

PHYSICAL EXERCISE MINIMIZES THE TOXIC TRIAD FOR CANCER: PHYSICAL INACTIVITY, LOW FITNESS, AND OBESITY

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ABSTRACT

The so-called toxic triad of factors linked to cancer, namely obesity, poor cardiorespiratory fitness (CRF) and physical inactivity, increase the risk of cancer and, when cancer is present, worsen its prognosis. Thus, obesity and a sedentary lifestyle have been linked to an elevated cancer risk whereas regular physical exercise and good CRF diminish this risk. Despite genetic risk factors, there is evidence to show that some lifestyle modifications are capable of reducing the incidence of cancer and its associated morbidity and mortality. Regular physical exercise targeted at maintaining body weight within healthy limits and improving CRF will reduce a person's cancer risk and, once diagnosed, will also improve its prognosis, reducing mortality and the risk of disease recurrence through similar effects. In this review, we describe how physical activity can be used as a pleiotropic, coadjuvant tool to minimize the toxic triad for cancer and update the mechanisms proposed to date for the effects observed.

Key Words: cancer, physical activity, adiposity, sedentarism, myokines, body mass index, breast cancer

EL EJERCICIO FÍSICO MINIMIZA LA TRIADA TÓXICA DEL CÁNCER: OBESIDAD, BAJA CONDICIÓN FÍSICA E INACTIVIDAD

RESUMEN

La conocida como triada tóxica del cáncer, compuesta por la obesidad, una baja función cardiorrespiratoria (FCR) e inactividad física, incrementa el riesgo de cáncer y, una vez presente la enfermedad, empeora su pronóstico. Así, la obesidad y estilos de vida sedentarios se han asociado con un elevado riesgo de cáncer mientras que el ejercicio físico regular y una buena FCR disminuyen dicho riesgo. A pesar de los factores de riesgo genético, existe evidencia que demuestra que algunas modificaciones en el estilo de vida son capaces de reducir la incidencia de cáncer y su morbilidad y mortalidad asociadas. El ejercicio físico regular dirigido a mantener el peso corporal dentro de límites saludables y a mejorar la FCR reducirá el riesgo de cáncer de una persona y, una vez diagnosticado, también mejorará su pronóstico, reduciendo la mortalidad y el riesgo de recurrencia de la enfermedad a través de mecanismos similares. En esta revisión, describimos cómo la actividad física puede ser utilizada como una herramienta coadyuvante y con efectos pleiotrópicos a fin de minimizar los efectos de la triada tóxica del cáncer y se actualizan los mecanismos propuestos hasta la fecha para los efectos observados.

Palabras clave: cáncer, actividad física, adiposidad, sedentarismo, mioquinas, índice de masa corporal, cáncer de mama

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INTRODUCTION

Cancer is defined as a disease in which the uncontrolled growth of cells damages and invades adjacent organs and healthy tissue. The molecular mechanisms shared by all cancer types are DNA mutations in tumor cells. The cancers most prevalent in men are prostate cancer followed by lung and colon cancer, while in women, these are breast cancer followed by lung and colorectal cancer (American Cancer Society, 2004). Since 1991, the mortality rate attributable to cancer has fallen by 23%, meaning that 1.7 million deaths have been avoided over this period (Siegel et al., 2016). Despite improvements in detection methods and adjuvant therapies, however, latest estimates by the American Cancer Society predict 1,685,210 new cases of cancer and 595,690 persons lost to cancer in 2016 in the United States (Siegel et al., 2016). The symptoms of cancer are innumerable and depend on the type of tumor, its localization, and its stage. Several other health problems are frequent in patients including cardiotoxicity due to anthracyclines used in therapies (Jones et al., 2007), cardiovascular disease (Patnaik et al., 2011), osteoporosis associated with aromatase inhibitor treatment and chemotherapy-induced menopause (Cameron et al., 2010; Coleman et al., 2008), reduced cardiorespiratory fitness (CRF) often accompanied by muscle atrophy (Christiansen et al., 2015; Floyd et al., 2005; Peel et al., 2014; Strasser et al., 2013) and fatigue, which affects 60-100% patients before or after treatment (Vermaete et al., 2013).

Besides genetics, many other factors play major roles in the development of cancer including chemical carcinogens (such as tobacco), physical inactivity, and diet, (Kushi et al., 2012; McGinnis & Foege, 1993). Inherited genetic factors are thought to contribute little to susceptibility to most malignancies, determining a major role of the environment in sporadic cancer (Lichtenstein et al., 2000; Rogers et al., 2008). According to a recent theory, the majority of cancers are the outcome of "bad luck," that is, random mutations that occur during DNA replication in normal stem cells (Tomasetti & Vogelstein, 2015). However, extrinsic cancer risk factors exist that are not due to chance and are seldom accounted for. For example, some interventions such as physical exercise are able to modulate the risk of developing some types of cancer or cancer progression and prognosis by improving obesity, physical activity and CRF (Sanchis-Gomar et al., 2015a), as discussed below.

1. *The toxic triad for cancer*

The factors obesity, low CRF and physical inactivity known as the "toxic triad for cancer" increase the risk of cancer and worsens its prognosis (Sanchis-Gomar et al. 2015a; Wang et al., 2012).

