Physical activity and cancer prevention

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PHYSICAL ACTIVITY AND CANCER PREVENTION

ACTIVITE PHYSIQUE ET PREVENTION DES CANCERS

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Abstract

Physical activity (PA) has a demonstrated role in three types of tumor cancer: breast, colon, endometrium, and a likely role in four to five other cancers with risk reduction of 25% in the most active subjects vs the least physically active. After cancer's diagnosis, there is a positive association between PA and reduction in the risk of recurrence and overall and specific mortality in patients with non-metastatic breast, colon and prostate cancer. In cancer survivors, post-diagnosis PA may also have beneficial effects on fatigue, quality of life, body image and self-esteem, emotional well-being, sexuality, sleep disturbance, social functioning, anxiety, and pain at varying follow-up periods. There is a growing body of research evidence that links sedentary behavior (time spent sitting) with cancer risk. These scientific data highlight the major role of PA and limitation of sitting time both in cancer prevention but also in the management of patients during and after cancer.
Keywords: sedentary behavior, cancer survivors, mechanisms, fatigue, physical activity

Résumé

L'activité physique a un rôle démontré dans la prévention de trois types de cancer : sein, colon et endomètre avec un risque diminué de 25% entre les sujets les plus actifs et les moins actifs. Après un diagnostic de cancer, il existe une association positive entre le niveau d'AP et la réduction du risque de récidive du cancer ainsi que la diminution de la mortalité globale et spécifique pour les cancers non métastatiques du sein, colon et de la prostate. Chez les sujets traités pour un cancer, l'AP démarrée lors du diagnostic (ou après) a aussi des effets bénéfiques sur la fatigue, la qualité de vie, l'image corporelle, l'estime de soi, le bien-être émotionnel, la sexualité, les troubles du sommeil, le fonctionnement social, l'anxiété et la douleur et ceci sur de longues périodes de suivi.
Il existe aussi de nombreuses données scientifiques qui établissent un lien entre les comportements sédentaires (temps passé assis) et le risque de cancer.
L'ensemble de ces données scientifiques souligne le rôle majeur de l'AP et de la limitation des comportements sédentaires à la fois pour la prévention des cancers mais aussi pour leur prise en charge pendant et après traitement.
Mots-clés : comportement sédentaire, après cancer, mécanismes, fatigue, activité physique

Cancers represent the first cause of death in France for men and the second cause for women. Preventing the occurrence of cancer therefore represents a major public health issue.

Thanks to technological and therapeutic advances, the five-year relative survival after cancer is currently 50%, all cancers combined, but survival varies according to the location of the cancer and reaches 90.5% for prostate cancer, 89.6% for breast cancer and 59.8% for colon cancer, in France (1). However, people who have suffered from cancer have a degraded state of health compared to the rest of the population, and this even after completion of the treatment, due to the adverse effects of the treatments received and the course of the disease, decreasing physical capacities, quality of life and hindering return to normal life (2).

Given the substantial health benefits of being physically active, physical inactivity can be considered as a real loss of opportunity for both healthy and diseased individuals (3).

In our developed countries, physical activity (PA) levels is insufficient compared to international WHO recommendations (150 minutes minimum of leisure activity): using objective measures of PA (accelerometers) between 30 and 70% of healthy adults (4-6) and less than 10 to 20% of children and adolescents (one in five school-going adolescents aged 11–17 years) achieve WHO recommendations (7). Moreover, patients with a chronic disease undertook less physical activity than healthy individuals (8) as reported in the large prospective cohort study from the UK Biobank. This is particularly relevant for subjects with malignant cancer who have lower levels of moderate PA between 1 and 2 hours per week than healthy subjects (accelerometer-measured PA) (8).

The objective of this review is to determine the relationships between PA and cancers on the following points:

- prevention of the occurrence of cancers
- reducing the risk of recurrence and/or death from cancer
- improving the quality of life after cancer.

I. PHYSICAL ACTIVITY AND PREVENTION OF CANCER

The relationship between PA and the occurrence of cancers, all locations combined, has been the subject of numerous collective expert appraisals and has led to the publication of recent scientific reviews (3,9). Levels of evidence for the effectiveness of PA vary depending on the location of the cancer.

1.1 Physical activity and risk of colorectal cancer

Colon cancer and colorectal cancer remains one of the mainly diagnosed cancer in both women and men.

