Treatment-Induced Cardiotoxicity in Breast Cancer: A Review of the Interest of Practicing a Physical Activity

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TREATMENT-INDUCED CARDIOTOXICITY IN BREAST CANCER: A REVIEW OF THE INTEREST OF PRACTISING A PHYSICAL ACTIVITY

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ABSTRACT

Physical activity is known to prevent cancer occurrence and to decrease the risk of breast cancer. At diagnosis of breast cancer, fewer than half of the patients reach the international recommendation for physical activity. However, breast cancer patients, and particularly HER2+ breast cancer patients, are exposed to treatment-induced cardiotoxicity because of a side effect of two molecules used in standard therapy to treat these tumors: anthracycline and trastuzumab. Cardiotoxicity can sometimes lead to the treatment being discontinued and even to the development of cardiovascular diseases. Exercise is known to protect the cardiovascular system in the healthy population. Consequently, being physically active during treatment appears as a way to prevent the negative impact of cancer treatment on the heart in this population. In particular, aerobic exercising could provide a protective effect against treatment-induced cardiotoxicity.

A supervised physical activity program seems to be the best way for breast cancer patients to be active during their period of treatment. However, there is very little information available to patients, and in particular a lack of guidelines, on exercising. Interventional trials that have been conducted on this topic are very heterogeneous and no standard recommendations have been made available for cancer patients thus far. An effective physical activity program needs to take each patient's barriers and motivations into account in order to encourage the practice of physical activity throughout treatment. To ensure the success of the program, it is essential to facilitate adherence and especially to maintain motivation. Further studies are needed to determine what practice guidelines oncologists should give their patients.

INTRODUCTION

Physical inactivity is the fourth mortality risk worldwide [1]. Regardless of the level of physical activity, reducing sedentary time decreases mortality, and also the risk of developing cardiovascular diseases, type 2 diabetes, obesity and certain cancers [2]. In 2010, the World Health Organization (WHO) issued international physical activity recommendations for the healthy population, by age group [3]. Over the following years, these recommendations were extended to breast cancer patients through different frameworks and by different authorities, for example, the *Plan Cancer* in France [4] and the American Cancer Society [5,6].

The link between high body mass index (BMI) at breast cancer diagnosis and poor prognosis has been well established, and highlights the importance of being physically active [7,8]. Physical activity from diagnosis has become a routine recommendation in breast cancer treatment, especially because of its many benefits on quality-of-life [9,10]. Physical activity also improves survival rates. Indeed, a meta-analysis has shown that being active after diagnosis is linked to a 34% reduction in breast cancer deaths, a 41 % reduction in deaths from all causes and a 24 % reduction in disease recurrence [11]. Another meta-analysis evaluating 5- and 10-year survival rates showed that the higher the level of physical activity, the better were the survival rates [12]. Indeed, the 5-year survival rate was 97 % for patients who engaged in 3 to 9 or more metabolic equivalent task (MET) hours per week, and 93 % for those who engaged in fewer than 3 MET-h/weeks. The 10-year survival rate of patients who engaged in 9 or more MET-h/week was 92 %, whereas for patients engaging in 3 to 8.9 MET-h/week it was 89 %, and 86 % for those who practiced for fewer than 3 MET-h/week. However, at diagnosis, the majority of patients are insufficiently active [13–15] and maintaining an adequate level of physical activity during treatment can be difficult on account of the numerous barriers encountered by patients. The most frequent barriers identified over the last decades are treatment side effects and the management of everyday routine activities. In addition to improving the outcomes of cancer, physical activity could limit some of the toxicity of anticancer treatments. There is strong evidence that meeting the international physical activity recommendation (i.e. 150 to 300 minutes of moderate-intensity or 75 to 150 minutes of vigorous-intensity aerobic activity on a weekly basis) reduces the incidence and recurrence of cardiometabolic disease [16,17]. It can thus be hypothesized that patients who develop

treatment-induced cardiotoxicity could draw benefit from a physical activity intervention.

In order to promote physical activity during treatment, interventional programs are offered to patients. Since 2010, the literature on this topic has been developing, and the number of trials involving physical activity interventions has multiplied. Nevertheless, the question arises as to what is the optimal program, particularly in terms of duration, type of exercise or intensity.