1.1. Obesity and cancer

The link between excess adiposity and cancer is a topic of growing concern (Azvolinsky, 2014; Renehan et al., 2010; Renehan et al., 2008), especially if we consider the increasing incidence of both disorders. It is estimated that 1.5 billion adults worldwide are overweight or obese (Patlak & Nass, 2012), and every year more than 12,000 cases of 10 types of cancer are attributable to a high BMI (Kmietowicz, 2014). Several studies have been able to correlate BMI with independent risks of both cancer development (Azvolinsky, 2014; Reeves et al., 2007; Renehan et al., 2010; Renehan et al., 2008; Wang et al., 2012) and cancer-associated mortality (Calle & Kaaks, 2004; Calle et al., 2003; Chan et al., 2014; Protani et al., 2010; Wang et al., 2012). This link was found to be more obvious for a weight gain of more than 10% after cancer diagnosis (Playdon et al., 2015). In the *Million Women Study*, a BMI increase was associated with an increased risk of 10 out of 17 cancer types analyzed in 1,200,000 women followed for 5.4 years: endometrial cancer, kidney cancer, esophageal adenocarcinoma, leukemia, multiple myeloma, pancreatic cancer, non-Hodgkin lymphoma, ovarian cancer, breast cancer in postmenopausal women and colorectal cancer in premenopausal women (Reeves et al., 2007).

Obesity is not only a cancer risk factor, it also acts as an indicator of disease progression. Thus, high adiposity levels in women with breast cancer have been related to adverse effects such as lymphedema, worse quality of life, and greater risks of relapse and cancer-associated mortality (Chan & Norat, 2015). Further, women who are obese when diagnosed with breast cancer show a 33% higher relapse and mortality risk than normal-weight breast cancer patients (Protani et al., 2010). Interestingly, over half the women with this type of cancer are obese at the time of diagnosis (Morimoto et al., 2002) or gain weight during anti-cancer treatment (Bower et al. 2009).

According to a metaanalysis, women who are obese before they are diagnosed with breast cancer showed a 41% greater risk of all-cause mortality and a 35% greater risk of mortality due to their cancer than normal-weight breast cancer patients. These figures were 23% and 25%, respectively, for women who were obese within the first 12 months of diagnosis, and 23% and 68%, respectively if they were obese at 12 months or longer following diagnosis (Chan et al., 2014). The incidence of cancer, mostly breast and colorectal, is higher among individuals with high abdominal adiposity, due to, among other causes, increased visceral fat metabolic activity, which leads to hormone and inflammatory disturbances (Le Marchand et al., 1992; Schapira et al., 1994). In the *Health, Eating, Activity, and Lifestyle Study (HEAL)*, a greater waist circumference and waist-to-hip ratio (markers of abdominal adiposity) was linked to a three times greater risk of mortality in women with breast cancer (George et al., 2014). Other mechanisms whereby obesity is associated

with a greater risk of cancer including insulin resistance, hyperinsulinemia, hyperglycemia, glucose intolerance and elevated adipocytokine production (Booth et al., 2015; Perez et al., 2016).

Other studies have identified a link between obesity and several cancers including colorectal (Ma et al., 2013; Moghaddam et al., 2007), ovarian (Liu et al., 2015), prostate, mostly advanced stage (MacInnis & English, 2006), endometrial (Jenabi & Poorolajal, 2015), gallbladder (Larsson & Wolk, 2007b; Tan et al., 2015), pancreatic (Aune et al., 2012; Larsson et al., 2007), liver (Larsson & Wolk, 2007c) head and neck (Gaudet et al., 2015), and colon and rectal in men (Larsson & Wolk, 2007a). Obesity has been therefore described as an avoidable cause of a wide variety of cancers (Campbell, 2014), as revealed by the link between BMI and an increased risk of developing 17 of the 22 most common cancer types (Bhaskaran et al., 2014). In addition, there is a positive feedback between obesity and the consequences on health and quality of life of a sedentary lifestyle and poor physical performance, which in turn leads to weight gain (Elme et al., 2013).

1.2. Cardiorespiratory fitness and cancer

Physical fitness is "the ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy (leisure) pursuits and to meet unforeseen emergencies" (Garber et al., 2011). CRF is a strong indicator of cardiovascular function (heart and blood vessels), respiratory function (lungs) and the efficiency of oxygen transport and use by skeletal muscle and other organs (Booth et al., 2012; Peel et al., 2014). Maximal oxygen uptake (VO_{2peak} ; sometimes referred to as maximal aerobic capacity) is a main indicator of CRF. In turn, CRF is so important for health that its clinical assessment is recommended given its impact on survival both in the general population (Kodama et al., 2009) and in cancer patients (Schmid & Leitzmann, 2015).

Cardiovascular diseases are the main cause of death among women older than 66 years who are diagnosed with early stage breast cancer (Patnaik et al., 2011). Similarly, the prevalence of cardiovascular comorbidity within 5 months of being diagnosed with colon cancer was 59% in an Australian population. In addition, 16% of the patients who had no cardiovascular disorders at baseline developed such problems 36 months after the diagnosis (Hawkes et al., 2011). There is also sufficient evidence to indicate that treatments against cancer significantly reduce CRF, such as those based on radiotherapy and chemotherapy with anthracyclines, which induce cardiotoxicity in the short and long term (Floyd et al., 2005). Effectively, results published in 2015 in long-standing survivors of childhood cancer (mean 23.4 years since diagnosis) who received anthracyclines as part of their anti-cancer therapy, indicated that 47%

showed considerable reductions in VO_{2peak} (Christiansen et al., 2015). Similarly, some authors reported a VO_{2peak} reduced by up to 17% in breast cancer patients before adjuvant therapy compared to healthy, physically inactive women. This reduction becomes more obvious once treatment has been completed and values up to 25% lower were recorded than in their healthy, sedentary peers (Peel et al., 2014).