Strong evidence demonstrates that greater amounts of physical activity are associated with a lower risk of colon cancer

PA is convincingly associated with a reduced risk of colon cancer (10,11). The meta-analysis by Wolin et al. (12), covering 52 studies, showed that the onset of colon cancer was reduced on average by 25% in the most active subjects compared to the least active (case-control studies and cohorts), in both women and men.

Although, there are embryologic, morphological, physiological, biochemical, molecular, genetic and epidemiological differences between the proximal and distal colon, the effect of PA is not differentially associated with the risks of proximal and distal colon cancers. The systematic review and meta-analysis of Boyle et al. indicated that the relative risk decreased by 27% for the proximal colon (RR = 0.73) and by 26% for the distal colon (RR = 0.74) in the most physically active individuals compared with the least active (11) (21 studies). These effects have been observed in case-control studies and in cohort studies.

Dose-response relationship between greater amounts of physical activity and lower colon cancer risk

This reduction in the risk of colon cancer is found in a fairly similar manner regardless of the domain of PA practiced (occupational, leisure, domestic PA and transport-related PA); in other terms, PA in any domain is associated with a reduced risk of colon cancer (10,11). For any increase of 30 min/day in leisure PA, the reduction in the risk of colon cancer has been estimated at 12% (10). There is evidence of a dose-response effect (12): the higher the level of PA, the lower the risk of colon cancer. On the other hand, the protective effect of PA for colon cancer was not found for rectal cancer (10). In most of the studies, no beneficial effect of PA on the occurrence of rectal cancer was found, regardless of the type of PA practiced (13).
Regarding the optimal period of PA practice to maximize its protective effect, regular lifelong PA practice is recommended. Concerning the dose, 30 to 60 minutes per day of moderate to intense PA seem sufficient to reduce the risk of colon cancer, whether this PA is carried out in the occupational field, during active transport, in domestic life or during leisure time (12).

Subgroups analysis
The protective effect of PA is independent of BMI: thus the risk reduction is also observed in overweight populations and in obese subjects. There is also no difference between the sexes (11, 12). Furthermore, the effect of PA appears to be independent of diet (14). On the other hand, being more physically active have been associated with higher odds of having healthy diets, also influencing the association between PA and cancer (14, 15).

1.2 Physical activity and risk of breast cancer

Worldwide, breast cancer is the most frequently diagnosed cancer among women, accounting for one in four of all new female cancer cases (16).

Strong evidence demonstrates that greater amounts of physical activity are associated with a lower risk of breast cancer
In 2008, the french collective INSERM expertise and y the World Cancer Research Fund-American Association for Cancer Research specified that scientific evidence on the beneficial effect of PA on the prevention of breast cancer is of the “probable” type in postmenopausal women and "Limited" in premenopausal women. More recently, in 2018, this evidence has been evaluated and summarized for the Physical Activity Guideline for Americans (PAGA) (15) as well as by the World Cancer Research Fund/American Institute for Cancer Research and they concluded that there is strong evidence that PA reduces the risk of colon cancer with an approximate range of relative risk reduction for high versus low levels of PA of 19-27% (15, 17, 18).

Dose-response relationship between greater amounts of physical activity and lower breast cancer risk
Strong evidence demonstrates that a dose-response relationship exists between greater amounts of PA and lower breast cancer risk (3, 19, 20). The risk of breast cancer was reduced by 2% for each 25 MET.h per week increase in non-work related PA (RR = 0.98; 95% CI: 0.97-0.99), which corresponds approximately to 10h per week of light household activities such as washing dishes or cooking. Using data on recreational activities from seven studies, Wu et al. (20) estimated that the risk of breast cancer was 3% lower (RR=0.97; 95% CI: 0.95-0.98) for every 10 MET.h per week increment in recreational activity, which corresponds approximately to 4h per week of walking at 3.5 km/h or 1h of jogging at 10.5-11km/h. The risk was also reduced by 5% for each increase of 2h/week of leisure PA of moderate to high intensity (RR = 0.95; 95% CI: 0.93-0.97), roughly equivalent to 4h per week of walking at 3.5 km/h (20).

According to the American Physical Activity Guideline (3), in women, each two-hour increase in weekly PA reduces the risk of developing breast cancer by 10%, whatever the intensity of PA, the total volume of PA (and not its intensity) being an essential criterion to consider in prevention.