The aim of this review was to explore treatment-induced cardiotoxicity and identify the interest, barriers and facilitators of physical activity practice during treatment in order to mitigate cardiac dysfunction.

I. BREAST CANCER AND CARDIOTOXICITY

1. Anthracycline-induced cardiotoxicity

Anthracyclines belong to the standard chemotherapy treatment for early breast cancer. Nevertheless, one limitation of this treatment is that it can cause cumulative, dose-dependent cardiac damage, mainly cardiomyopathy and heart failure [18,19].

Patients treated with anthracycline-based chemotherapy are five times more at risk of developing cardiotoxicity than those treated without anthracycline [20]. Some meta-analyses have also shown that the risk of severe cardiotoxicity is higher in patients under anthracycline-based chemotherapy than among those treated with taxanes without anthracycline [21,22]. Cardiotoxicity is defined by a left ventricular ejection fraction (LVEF) < 50 % or a decrease of 10 % in the LVEF compared to baseline [23–26]. It is the first cause of heart failure among women and is responsible for 15-20 % of cases of treatment discontinuation [27].

Two main hypotheses have been put forward to explain the potential mechanisms implicated in anthracycline-induced cardiotoxicity. Some authors have suggested that the reactive oxygen species (ROS) generated by anthracycline treatment cause damage to the DNA and changes in protein and lipid levels, ultimately leading to cardiomyocyte death [28–30]. It has also been shown that doxorubicin-induced cardiotoxicity is linked to the activation of p53 and the apoptotic pathway, leading to a loss of myocardia mass, which contributes to cardiotoxicity [31].

2. Trastuzumab-induced cardiotoxicity

Approximately 20 % of breast cancer patients overexpress the human epidermal growth factor receptor 2 (HER2) [32]. This characteristic of the tumour has been associated with poorer disease-free and overall survival [32,33]. One of the standard treatments for this specific cancer is a targeted therapy, trastuzumab (Herceptin®), which can be administered alone [23,34] or in combination with chemotherapy [35,36]. Trastuzumab is a recombinant humanized monoclonal anti-body that binds selectively to subdomain IV of the extracellular ErbB2 domain, which downregulates HER2 expression [37]. Adjuvant treatment with trastuzumab reduces by half the rate of recurrence and by one third the mortality rate [38].

It is estimated that 1 % to 4 % of patients treated with trastuzumab develop heart failure [39,40] and nearly 10 % have asymptomatic LVEF reduction [35,41]. The cumulate incidence rate for major cardiac events has been estimated at 6.6 % for sequential therapy (anthracycline and trastuzumab) and 5.1 % for trastuzumab alone [42]. A meta-analysis has shown that patients treated with trastuzumab were about five times more at risk of developing congestive heart failure in early breast cancer compared to patients not treated with this targeted therapy [43]. Nevertheless, if trastuzumab is discontinued at the time of the first cardiac symptoms , the damage can be reversible [44].

It can be hypothesized that trastuzumab-induced cardiotoxicity is linked to antibody-dependent cellular cytotoxicity (ADCC), leading to an immune-mediated destruction of cardiomyocytes or to a disruption of HER2 signalling, which is essential for myocardial contractility, see for example [44,45]. It is also important to note that HER2, the target of trastuzumab, is expressed in adult cardiomyocytes and is implicated in cardiomyocyte development [45–49]. When trastuzumab blocks HER2 signalling, it prevents the repair mechanisms in cardiomyocytes [50].

3. Cardiotoxicity associated with anthracyclines and trastuzumab treatment

When trastuzumab and anthracycline-based chemotherapy are associated, the incidence of cardiotoxicity is 27 % against 13 % when trastuzumab is associated with paclitaxel [51]. More generally, the risk of cardiac failure is higher when trastuzumab is administered after anthracycline-based chemotherapy than after non-anthracycline chemotherapy [22]. Patients treated with

trastuzumab and chemotherapy are twice as likely to develop heart failure or LVEF decrease [52]. Cardiotoxicity can occur acutely but it can also lead to cardiovascular disease development in the long term. A retrospective study compared the incidence of cardiotoxicity in the five years following treatment associating anthracycline and trastuzumab or anthracycline alone. Among the 29.6 % of the patients treated with anthracyclines alone, cardiotoxicity at five years involved 4.3 %, while for the 3.5 % of population who received an association of the two drugs, the proportion was 20.1 %, more than 4.5 times greater [53].