In a recent study examining cardiopulmonary function in women with breast cancer during their illness, it was noted that about one third of these women had a VO_{2peak} lower than the value indicating functional independence (i.e., lower than 15.4 ml/kg/min), suggesting they were not capable of conducting daily living activities (Jones et al., 2012). In a 17-year follow-up study, it was reported that subjects with a VO_{2max} greater than 33.2 ml/kg/min showed both an incidence of cancer reduced by 27% and a 37% reduced mortality from the disease (Laukkanen et al., 2010). In a prospective study, the *Aerobics Center Longitudinal Study*, the relationship among CRF, measures of adiposity (BMI, waist circumference, percentage body fat) and cancer-related mortality was assessed. Results indicated a lower mortality for men in good physical condition independently of several confounding factors, including all the adiposity measures. Thus, men with good CRF showed a lower risk of dying from their cancer than their matched peers with worse CRF, regardless of adiposity. This means that high CRF levels may significantly minimize the link mentioned above between adiposity and cancer-related mortality in men (Farrell et al., 2007).

Low CRF levels detected in cancer survivors should not be ignored because a MET level less than 8 has been linked to an increased risk of mortality and cardiovascular events in men and women aged 40 to 60 years (Kodama et al., 2009; Ruiz-Casado et al., 2014). Cardiovascular disease is effectively the leading cause of long-term morbidity and mortality among long-term cancer survivors (Horner et al., 2009). There is also epidemiologic evidence supporting a protective role of CRF against bowel, colorectal, and liver cancer-related deaths in men over a wide age range (20–88 years). Thus, individuals with a CRF level below 8 MET show a 3-fold higher risk of death from bowel cancer than those with METs ≥ 11 (Peel et al., 2009).

1.3. *Physical inactivity and cancer*

According to the physical activity guidelines issued by the U.S. Department of Health and Human Services (Physical Activity Guidelines for Americans, 2008) and the World Health Organization, WHO (WHO, 2010), adults should undertake ≥ 150 min/wk of moderate to vigorous physical activity (MVPA). Sedentary behaviors are defined as "any waking behavior characterized by an energy expenditure ≤ 1.5 MET while in a sitting or reclining posture" according

to the Sedentary Behaviour Research Network (SBRN), whereas "physical inactivity" refers to those who perform insufficient amounts of MVPA (i.e., <150 min/wk) (Sedentary Behaviour Research Network, 2012). According to Booth et al. (Booth et al., 2012), physical inactivity is defined as "physical activity levels less than those required for optimal health and prevention of premature death".

Physical inactivity is considered the fourth mortality risk factor worldwide causing 6% of all deaths (WHO, 2010). Physical inactivity augments the risk of some site-specific cancers (colon, breast, and endometrial cancers), but, at least to date, not all cancer types. The specificity of cancer types enhanced by physical inactivity supports the notion that mechanisms of inactivity-induced cancers are specific to each cancer (Booth et al., 2012). Physical inactivity has been estimated to contribute to more than 10% of the disease burden of two of the most prevalent cancers among westerners, that is, breast and colon (accounting for 13.8% and 14.9% of the burden, respectively, among the Spanish population and 12.4% and 12%, respectively, in the United States) (Lee et al., 2012). According to recent evidence, physical inactivity is a strong, independent risk factor leading to the build-up of abdominal fat and consequently to macrophage infiltration and subsequent activation of a network of inflammatory pathways, through which is promoted neurodegeneration, insulin resistance, atherosclerosis, and the growth of some types of tumor (Pedersen, 2011). According to data from the WHO, physical inactivity is the main cause of approximately 21%-25% of breast and colon cancers (WHO, 2010). Similarly, physical inactivity and obesity have been linked to a significant increase in the risk of numerous cancer types (Wang et al., 2012).

In cohorts of US cancer survivors in whom physical activity was measured objectively (i.e., by accelerometry), mean MVPA levels were clearly below the recommended 150 min/wk threshold at approximately 26 (breast) and approximately 42 (prostate) min/wk (Lynch et al., 2010; Lynch et al., 2011). Moreover, in a recent US National Health and Nutrition Examination Survey (NHANES) of more than 7 million cancer survivors, only 4.5% met the physical activity recommendations whereas obesity prevalence was 33.9% (Smith et al., 2011). Campbell et al. observed a link between a longer sitting time and greater mortality risk in colorectal cancer survivors. These authors reported that following diagnosis, spending 6 hours or longer sitting down increased the risk of all-cause mortality by 27% and of mortality due to the cancer itself by 62% (Campbell et al., 2013).

2. *The effect of physical exercise on the toxic triad of cancer risk factors*

Sufficient scientific evidence exists to confer physical activity a protective role against all-cause mortality, cardiovascular disease, high blood pressure, stroke, metabolic syndrome, diabetes type 2, some types of cancer, depression and falls (Lee et al., 2012). In a review recently published (Fiuza-Luces et al., 2013) it emerged that physical exercise produces greater benefits in preventing cardiovascular disease than the "polypill", which consists of a cholesterol-lowering drug (atorvastatin or simvastatin) one to three anti-hypertension agents (calcium channel blocker, thiazide, angiotensin converter enzyme inhibitor or angiotensin receptor blocker or a combination of these), with or without aspirin. Thus, it seems that the benefits of regular physical activity are clear and the current trend is to think that exercise acts in a dose-dependent manner, such that greater levels of exercise will offer greater benefits for health (Eijsvogels & Thompson, 2015). According to American College of Sports Medicine (ACSM) recommendations for cancer survivors (Schmitz et al., 2010b), physical exercise has proven to be a safe and effective non-pharmacological therapy for patients during and after adjuvant treatment and should be encouraged by doctors managing these patients (Ruiz-Casado & Lucia, 2014). Below, we describe the benefits of physical exercise in terms of primary and secondary prevention of the adverse effects of the toxic triad for cancer.