Subgroups analysis

- Weight status

In the review by Lynch et al., an inverse association was reported between PA and the risk of breast cancer, regardless of BMI, except in the case of obesity. Thus, the average risk is reduced by 27% for a BMI <22 kg/m², by 24% for a BMI between 22 and 25 kg/m², by 18% for a BMI between 25 and 30 kg/m², and by1% for a BMI> 30 kg/m² (19). For Wu et al., the inverse association between PA and breast cancer risk was observed across different BMI values (<25 kg/m² or >25 kg/m²), but with stronger association of PA with breast cancer risk for subjects with BMI <25 kg/m² (RR = 0.72, 95 % CI = 0.65–0.81, I2 = 0.00 %) (20).

- Menopausal status

In the review by Lynch et al. the inverse association between PA and breast cancer risk was observed across different population subgroups by menopausal status (premenopausal or postmenopausal) but stronger association of PA with breast cancer risk was found for premenopausal women (RR = 0.77, 95 % CI = 0.72–0.84, I_2 = 14.5 %) (19). On the other meta-analysis and pooled analyses which examined the effects of PA on breast cancer risk by menopausal status, there appears to be a somewhat greater breast cancer risk reduction associated with higher amounts of physical activity among postmenopausal women than premenopausal women (3).

- Tumor receptor status

Overall, PA appears to have a protective effect independently of the tumor receptor status (ER-/PR- or ER+/PR+) (3,20).

Some evidence suggests a protective role of physical activity against breast cancer in BRCA1 mutation carriers, especially physical activity in adolescence or early adulthood (21).

-Other factors

This protective effect of PA has been observed regardless of ethnicity (15).

What physical activity to prevent breast cancer?

Risk reduction has been reported in the most active women compared to the least active, regardless of the type of activity: sports and leisure PA (-13%), household and domestic PA (-13 to -21%), PA related to active transport such as walking and cycling (-18%) and occupational PA (-10 to -13%) (19,20).

Studies have shown that at least 3 to 4 hours per week of moderate to vigorous PA would be necessary to reduce the risk of breast cancer, whether this PA is performed in the occupational field, during active travel, in domestic life or during leisure time (19,20).

When to practice?

The meta-analysis by Wu et al. (20) showed that PA had a lifelong preventive effect (before 25 years, 25 to 50 years and after 50 years). However, contrary to previous conclusions (10), this meta-analysis highlighted a more pronounced effect of PA in preventing breast cancer in premenopausal women (RR = 0.77) than in postmenopausal women (RR = 0.88).

1.3 Physical activity and risk of endometrial cancer

Strong evidence demonstrates that greater amounts of physical activity are associated with a lower risk of endometrial cancer

Three meta-analysis (22-24) and one pooled study (25) have highlighted the protective role of PA on the risk of developing endometrial cancer. Overall, comparing the most active women compared with the least active women, the risk of endometrial cancer is reduced by 20% among the most active women (average percentage of the three articles).

Dose-response relationship between greater amounts of physical activity and lower endometrial cancer risk (3)
In all the previous meta-analyses, the risk reduction was obtained comparing high versus low level of PA but the corresponding level of PA is not specified. The meta-analysis by Keum et al. (24) was carried out for this purpose: the analysis of 20 observational studies (10 case-control studies and 10 cohort studies) shows that the risk of endometrial cancer decreases by 2% for each increase in 3 MET/h per week of leisure PA (95% CI: 0.95–1.00, p = 0.02) and that each increase of 1h per week of leisure PA is associated with a 5% reduction in the risk of developing endometrial cancer (95% CI: 0.93–0.98, p <0.001) with a linear dose-response effect for quantities of leisure PA ranging from 0 to 50 MET/h per week and durations ranging from 0 to 15 h per week. Thus, for a woman with PA according to international recommendations (150 min per week), the risk of developing endometrial cancer would be reduced by 8%, compared to women with very low PA level. Here, the effects of PA are independent of body composition, and persist after adjustment for BMI. Interestingly, Schmid et al. (22) presented the results for all types of PA combined as well as by type of activity. They found a statistically significant reduction for endometrial cancer incidence when comparing the highest versus the lowest amounts of all types of physical activity combined (OR=0.80; 95% CI: 0.75-0.85). When examining the associations by type of activity, they reported risk reductions for recreational (OR=0.84; 95% CI: 0.78-0.91), occupational (OR=0.81; 95% CI: 0.75-0.87), activities as well as for walking (OR=0.82; 95% CI: 0.69-0.97). Schmid et al. also presented their results by the intensity of PA and reported that endometrial cancer risk was decreased with all intensity levels of PA (light, moderate-to-vigorous, and vigorous) and these risk reductions were all statistically significant. The greatest reduction in endometrial cancer incidence was associated with light-intensity PA for which a relative risk of 0.65 was observed (95% CI: 0.49-0.86). Moderate-to-vigorous and vigorous-intensity PA presented similar associations with endometrial cancer risk of RR=0.83 (95% CI: 0.71-0.96) and 0.80 (95% CI: 0.72-0.90), respectively (22).