Today, new targeted anti-HER2 therapies are available, such as pertuzumab, trastuzumab emtansine (T-DM1), lapatinib, neratinib and afatinib, but they do not have an indication for early breast cancer. A study was conducted to determine the cardiac tolerance of pertuzumab. The TRYPHAENA study assessed cardiac tolerance of the concomitant or sequential addition of pertuzumab and trastuzumab to docetaxel with or without anthracycline in neoadjuvant treatment [54]. The results did not show an increased incidence of cardiac dysfunction. However, more data is needed to confirm the results of this study.

A recent literature review concluded that the cardiac impact of these novel drugs was lower than that of trastuzumab, and they mainly led to an asymptomatic decrease of the LVEF [55]. The mechanisms responsible for the lower cardiotoxicity of these novel drugs are still not completely understood. However, lapatinib is known to activate the adenosine monophosphate kinase (AMPK) pathway, which could protect heart cells against tumor necrosis factor alpha (TNF-α)-induced cell death by inhibiting its stimulation [45].

II. PHYSICAL ACTIVITY TO PREVENT TREATMENT-RELATED CARDIOTOXICITY IN BREAST CANCER

1. Benefits of being physically active for breast cancer patients

The amount of moderate-to-vigorous physical activity is inversely associated with cardiovascular mortality, and the incidence of cardiovascular disease, stroke and heart failure [16]. Physical activity is also a cornerstone in cardiometabolic chronic diseases such as diabetes or high blood pressure. Among

healthy subjects, regular physical activity reduces the incidence of cardiac events such as hypertension or coronary heart disease [1]. In addition, among breast cancer patients, physical activity can to some extent improve cardiopulmonary function (increased LVEF, improved heart rate and systolic blood pressure, etc.) [56–66], suggesting that physical activity could prevent some of the potential negative effects of treatment-related cardiotoxicity in HER2+ breast cancer subtypes.

A recent literature review highlighted the interest in implementing an exercise intervention program in the population at risk for cardiotoxicity [67], as is the case with HER2+ breast cancer patients, especially because breast cancer patients can also have pre-existing comorbidities, such as diabetes and hypertension, that predispose them to cardiotoxicity [67,68]. The mechanisms explaining the benefit of physical activity on cardiovascular function are still not clearly known. A preclinical study conducted on a murine model showed that physical exercising for 5 consecutive days protected the cardiomyocyte mitochondria from the oxidative damage and dysfunction induced by doxorubicin [69]. Indeed, the authors found that in physical exercising conditions, there was a reduction in doxorubicin-induced ROS release from the cardiac mitochondria. In addition, aerobic training induced endogenous antioxidant mechanisms that protect the heart against ROS [70]. A study conducted on 2973 non-metastatic breast cancer patients assessed the relationship between exposure to physical exercise and cardiovascular events [71]. The results, with a median follow-up of 8.6 years, showed a reduction of 23 % in the risk of cardiovascular events for patients that followed physical activity recommendations (i.e. ≥ 9 MET-h/week.) after the end of their treatment (≥ 9 MET-h/week) compared to those who did not follow the recommendations.

2. Physical activity interventions improving cardiopulmonary capacities

Haykowsky *et al.* were the first to specifically study the impact of physical activity on trastuzumab-induced cardiotoxicity. They conducted a trial on 17 HER2+ breast cancer patients. A supervised physical activity intervention took place in the course of the first 4 months of trastuzumab administration. The intervention was composed of 3 aerobic sessions of 30 to 60 minutes per week on