2.1. *Physical exercise, obesity and cancer*

The high indices of obesity pre- and post cancer diagnosis determines a need to design strategies targeted at maintaining a healthy body weight [BMI < 25 kg/m² as defined by the American Heart Association (AHA) (Lloyd-Jones et al., 2010)]. For this purpose, exercise is emerging as a powerful tool to reduce adipose tissue, which in itself could be an important factor for reducing the risk of cancer along with its morbidity-mortality (Booth et al., 2012).

Within the role ascribed to physical activity in the primary prevention of obesity (Booth et al., 2012), a recent controlled randomized trial in 243 overweight postmenopausal women randomized to three groups (diet, physical exercise and control), showed that 16 weeks after the intervention, both intervention groups lost weight yet greater effects on high-sensitivity C-reactive protein (hsCRP) were produced in the exercise group. In addition, leptin levels were reduced in both groups. Hence, weight loss linked to a reduction in hsCRP and leptin could be related to a lower risk of breast cancer (van Gemert, 2016). The few studies that have examined the impact of physical activity on body weight in cancer patients have been highly variable. In a metaanalysis including 34 randomized controlled trials performed in cancer survivors who had completed their treatment, slight reductions were observed

in BMI (-0.4; -0.6 to -0.2) and body weight (-1.1 kg; -1.6 to -0.6 kg) after completing a physical exercise program (Fong et al., 2012).

In another metaanalysis of 10 studies assessing the effects of aerobic exercise on cardiopulmonary function and body composition in women with breast cancer, a significant increase was recorded in VO_{2peak} and a significant reduction in percentage body fat. Aerobic exercise also led to reduced body weight and increased lean mass, though significance was not reached in both cases (Kim et al., 2009). Likewise, in a controlled randomized trial in 123 women with stage I-II breast cancer, supervised physical exercise significantly reduced body weight compared to the control group of participants who did not receive chemotherapy (Segal et al., 2001). When comparing the effects of high volumes (300 min/wk) and moderate volumes (150 min/wk) of MVPA on adiposity levels in postmenopausal women, it was observed that those undertaking the larger weekly exercise volume achieved significantly greater reductions in total body fat, subcutaneous abdominal fat and waist-to-hip ratio (Friedenreich et al., 2015). Schwartz and Winters-Stone determined the type of exercise producing greatest benefits on body fat loss in cancer survivors (Schwartz & Winters-Stone, 2009). Their study compared the effects of strength and aerobic exercise on this variable. After 12 months of training, body fat was reduced in both exercise groups compared to controls but a greater reduction was observed in the aerobic exercise group. Results were similar for body weight.

Maintaining a healthy body weight is one of the main recommendations of the American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Survivors (Rock et al., 2012), given that weight gain is a complication of anti-cancer treatments (Chlebowski et al., 2002). This means that a key objective is not so much weight loss rather that weight should not be gained in patients with a BMI ≤ 25 kg/m², while for those with a BMI > 25 kg/m², the target should be a 10% weight loss (Ballard-Barbash et al., 2009). In a study in elderly patients (59-82 years) with prostate cancer, a strength training program during treatment produced beneficial effects on muscular strength, functional capacity and equilibrium, maintaining lean body mass without changes produced in body fat (Galvão et al., 2006).

2.2. Physical exercise, cardiorespiratory fitness and cancer

Although physical activity is the only behavioral intervention that seems to improve CRF, it should not be forgotten that CRF has a strong genetic component; after adjustments for age, gender, body mass and body composition its heritability was calculated at around 50% (Bouchard et al., 1998). Cancer and its treatments reduce functional capacity and thereby CRF. Despite its strong genetic component explaining 25-40% of its variation (Wei et

al., 1999), regular physical activity is another key determinant of CRF, which in most individuals may be improved with an adequate physical exercise program (Garber et al., 2011). This improvement has also been observed in cancer patients (Jones et al., 2011).

The effect of physical exercise on CRF in cancer patients was examined in a metaanalysis including 6 articles and 571 patients. The data obtained indicated that exercise was able to increase VO_{2peak} by 2.90 ml/kg/min while this variable showed a reduction of 1.02 ml/kg/min in the control group (Jones et al., 2011). This finding has clinical implications since a 1 ml/kg/min drop in VO_{2peak} has been associated with a 4% increase in mortality among these patients (Jones et al., 2010). In a recent systematic revision of the effects of physical exercise during chemotherapy, CRF improvements due to training were observed in 10 of 17 intervention groups with improvements varying from 8-31%, while CRF reductions of 1-32% were detected in 9 of the 13 control groups. Muscular strength improvements from 2% to 38% were noted in 17 of the 18 intervention groups while minimal improvements of 1.3-6.5% were recorded in 11 of the 14 control groups (Van Moll et al., 2016).

Peel et al. observed that women with a CRF of less than 8 MET showed an almost 3 times greater risk of dying from breast cancer compared to those with a higher MET level (Peel et al., 2009). Further, a CRF of 8 MET has been described as the minimum threshold for optimal health (Lucia et al., 2008). Accordingly, these data suggest an exercise capacity of at least 8 MET would be needed for beneficial effects on health. However, in a Spanish population with different cancer types, despite most showing good adherence to international physical activity recommendations, there was a high rate of obesity (33%) and a mean CRF of some 7.7 MET (Ruiz-Casado et al., 2014), below the 8 MET health threshold mentioned earlier. In a study in patients with prostate cancer undergoing radiotherapy, the effects of a strength training versus aerobic training program on CRF were compared. After 24 weeks of training, VO_{2peak} increased in the strength training group, remained stable in the aerobic training group and decreased in the control group (Segal et al., 2009).