Effects of weight
Some studies but not all suggest that the effects of PA is mediated via its effects on fat mass. This explains why most of the studies showed either a greater risk reduction (22) or only an effect in women with a BMI ≥25 kg/m² (25).

1.4 Physical activity and primary prevention of other cancer sites

According to the latest review of the PA recommendations 2018 Physical Activity Guidelines Advisory Committee Scientific Report of writing committee (3), PA has a demonstrated role in seven types of tumor cancer: breast, colon, endometrium, kidney, bladder, esophagus (adenocarcinoma), stomach (cardia), and a likely role in lung cancer (especially in smokers and former smokers). However, the level of evidence and the importance of PA protection depends on the type of cancer.

More recently, a study with pooled data from 1.44 million adults (12 prospective US and European cohorts with self-reported physical activity), found that high leisure-time PA (at the 90th percentile) was associated with reduced risk of 13 of 26 types of cancer examined, with risk reduction of 20% or above for seven of the cancers (esophageal adenocarcinoma, cancers of the liver, lung, kidney, gastric cardia, endometrium and myeloid leukemia), regardless of body size or smoking history (25). As concluded by the authors “These findings support promoting physical activity as a key component of population wide cancer prevention and control efforts”.

II- Physical activity and mortality in patients with cancer (during and after treatment)

For all these analysis, cancer survivors are defined as subjects who have been diagnosed with invasive cancer, at stages I to III, excluding those initially diagnosed with metastatic (stage IV) cancer. In most interventions studies metastatic patients have been excluded and studies are limited in metastatic cancer. For this reason, subjects with metastatic cancer have been excluded from this review.

2.1 Breast cancer

Positive role of physical activity on breast cancer survival

Post-diagnosis physical activity

Two meta-analyzes examined the effects of PA on survival and prognosis of breast cancer. In the first one, seven prospective cohorts of women with localized and non-progressive breast cancer (followed 4-12 years after the end of treatment) were eligible (26) and 16 in the second one (27). Both studies revealed a favorable effect of PA after breast cancer diagnosis on breast cancer deaths (RR = 0.66 [95% CI 0.57-0.77, P<0.000001] for (26); RR = 0.72 [95% CI 0.60-0.85] for (27)), and all-c mortality (RR = 0.59 [95% CI 0.53-0.65, P<0.00001] for (26); RR = 0.52 [95% CI 0.42-0.64] for (27)).

These results are in agreement with of a more recent meta-analysis, gathering 22 different prospective cohort studies (including many of the prospective cohort studies of the two previous meta-analysis) and more than 120,000 patients with breast cancer (average follow-up periods ranging from 4.3 to 12.7 years) (28). Significant risk reductions for all-cause and breast cancer-related deaths was demonstrated for post-diagnosis PA (HR = 0.59, 95% CI 0.45–0.78, $p < 0.05$) and meeting recommended PA guidelines post-diagnosis (≥ 8 MET-h/wk) (HR = 0.67, 95% CI 0.50–0.90, $p < 0.01$). Post-diagnosis PA was also associated with reduced risk of breast cancer events (breast cancer progression, new primaries and recurrence combined) (HR = 0.79, 95% CI 0.63–0.98, $p < 0.05$).

The benefit of post-diagnostic PA in terms of overall survival at 5 and 10 years is then 4 to 6%. This gain in survival in the case of PA practice after breast cancer care is found regardless of conventional prognostic factors such as age, tumor stage, the presence of hormone receptors, place of residence, alcoholism or smoking, BMI, hormonal status of the patient and the tumor. However, it should be noted that, as stated by Lahart et al. (29) effect estimates for these associations should be treated with caution due to evidence of heterogeneity.