an electrically braked cycle ergometer at 60 to 90% of the oxygen peak consumption (VO_{2peak}). The results of the trial concluded that although the aerobic activity took place during the chemotherapy, trastuzumab induced left ventricular cavity dilation and a significant decrease in the ventricular ejection fraction [72]. Nevertheless, according to the authors, the relatively low program adherence (59 %) could explain the absence of a cardioprotective effect of physical activity. Indeed, they highlighted the fact that exercise adherence was predictive of change in peak oxygen consumption and that patients need to attend ≥ 55 % of the prescribed sessions to derive any benefit on cardiopulmonary function. Other studies assessed the effect of physical activity interventions during treatment on the cardiovascular system and cardiorespiratory function among non-HER2+ breast cancer patients (Table 1). The studies were conducted at different moments in treatment: during adjuvant chemotherapy [73,74], during other adjuvant treatments [65–70], or after the end of breast cancer treatment [59]. Rates of adherence to the program were higher than in Haykowsky's study, ranging from 66 % to 98.4 %, and an improvement in cardiopulmonary function was rapidly observed after the physical activity program was started. For example, after 8 or 12 weeks of an aerobic exercise intervention, an increase in the VO_{2peak} and a decrease in systolic blood pressure were observed [63,66]. Furthermore, patients following a 12-week aerobic intervention enhanced their VO_{2max} by 2.6 ± 3.5 mL/min/kg [60] and there was an increase of 2.37 ± 0.68 mL/min/kg for those who attended 27 weeks of an aerobic and reinforcement program [58]. Overall, randomized controlled clinical trials have shown that patients taking part in a physical activity program have better cardiopulmonary outcomes than those who do not take part [57–60]. Phase II of Hornsby's randomized study was the only one conducted on HER2+ patients treated with neoadjuvant chemotherapy (+ aerobic training) [60]. The intervention consisted in a one-to-one supervised cycle ergometry session (3 sessions/week) covering the 12 weeks of neoadjuvant chemotherapy, with progressive intensification of both duration and intensity of the exercise. There was no resistance training offered in this trial. However, cardiopulmonary function improved in the intervention group, unlike the control group, in which it decreased. According to De Luca, a supervised program (24 weeks, 2 sessions of 90 min per week, aerobic and strength training) at least six months after completion of all cancer therapies, improved VO_{2max} by about 38.8 % from baseline to the end of the program [59]. One limitation of these studies was the small numbers of

patients included (N = 20). Studies on larger populations are required. Recently, it has been shown that a 16-week physical activity intervention for physically inactive overweight or obese breast cancer patients after treatment improves physical fitness (N = 91) [61]. The authors highlighted the high adherence rate (96 %) and noted that this could be linked to a reduction in the patients' barriers to physical activity. Indeed, patients were free to go to one-to-one supervised exercise sessions every day of the week from 5 am to 8 pm. Furthermore, parking and bus passes were made available in order to facilitate access to the facility.

3. Ongoing interventional clinical trials for HER2+ breast cancer patients

At present, only two French trials, including our own, are studying the effect of an exercise program on cardiotoxicity among HER2+ patients. CARDAPAC (NCT02433067) is a phase II, prospective, randomized, multicenter study conducted by a research team in Besançon [76]. It aims to evaluate the impact on cardiac function of aerobic exercise among HER2+ patients exclusively treated with trastuzumab. The exercising regime is individualized and consists in 45-minutes of endurance exercises (of moderate and high intensity), 3 times a week for 3 months. The program starts after the end of the chemotherapy and radiotherapy if indicated, and patients are monitored for 6 months. The primary objective of CARDAPAC is to evaluate the incidence rate of cardiotoxicity, defined as a decrease in the LVEF to less than 50 % or an absolute drop in the LVEF of 10 % from baseline.

Our own study, the APACAN2 (NCT02963363) trial, aims to evaluate the feasibility of home-based adapted physical activity for HER2+ breast cancer patients treated with neoadjuvant chemotherapy and anti-HER2 targeted therapy. It is a prospective, non-randomized, interventional study. The physical activity program takes place precisely during the period of the anthracycline-based chemotherapy. It comprises both aerobic and resistance exercises. The main objective of the study is to show the feasibility of a physical activity intervention conducted at home, for patients treated with neoadjuvant chemotherapy and anti-HER2 targeted therapy, in order to comply with the international recommendations defined by the WHO (i.e. at least 150 minutes of moderate-intensity aerobic physical activity or at least 75 minutes of vigorous-intensity activity or an equivalent combination of moderate-to-vigorous intensity activity throughout the week [3]). There is a lack of data concerning

physical activity practice from the beginning of breast cancer treatment in case of neoadjuvant chemotherapy, and this study will allow the feasibility of home-based adapted physical activity to be assessed (aerobic and resistance training) for the first time in this early period of treatment.

According to the data, the need for HER2+ breast cancer patients is to increase or maintain their level of physical activity until they reach the international recommendations. It also enables their sedentary time to be reduced in order to offset treatment-induced cardiotoxicity. The intervention for this patient subgroup needs to be initiated as soon as possible in order to anticipate and prevent any cardiac events. A cardiopulmonary exercise test enables the intensity of physical activity to be adjusted according to each patient's capacities and to ensure that there is no contraindication to exercise.