With regard to exercise intensity, high interval training (HIT) programs are becoming popular to improve physical fitness in non-cancer populations. In cancer survivors, this type of training is uncommon because of the scarce scientific evidence of its safety in these patients. In a recent pilot study (Dolan et al., 2016), the effects of different training intensities were assessed in 33 postmenopausal breast cancer patients. Participants were randomized to three groups: i) supervised aerobic interval training (AIT) at 70-100% of VO_{2peak} ; ii) supervised continuous moderate training (CMT) at 60-70% of VO_{2peak} ; and iii) non-supervised. At 6 weeks post intervention, exercise groups showed similar VO_{2peak} improvements (~12% compared to outset), while a reduction was

produced in the control group. In addition, leg strength was significantly improved in the AIT group. Among the anthropometric variables analyzed, slight reductions in weight and waist circumference were recorded in the exercise groups compared to the control group (Dolan et al., 2016). A recent study compared the benefits on mortality following a diagnosis of breast cancer of two common activities, running and walking. Mortality due to breast cancer was significantly reduced by 40% per MET/h/day of running (vigorous intensity exercise) but only by 4.6% per MET/h/day of walking (moderate intensity exercise) (Williams, 2014). Thus, regular physical exercise and good CRF are linked to a lower incidence and better prognosis of cancer (Sanchis-Gomar et al., 2014, 2015b).

2.3. *Physical exercise, sedentarism and cancer*

Physical activity refers to "any bodily movement produced by skeletal muscles that results in energy expenditure" (Caspersen et al., 1985). Besides the beneficial effects of exercise on energy balance, high levels of regular physical activity *per se* have been also shown to decrease the risk of cancer (Abioye et al., 2014; Campbell et al., 2012; Friedenreich & Cust, 2008; Irwin, 2009; Laukkanen et al., 2009; Winters-Stone et al., 2014) and of mortality among cancer survivors, particularly survivors of breast and colorectal cancer (Schmid & Leitzmann, 2014).

In 2007, the *World Cancer Research Fund* and *American Institute for Cancer Research* published a report examining the role of physical activity and nutrition in developing cancer. The report concluded that the existing evidence for a protective role of physical activity against colon cancer was convincing, that it seems to also to protect against postmenopausal breast cancer, and endometrial cancer but that evidence that it acts against premenopausal breast cancer, and lung and pancreatic cancer was limited (Marmot et al., 2007) (Table 1). In a systematic review addressing this protective role of physical activity in developing cancer including 29 case-control and 19 cohort studies, it was observed that leisure-time physical activity was inversely associated with breast cancer in postmenopausal women. Risk reductions varied from 20 to 80%, while evidence for this relationship in premenopausal women was weaker (Monninkhof et al., 2007).

TABLE 1
Evidence for cancer prevention by physical activity. Adapted from
(Kruk & Czerniak, 2013).

Type of cancer	Evidence	Risk reduction (%)
Colon	Convincing/Probable	20-25%
Endometrium	Convincing/Probable	20-30%
Prostate	Probable	10-20%
Breast (postmenopausal)	Probable	20-30%
Breast (premenopausal)	Limited	26%
Ovarian	Limited	10-20%
Lung	Limited	20-40%

According to data from the National Physical Activity Guidelines Advisory Committee Report (NPAGCR), physical activity leads to a mean risk reductions of 30% for colon cancer and 20% for breast cancer along with a lower risk of endometrial cancer in women who are physically active than in their sedentary peers (Physical Activity Guidelines for Americans, 2008). Thus, physical activity could be considered a basic tool in the primary prevention of breast, colon and endometrial cancer (Booth et al., 2012). Further, other metaanalyses support these data with similar results: risks lowered by 27% and 26% of colon and rectal cancer, respectively (Boyle et al., 2012); and a 30% lower risk of endometrial cancer for active women (Moore et al., 2010). In another metaanalysis it was observed that fulfilling WHO physical activity recommendations for healthy individuals (at least 150 min/week of moderate physical activity or 75 min/week of vigorous activity or a combination of both) led to a reduction in the risk of cancer by 7%, which was mainly attributed to its protective role against breast and colorectal cancer (Liu et al., 2016).

Physical exercise also reduces the risk of other cancer types such as lung cancer. Thus, the results of a study including 81,516 subjects followed for 19 years indicated a 25% reduction in the risk of lung cancer in men who walked or cycled at least 4 h/wk (Thune & Lund, 1997). Further, undertaking twice or more times current physical exercise recommendations meant a 95.4% lower risk of death due to breast cancer (Williams, 2014). However, in other cases, fulfilling current physical activity recommendations was insufficient to produce improvements in insulin sensitivity with its consequent protective effect on the development of cancer (van Gemert et al., 2015). However, when assessing the relationship between physical activity following a diagnosis of cancer and survival, it was found that subjects who were physically active in that they at least fulfilled the general recommendations of the Centers for Disease Control and Prevention (150 min of moderate-intensity aerobic activity, 75 min of vigorous-intensity aerobic activity, or an equivalent mix of the two each week), lived almost twice as long as inactive individuals (Holmes et al., 2005; Ibrahim

& Al-Homaidh, 2011; Meyerhardt et al., 2006a; Meyerhardt et al., 2006b; Peel et al., 2009).

Leisure time physical activity (some 150 min/wk of brisk walking or ≥ 8.75 MET/h/wk) was linked to reduced mortality from colorectal cancer than < 3.5 MET/h/wk, while a greater proportion of leisure time spent sitting was correlated to increased mortality from this cancer type (Campbell et al., 2013). In a metaanalysis, risk reductions of 6% for colorectal cancer and 12% for colon cancer were observed per MET/h/wk and per 30 min/d respectively of leisure time physical activity, via reduced inflammation, and insulin resistance leading to lower circulating insulin levels (World Cancer Research Fund/American Institute for Cancer Research, 2011). Yet another metaanalysis revealed reductions of 20% in men and 14% in women in the risk of developing colon cancer for a greater amount versus lower amount of leisure time physical activity (World Cancer Research Fund/American Institute for Cancer Research, 2011). In addition, a study has shown a lower prevalence of breast and reproductive system cancers among former college female athletes compared with nonathletic controls (Frisch et al., 1987). Evidence also exists of the risk of breast cancer lowered in a dose-dependent manner by regular physical activity (Wu et al., 2013).

