awareness and education programs”. Considering the importance of cardiorespiratory fitness being associated with a lower risk of liver cancer, a treadmill test was performed in another study. The 38,801 male subjects aged 20 - 88 years were subsequently divided into low fit (lowest 20%), moderately fit (middle 40%) and high fit (upper 40%) groups and followed from 1974 until their date of death or December 31, 2003 with the final outcome that being a part of the moderately and high fit groups showed significant reduction of risk from liver cancer.

2.2.2 Sports & Exercise Training on Liver Cancer Mortality

Sports and exercise training is considered to be an appropriate method for liver cancer patients undergoing hepatectomy. A study therefore allo-
cates 51 HCC patients aged 20 - 80 years into a diet only and a combined diet and exercise group and testing their anaerobic thresholds one week after hepatectomy while the sports and exercise training program consisted of 3 resp. 5 - 6 weekly sessions of 60-min. walking and stretching sports and exercise training program and the diet program included a daily energy intake of 25 - 30 kcal/kg of body weight resp. 20 - 25 kcal/kg of BW in patients with diabetes or fatty livers, a daily protein intake of 1.0 - 1,2 g/kg of BW and a daily sodium chloride intake of 5 - 7 g/kg of BW, altogether during the 1-month preoperative and 6-month postoperative periods and came to the conclusion of a more obvious fat reduction and improvement in insulin resistance in patients of the combined group in comparison to the diet only group.70 Another study carried out between December 2008 and April 2010, which included 61 HCC patients undergoing curative resection and being previously tested by cycle ergometry at 60 repetitions per minute (rpm) involving 2 min. incremental stages (5,0, 7,5 and 10W/min.) until the 60 rpm could not be pedaled any longer whereby the maximal oxygen uptake at the point of voluntary stopping (VO₂peak) as well as the anaerobic threshold (AT) was individually measured by breath-by-breath analysis of expired air. All patients were followed up at least every 3 months after discharge also inclusive of physical examination and liver function testing with the result that the 3-year survival rate in HCC patients with a level of the maximal oxygen uptake at the point of voluntary stopping (VO₂peak) of greater or equal 16,5 ml/min/kg was 50,3% as compared with 10,8% of those having less than 16,5 ml/min/kg and with an anaerobic threshold (AT) of greater or equal 11,5 ml/min/kg was 42,3% as against 33,4% of those having less than 11,5 ml/min/kg, but significantly higher 3-year survival rates were also achieved by higher platelet counts, branched-chain AA/tyrosine ratio (BTR) and albumin levels resp. lower aspartate transaminase (AST), alanine transaminase (ALT) and retinol-binding protein (RBP) levels.71 A study found out that a 3-month treadmill-based
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