It is essential to integrate aerobic exercising into the program because of the benefits on the cardiovascular system. It enables cardiopulmonary function, notably VO_{2max}, to be relatively rapidly improved among breast cancer patients (**Table 1**). Nevertheless, muscular strength is also required because increase in muscle mass is linked to a decrease in fat mass, and thus contributes to better body composition [73]. Furthermore, De Luca *et al*. among breast cancer survivors showed that resistance training limited body mass gain, which is often associated with an increase in fat mass and a loss of muscle mass [59]. Indeed, adjuvant breast cancer treatments, such as endocrine therapy , are linked to weight gain mainly corresponding to fat mass gain in the abdominal region [77,78] and physical activity practice could improve these negative long term side effects.

A particularity of the physical activity program is that it can offer support in many forms to encourage practice [79–81]. For example, a pedometer can be given to patients to measure the distance that needs to be reached every week. It can even be a pedometer connected to a smartphone application. Patients could thus see their daily activity and sedentary time, or even monitor their personalized objectives and their progress. The advantage of this tool is that their sports instructor can also see their patient's physical activity and adapt the program according to the patient's physical fitness.

III. BARRIERS AND FACILITATORS TO PRACTICE: HOW CANPHYSICAL ACTIVITY PROGRAMS BE OPTIMISED?

The success of physical activity interventions lies in the participation of patients. There is therefore a real challenge to identify the barriers and facilitators in order to optimize adherence to a physical activity program.

1. Barriers to exercising

Possible barriers to practice are numerous and can be physical, psychological or even organisational. It is essential to identify these barriers so that they can be overcome for the purpose of improving physical activity practice. Some factors hindering physical activity practice have already been identified.

Barriers linked to disease or treatment side effects are among the most important. Indeed, Courneya *et al.* studied barriers to physical activity in a three-arm randomized trial (aerobic exercise training *versus* resistance exercise training *versus* usual care) and reported that side effects were the reason for more than 50 % of missed supervised exercise sessions on offer in their trial during chemotherapy [82]. Patients mentioned mainly fatigue, nausea, and not feeling well on the day of the chemotherapy administration as barriers to physical activity, since it interfered with their ability to exercise. Nevertheless, it should be considered that before treatment initiation, patients can have comorbidities that already affect their ability to engage in physical activity [83]. Further to this, the notion of self-image should also be considered. Changes in appearance and body image are also barriers to physical activity because patients can be wearing a wig or a prosthesis [84]. This makes the practice of certain activities more complicated, such as swimming for example, because of the close-fitting swimsuits [85]. It adds a further barrier to exercise, especially because of the embarrassment patients might feel in public. Organisational barriers are the second theme among limitations to physical activity practice. Firstly, the distance between home or the workplace and the sports facility frequently appears as a considerable limitation [83,86–88]. What is more, infrastructures are often located in cities, so that access is more difficult for those who live in the countryside. Nevertheless, even for patients living in the city, the risk of encountering traffic problems should also be taken into account as a barrier [86].

When the disease occurs, patients struggle to maintain a balance between work and family life and give more value to the time spent with family and/or friends than doing exercise [84]. They want to

take responsibility for their families as they did before diagnosis, and this can also be a barrier to exercise [88,89]. Patients who did not have time to practice any physical activity before, find it all the more difficult after diagnosis [90,91], especially as a lack of willpower is also a considerable barrier [82,89–91]. Furthermore, being able to continue to go to work is a real need for certain patients, to fight emotional distress and to feel that they are in control. However, this requires a lot of energy and patients are often too tired to engage in a physical activity on top of everything [84]. Furthermore, it has been shown that socioeconomic status also influences physical activity. Indeed, women with a higher level of education are more likely to work full time, and alongside to have a lower moderate exercise level. Thus, employment status could interfere with leisure time and reduce the opportunity to engage in exercising [92].

The psychological aspect is another theme highlighted in certain studies [85–87,93,94]. Overprotection by the patients' entourage has been recognised as a limitation to physical exercise. Furthermore, some patients do not know that they can exercise during treatment or are afraid that it might worsen their symptoms. This raises the problem of the lack of information on physical activity that should be provided by the medical staff [93,94]. And although they may feel uncomfortable exercising in front of healthy people, as mentioned above, patients also report the importance of support to increase their motivation [89,92–94].