The relationship between physical activity before a cancer diagnosis and its prognosis has also been explored. A metaanalysis of colorectal cancer studies determined that performing physical activity before its diagnosis gave rise to a 25% drop in colorectal cancer-associated mortality and 26% reduction in all-cause mortality compared to subjects who were not physically active before diagnosis (Je et al., 2013). Post-diagnosis levels of physical activity equivalent to international recommendations (≥ 150 min/wk of moderate to vigorous physical activity) were associated with a mortality risk reduced by 24% in survivors of breast cancer and 28% in survivors of colorectal cancer (Schmid & Leitzmann, 2014). These results are similar to those reported by Li et al., who analyzed the link between fulfilling WHO recommendations and a reduced cancer risk and noted a 27% lower risk of mortality for cancer survivors who completed 15 MET/h/wk. Further, survivors who commenced physical activity after being diagnosed with cancer showed a mortality risk reduced by 35% (Li et al., 2016).

In one of the best known cohort studies, the *Nurses' Health Study* (Holmes et al., 2005), it was found that women who were most physically active (> 24 MET/h/wk) after being diagnosed with breast cancer had a 26-40% lower risk of tumor recurrence and all cause-death than those who remained inactive (< 3 MET/h/wk). Moreover, those who walked from 3 to 5 h/wk at a moderate pace (3.2-4.7 km/h) obtained the greater health benefits (Holmes et al., 2005). Similarly, in a metaanalysis including 22 cohort studies in breast cancer

survivors, Lahart et al. noted that physical activity showed an inverse relationship with death due to breast cancer and other causes and events associated with cancer (progression, new primary tumors and disease recurrence). These authors concluded that physical activity plays a protective role against death due to breast cancer (Lahart et al., 2015).

The results of the *National Health and Nutrition Examination Survey* (2003–2006), which was the first study to objectively assess physical activity levels (through accelerometry) in prostate cancer survivors, indicated that this patient population is extremely inactive, spending most of their time performing sedentary activities (69%) or only light exercise (30%). Only 1% of time was spent undertaking moderate-vigorous physical activity (Lynch et al., 2011). Nevertheless, despite the evident benefits of physical activity postdiagnosis, we should underscore that cancer patients often diminish their physical activity levels once diagnosed with the disease. For example, Irwin et al. observed that women with breast cancer were physically less active in the first year postdiagnosis than in the preceding year (Irwin et al., 2003). Also, women showing this reduction in physical activity after diagnosis showed a 4 times greater mortality risk than those who were always inactive (Irwin et al., 2008). It should be noted that each 15 MET/h/wk increase in physical activity level postdiagnosis has been linked to a 38% reduction in mortality risk in survivors of colorectal cancer and a 34% reduction in those of breast cancer (Schmid & Leitzmann, 2014). In addition, in a recent metaanalysis we observed a 40% lower standard mortality ratio due to cancer in those engaging in the highest physical activity levels, that is, elite athletes of various sport disciplines (n = 12,119, mostly men) including "Tour de France" finishers, compared with the general population (Garatachea et al., 2014).

3. *Epidemiological evidence of the effect of physical exercise on cancer*

Many studies have addressed the link between physical activity and cancer risk. In a study by Liu et al. performed in 7,304,954 subjects without chronic diseases, those who fulfilled WHO physical activity recommendations showed a 7% lower risk of developing breast and colorrectal cancer (Liu et al., 2016). Wu et al. described a dose-response relationship between breast cancer risk and physical activity in that this risk was reduced 2% for each 25 MET/h/wk of non-occupational physical activity, 3% for each 10 MET/h/wk recreational activity, and 5% for each 2 h/wk of moderate-vigorous recreational activity (Wu et al., 2013).

A recent metaanalysis including 16 randomized controlled trials determined that patients with prostate cancer who had performed physical exercise improved their quality of life and fitness and showed less cancer-related fatigue compared to those who had not undertaken exercise (Bourke et

al., 2016). Several previous metaanalytical studies and reviews have assessed the effects of physical exercise on cancer-related fatigue.

Brown et al. noted that cancer survivors who conducted moderate intensity strength exercise (3-6 MET, 60%-80% of 1-RM) reduced their levels of cancer-related fatigue in greater measure than those who did so at lower intensity or performed any intensity of aerobic exercise (Brown et al., 2011). However, McMillan & Newhouse observed that it was aerobic exercise that significantly produced greater benefits on cancer-related fatigue over the effects of strength exercise, or both, which were not significant (McMillan & Newhouse, 2011). In another recent metaanalysis including 2830 participants, Tian et al. reported that aerobic exercise, effectively, had a significant impact on reducing cancer-related fatigue although this impact was modest (Tian et al., 2016). However, in an earlier metaanalysis it was observed that 72 randomized controlled studies had concluded that any type of physical exercise has beneficial effects of cancer-related fatigue, insomnia and depression (Tomlinson et al., 2014).

In a Cochrane review, the authors detected significant reductions in cancer-related fatigue after completing a physical exercise program during or after cancer treatment (Cramp & Byron-Daniel, 2012). Finally, Velthuis et al. observed that supervised aerobic exercise programmes were more effective in reducing cancer-related fatigue than non-supervised (Velthuis et al., 2010). In another metaanalysis, this time on the effects of strength training in cancer survivors (Strasser et al., 2013), benefits were obtained on muscular strength both of the upper and lower limbs and on body composition, effects being greater on upper limb strength and percentage body fat when training was moderate intensity ($\leq 75\%$ of 1-RM). Likewise, doing strength exercise (at least 1 day per week) during cancer treatment has been associated with a 33% lower all-cause mortality risk (Hardee et al., 2014). In a controlled randomized study in which the effects of aerobic and strength training were compared in patients with prostate cancer undergoing radiotherapy, both modalities reduced cancer-related fatigue while greater benefits on quality of life, muscle strength, triglyceride levels and percentage body fat were related to the strength training program (Segal et al., 2009). A metaanalysis of the effects of physical exercise on breast cancer survivors examining 14 controlled randomized studies showed that exercise leads to significant improvements in quality of life, CRF, physical function and cancer-related fatigue (McNeely et al., 2006). Also, in survivors of breast cancer, the combination of strength training and impact exercises was able to preserve bone mass and reduce the rate of bone remodeling, both of which increase the risk of falls (Winters-Stone et al., 2011).

Exercise has proven safe against another of the most common complications of cancer and its treatment, lymphedema (Ahmed et al., 2006; Schmitz et al., 2010a). Thus, physical activity did not worsen symptoms in

women with lymphedema (Ahmed et al., 2006; Schmitz et al., 2009), even when these performed high intensity strength training (Cormie et al., 2013). Two systematic reviews have shown the beneficial effects of physical exercise on quality of life in patients with cancer both during (Mishra et al., 2012b) and after treatment (Mishra et al., 2012a).

4. *Biological effects of physical exercise on cancer*

The triad physical inactivity-poor CRF-obesity has been linked to a significantly higher risk of several cancers (Sanchis-Gomar et al., 2014; Wang et al., 2012). As another modifiable phenotype, regular physical activity produces the opposite effect through several biological mechanisms such as the release of myokines with anticancer effects from working muscles (Fiuza-Luces et al., 2013; Pareja-Galeano et al., 2015) or the reduced expression of adipokines as the consequence of reduced total adipose tissue (Perez et al., 2016; Sanchis-Gomar et al., 2014). Numerous biological mechanisms associated with the risk and progression of cancer in relation to physical activity are mediated by the link between cancer and obesity (Byers & Sedjo, 2015; McTiernan, 2008). However, the pleiotropic effects of physical exercise on cancer are becoming ever more clear (Pareja-Galeano et al., 2015; Pedersen & Saltin, 2006; Sanchis-Gomar et al., 2014).

The link between obesity and the risk of cancer progression may be explained through the direct relationship between excess adiposity and insulin resistance along with a compensatory hyperinsulinemia as a consequence of the former since elevated blood insulin levels promote the faster growth of cells (De Pergola & Silvestris, 2013). Thus, BMI usually shows a positive linear relationship with insulin levels (Calle & Kaaks, 2004). In a metaanalysis examining correlations between insulin levels and cancer risk, it was concluded that the greater incidence of colorectal and pancreatic cancer was recorded among subjects whose blood insulin levels were higher upon diagnosis of their cancers (Pisani, 2008). Physical activity increases the expression of GLUT-4 transporters to increase the amount of glucose available to skeletal muscles with a possible increase in insulin sensitivity (Ojuka & Goyaram, 2014). This suggests that physical activity could resolve the compensatory hyperglycemia produced as the consequence of insulin resistance, therefore, preventing the proliferation of cancer cells (Sawada et al., 2014). Similarly, moderate-vigorous intensity exercise led to significant reductions in insulin levels and the HOMA-IR index (an indicator of insulin resistance), but not in insulin-like growth factor-1 (IGF-1) (Friedenreich et al., 2011), unlike the reduced IGF-1 levels observed by others (Yu & Rohan, 2000).

In postmenopausal women, most estrogens are produced through the conversion of androgens into estrogens, mainly occurring in adipose tissue.

Accordingly, adiposity could increase the risk of hormone-dependent cancer via its estrogenic effects (Calle & Kaaks, 2004). In postmenopausal women, BMI has been correlated with cancers of the breast and endometrium and with other hormone-dependent tumors, as an increase in sex hormones due to excess weight is one of the mechanisms implicated in the onset of cancer (De Pergola & Silvestris, 2013). Regarding the relationship between physical exercise and the biological mechanisms involved in reducing the risk of breast cancer in postmenopausal women, 12 months of exercise was found to significantly reduce levels of estradiol, estrone and free estradiol and increase concentrations of sex hormone-binding globulin (SHBG); these results being consistent with a lower breast cancer risk (Friedenreich et al., 2010; McTiernan et al., 2004). Thus, the link between physical activity and reduced postmenopausal breast cancer risk may be partly explained by effects on blood estrogen levels (McTiernan et al., 2004).

Obesity is associated with modified plasma levels of adipokines, characteristic of chronic systemic inflammation states (Lund et al., 2011) among which we find adiponectin and leptin. Unlike other adipokines such as leptin, the adipose tissue expression and plasma concentration of adiponectin is reduced in overweight and obese individuals (Palomer et al., 2005), and shows inverse correlation with BMI. In terms of developing tumors, adiponectin has antiangiogenic and antiinflammatory properties, besides promoting insulin sensitivity (Renehan et al., 2008). In a prospective study assessing the link between adiponectin and colorectal cancer risk, it was observed that men with lower plasma adiponectin levels had a higher risk of cancer than those with higher levels (Wei et al., 2005). Leptin is a key regulator of appetite, satiety and body weight, which makes it also an important factor in energy homeostasis, metabolism and adiposity (Gautron & Elmquist, 2011). With respect to its role in cancer, it has been observed that high leptin levels could promote the development and progression of cancer as it is known to have mitogenic, proinflammatory, antiapoptotic and proangiogenic properties (Vona-Davis & Rose, 2007). Further, leptin intensifies the expression of aromatase and, consequently, the production of estrogens (De Pergola & Silvestris, 2013), thus increasing the risk of hormone-dependent cancer. A controlled randomized trial conducted in overweight and obese postmenopausal women compared the individual and combined effects of a weight loss diet program (with and without exercise) and physical exercise on serum adiponectin and leptin levels. Independently of the intervention, weight loss showed a dose-dependent relationship on these levels, greater adiponectin increases and leptin reductions being produced among women in the groups diet + exercise and diet alone (Abbenhardt et al., 2013).