It has been shown that the more barriers there are for patients, the lower their level of physical activity [82,95], and also that reducing barriers to exercise is correlated with an increase in physical activity levels. Indeed, Ottenbacher *et al.* showed that patients who reduced their barriers from baseline to 1 year increased their physical activity levels by 91 minutes per week [91]. Facilitating access to training sessions (flexible times, car or bus access, etc.) evidences better adherence rates [61].

2. How can patients be encouraged to be physically active during treatment?

Identifying barriers to physical activity provides an understanding of how to encourage patients to be physically active. First of all, receiving information about the benefits of physical activity during treatment is highly important [83]. Some studies have shown that patients who are aware of the benefits of exercise during treatment are more active than those who do not have this information [96].

345 Other studies have shown that the influence of the physician proves to be the most decisive incentive
346 among patients to practice a physical activity: by providing reassurance on potential health issues
347 (restoring confidence in their health, reassurance about fear of injury and fatigue), along with the
348 physician's involvement and interest (specific request and monitoring of the patient's physical
349 activity) [97,98]. All these elements point to the importance of information to patients and the training
350 of physicians/oncologists on the effects of physical activity. Finally, a personal background of
351 physical activity is also important, because it is easier for patients to continue a physical activity
352 practice during treatment if they were already active before. For other patients, diagnosis appears as a
353 trigger and a motivational factor that motivates them to take care of themselves [83].
354 Another key point in promoting physical activity is to personalize the program for each patient. A
355 randomized controlled study, after a one-year follow-up, showed that patients in the tailored-
356 intervention arm adhered better to the diet and exercise recommendations than the control group who
357 were only given standardized diet and exercise brochures [99]. This trial underlines the importance of
358 personalizing the intervention for each patient in order to facilitate enrolment on a training program. It
359 is also essential to define realistic goals for each patient so as to enhance their feeling of self-efficacy
360 [100,101], especially since it has been shown that patients who are less inclined to take part in a
361 physical activity program are also those who feel unable to carry it through [102].
362 Social support plays a favourable role in physical activity levels. Patients feel comfortable when
363 exercising with other breast cancer women and developing relationships is a source of motivation
364 [85,86].
365 Lastly, the emergence of mobile applications and connected devices promoting diet and physical
366 activities has upgraded the classic approach to practice. Using new technologies through applications
367 for smartphones or other electronic devices has proved to be a motivation for patients [103]. It has
368 been shown that a physical activity program associated with receiving weekly review emails and
369 access to an e-counsellor for advice on exercise and physical activity is more efficient than a standard
370 physical activity program for improving levels of physical activity among breast cancer patient
371 survivors [104]. Furthermore, new information and communication technologies appear as a good way
372 to establish regular patient follow-up, which is paramount during a physical activity program.

CONCLUSION

As a result of the side effects of the treatment they receive, HER2+ breast cancer patients are particularly exposed to cardiac events during or after therapy. Over the years, the idea has emerged that being active during treatment could present several advantages for patients, and studies have confirmed an improvement in numerous aspects of patient condition during and after treatment (quality of life, asthenia, treatment compliance, cardiac function, etc.). Trials that have been conducted on this issue are very heterogeneous and no standard recommendations are available for HER2+ breast cancer patients. Nevertheless, the importance of practising aerobic exercise is obvious on account of its benefits for the heart. It is essential to facilitate adherence, in particular, so as to maintain patient motivation. The practice of physical activity should be viewed as leisure and integrated into the patient's daily life. Further studies are certainly required to determine how to integrate physical activity practice into HER2+ breast cancer patients' treatment plans. Studies on cost-effectiveness are also needed to assess the medical- and economic consequence of physical activity practice during treatment, which could promote a return to professional activity, thereby reducing the long-term costs.