Another of the mechanisms whereby physical exercise exerts positive influence on the physiopathology of cancer is via its effects on immune function. Hence a state of hyperinflammation such as that associated with obesity is also linked to suppressed immune function (Louie et al., 2013). The detrimental effects of obesity on immune function have been linked to the systemic proinflammatory profile generated by adipocyte-derived secretory factors, among which are included inflammatory peptides such as tumor necrosis factor alpha (TNF- α), CRP and interleukin-6 (IL-6), (Huang et al., 2013). Studies have shown an inverse relationship between regular physical activity and these inflammatory biomarkers (Kasapis & Thompson, 2005; Petersen & Pedersen, 2005). Physical activity improves immune function also through an increase in leukocyte function, as this could block tumor formation by controlling the activation and proliferation of natural killer cells (NK) (Lanier, 2008; Smyth et al., 2005). Physical activity could also improve the function of antigen-specific T cells, which could translate to improved protection against infectious agents and enhanced immunosurveillance (Walsh et al., 2011).

Chronic inflammation has been similarly implicated in the pathogenesis of certain chronic diseases such as cancer (Walsh et al., 2011). However, in response to muscle contraction during physical exercise, muscle fibers release myokines such as IL-6 (which also has pro-inflammatory effects), IL-8, IL-15, brain-derived neurotrophic factor (BDNF), leukemia inhibiting factor (LIF), visfatin or fibroblast growth factor 21 (FGF21). These exert antiinflammatory effects which could render physical exercise a protective role against chronic diseases (Fiuza-Luces et al., 2013; Pareja-Galeano et al., 2015; Pedersen, 2011). Therefore, and given that many mechanisms whereby physical exercise acts upon cancer seem to be mediated through its effects on obesity, physical exercise has become an essential strategy in the fight against cancer based on its known effects on the control and maintenance of a healthy body weight (Azvolinsky, 2014; Bhaskaran et al., 2014; Campbell, 2014; Kmietowicz, 2014). In the same way, several studies have identified the existence of "anti-cancer" myokines (Hojman et al., 2011; Pareja-Galeano et al., 2015; Sanchis-Gomar et al., 2015b), which are released in response to a single session of physical exercise (Mortensen et al., 2008; Norheim et al., 2011). Such myokines are secreted protein acidic and rich in cysteine (SPARC), and calprotectin. The former is a cell matrix protein that regulates cell migration and proliferation (Brekken & Sage, 2001) whose expression has been observed to increase with regular physical activity (Norheim et al., 2011). Studies have shown that SPARC could modulate inflammatory and metabolic states in experimental conditions (Nie & Sage, 2009; Song et al., 2010). SPARC, which is a potential immunotherapy target for several cancer types (Inoue et al., 2010), could mediate the preventive effects of exercise on colon cancer by avoiding the formation of

aberrant crypt foci through the stimulation of apoptosis via caspases-3 and -8 (Aoi et al., 2013). Calprotectin induces cell apoptosis in several tumor lines (Yui et al., 1995). Physical exercise, mainly in the form of aerobic exercise, apart from promoting the secretion of antitumorigenic myokines such as SPARC (also known as basement membrane protein [BM]-40), calprotectin, or leukemia inhibitory factor (Broholm & Pedersen, 2010), could reduce cancer incidence and help improve its prognosis through several mechanisms. Those proposed so far have been greater NK cell activity, improved antigen presentation, diminished inflammation, and reducing the build-up of functional senescent cells (Bigley et al., 2013).

In addition, oxidative damage produced by oxygen reactive species that accumulate during the cell cycle and affect DNA, proteins and lipids plays a key role in the development of diseases such as cancer (Valko et al., 2006). In this case, modulation of oxidative stress could affect cancer progression. Thus, it has been shown that regular physical exercise improves the antioxidant system, protecting the organism against cell damage (Gomez-Cabrera et al., 2008). This increase in antioxidants could be beneficial both in preventing and treating cancer (Rebillard et al., 2013).

Finally, physical exercise improves health indicators such as muscle strength and CRF (Blair et al., 1995; Jurca et al., 2005; Lee et al., 2011), which in turn will lead to improved physical function and reduced cancer-related fatigue (Kalter et al., 2016).

CONCLUSIONS

Obesity and sedentary lifestyles have been linked to an elevated cancer risk whereas regular physical exercise and high CRF have the opposite effects, with several biologic mechanisms mediating such associations. Regular physical activity raises the metabolic rate and improves CRF via enhanced cardiovascular function, muscle mitochondrial biogenesis and oxidative enzyme activity (particularly of the enzymes responsible for fat oxidation), and also reduces body adiposity (Holloszy & Coyle, 1984).

Despite the genetic component underlying any cancer type, evidence has shown that lifestyle modifications may be a useful non-pharmacological tool to reduce the incidence and morbidity-mortality of cancer. Thus, being physically active reduces the risk of cancer and improves its prognosis once a diagnosis has been made, as it reduces and helps maintain body weight at a healthy level. Physical exercise also helps improve CRF, while its postcancer diagnosis effects include the reduced risk of relapse via these same effects. Physical activity is a pleiotropic adjuvant tool that minimizes the so-called toxic triad of cancer risk factors.

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