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FIGURE LEGENDS

Table 1: Physical activity interventions reporting cardiopulmonary outcomes among breast cancer patients during and after treatment

Adj: Adjuvant; AET: aerobic exercise training; CT: chemotherapy; Ctrl: Control; HR_{max}: maximum heart rate; HT: Hormone therapy; NA: Not applicable; NACT: Neoadjuvant chemotherapy; ND: Not done; RCT: Radiochemotherapy; RET: Resistance exercise training; RM: repetition maximum; RPE: Rate of perceived exertion; RT: Radiotherapy; UC: usual care; VO_{2max}: maximum peak oxygen consumption

STUDY	N	TREATMENT	MODALITY	PROGRAM DURATION	FREQUENCY	ACTIVITY	INTENSITY	ADHERENCE	IMPROVEMENT
Courneya KS, 2007	82	Adj CT	NA	NA	NA	UC	NA	NA	NA
	82		Group (supervised)	17 weeks (±4 months)	3 sessions/week	RET	60% to 70% of their estimated one repetition maximum	68%	↑ Body strength ↑ Lean body mass
	78					AET	From 60 to 80% of VO_{2max}	72%	↑ Aerobic fitness
Fairey AS, 2003	25 Intervention group)	Completed surgery, RT and/or CT with or without current HT use	Group	15 weeks	3 sessions/week	AET	70-75% of VO_{2max}	98.4%	Between group difference for VO_{2max} : + 0.29 L/min ($p<0.001$)
	28 (Ctrl group)		No training	NA	NA	NA	NA	NA	
Cornette T, 2016	22 (Intervention group)	NACT or Adj CT and RT	At home	27 weeks	2 sessions/week 1 session/week	AET RET	> 3 METs	88%	VO_{2max} : + 1.83 ± 0.68 ml/min/kg
	22 (Ctrl group)		NA	NA	NA	UC	NA	NA	VO_{2max} : - 1.31 ± 0.65 mL/min/kg

De Luca V, 2016	10 (Intervention group)	Surgery + all cancer therapies completed at least 6 months before	Group (supervised)	24 weeks	2 sessions/week	AET RET	70% to 80% of estimated HR_{max} A load of 40% to 60% of estimated 1RM	ND	↑ Vo_{2max} + 38.8 % between baseline and end of intervention
	10 (Ctrl group)		NA	NA	NA	NA	NA	NA	No significant change
Hornsby, 2014	10 (Intervention group)	NACT	One-to-one supervised sessions	12 weeks	2 to 3 sessions/week	AET	Moderate to high intensity	66%	VO_{2max} : + 2.6 ± 3.5 mL/min/kg
	10 (Ctrl group)	NA	NA	NA	NA	UC	NA	NZ	VO_{2max} : - 1.5 ± 2.2 mL/min/kg
Travier, 2015	102 (Intervention group)	Adj CT	Group	18 weeks	2 sessions/week	AET RET	Based on the heart rate at the ventilatory threshold as determined during baseline cardiopulmonary exercise test	83%	VO_{2max} : - 0.7 mL/min/kg
	102 (Ctrl group)		NA	NA	NA	UC	NA	NA	NA
Dieli-Conwright CM, 2018	46 (Intervention group)	< 6 months post-treatment (chemo or radiotherapy)	One-to-one supervised sessions	16 weeks	3 sessions/week (2 AET+RET and 1 AET)	AET RET	Moderate-vigorous intensity	96 %	↑ Vo_{2max} ↓ Resting heart rate

	45 (Control group)		NA	NA	NA	NA	NA	NA	No change in physical fitness
Foucaut AM, 2014	61	Adj RCT	Group	3 months	1 session/week 1 session/week	AET RET	Moderate to vigorous	80%	VO_{2max} : + 0;6 ml/min/kg
Kim CJ, 2006	41	Adj therapy	Group	8 weeks	2 sessions/week	AET RET	Moderate	78.3%	↑ Vo_{2peak}
Kolden, 2012	40	Adj therapy	Group	16 weeks	3 sessions/week	AET RET Flexibility	40-60% of estimated maximal aerobic capacity	88%	↑ aerobic capacity
Leach, 2016	102	currently treated by CT or CT/RT discontinued within 3 months	Group or home-based exercise according to patient's preference	24 weeks	2 sessions/week 1 session/week 5-7 sessions/week	AET RET Flexibility	Mild to vigorous	80.6% (12 week assessment) 42% (24 week assessment)	VO_{2max} : + 1.9 mL/min/kg
Noble, 2012	575	Surgery or CT or RT or HT	Group	12 weeks	2 sessions/week	AET RET Stretching	RPE 11-13	69%	↓heart rate response ↓ systolic blood pressure ↓ RPE

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