Pre-diagnosis physical activity

This meta-analysis (six studies) reported a 18% reduction in the risk of all-cause deaths but no reduction in risk of breast cancer-related deaths with pre-diagnosis PA (29).

Dose–response relation between physical activity and total and cancer-specific mortality

A meta-analysis of four cohort studies found that, in comparisons of less active to more active individuals, each 5, 10, or 15 MET-hours per week increase in amounts of post-diagnosis physical activity was associated with a 6 percent (95% CI: 3%–8%), 11 percent (95% CI: 6%–15%), and 16 percent (95% CI: 9%–22%) reduction in risk of breast-cancer mortality, respectively (27). Furthermore, each 5, 10, or 15 MET-hours per week increase in amounts of post-diagnosis physical activity was associated with a 13 percent (95% CI: 6–20%), 24 percent (95% CI: 11%–36%), and 34% (95% CI: 16%–38%) decreased risk of all-cause mortality, respectively (27).

2.2 Colorectal cancer

Positive role of physical activity on colorectal cancer survival

Post-diagnosis physical activity

Three meta-analyses (27,30,31) have examined the associations between colorectal cancer (colon cancer and/or colorectal cancer and/or rectal cancer) and PA and found the inverse association between PA and total mortality and colorectal cancer-specific mortality. Recently, Qiu et al. (32) performed a new meta-analysis. Compared to the most recent one (31) which was based on 11 studies, involving 17 295 colorectal cancer survivors, this meta-analysis included seven additional studies with 14 578 additional colorectal cancer survivors and 557 150 individual from the general population.
The current meta-analysis found a similar result for post-diagnosis effect of PA on survival: compared with the lowest levels of PA, the highest levels of post-diagnosis PA showed a 37% and 36%, decreased risks of total mortality and colorectal cancer-specific mortality among colorectal cancer survivors, respectively.

Pre-diagnosis physical activity
In line with previous study, pre-diagnosis PA was also associated with better outcomes: compared with the lowest levels of PA, the highest levels of pre-diagnosis PA showed a 19% and 15% decreased risks of total mortality and colorectal cancer-specific mortality among CRC survivors, respectively. However, post-diagnosis PA was apparently associated with lower cancer mortality than pre-diagnosis activity (no statistical comparison).

Dose–response relation between physical activity and total and cancer-specific mortality
The recent meta-analysis of Qiu et al. (32) are in line with the previous one and show that each 10 MET.h per week increase in pre-diagnosis PA was related to an 11% (95% CI: 3–17%; P < 0.001) and 9% (95% CI: 2–16%; P = 0.002) reduction in risk of total mortality and colorectal cancer-specific mortality among colorectal cancer survivors, respectively. By comparison, each 10 MET.h per week increase in post-diagnosis PA was associated with a 21% (95% CI: 10–31%; P < 0.001) and 24% (95% CI: 8–38%; P = 0.05) lower risk of total mortality and colorectal cancer-specific mortality, respectively.

Subgroups
These inverse associations between PA and improved outcomes is observed in both the Western regions and the Asia-Pacific regions, and both men and women and was independent of smoking, BMI, tumor stage, and receiving treatment (32).
In line with the different relationships between PA and incidence of colorectal cancer by anatomic sites, the inverse association between pre-diagnosis PA and cancer mortality was more pronounced for colon cancer than that for rectal cancer (P = 0.08) (32).

2.3 Prostate Cancer

Positive role of physical activity on prostate cancer survival
Four studies evaluated the relationships between PA and risk of recurrent prostate cancer (no meta-analysis). There is a reduction in total mortality of 40% and specific mortality of 40% with PA (this last effect is found only for leisure PA: PA >13 vs <4MET.h per week) (3, 33).
A prospective study was conducted in Alberta, Canada, in a cohort of 830 stage II-IV incident prostate cancer cases diagnosed between 1997 and 2000 with follow-up to 2014 (up to 17 yr). Pre-diagnosis lifetime activity was self-reported at diagnosis. Post-diagnosis activity was self-reported up to three times during follow-up. Post-diagnosis total activity (>119 vs ≤42 metabolic equivalent [MET]-hours/week per year) was associated with a significantly lower all-cause mortality risk (hazard ratio [HR]: 0.58; 95% confidence interval [CI], 0.42-0.79; p value for trend <0.01). Post-diagnosis recreational activity (>26 vs ≤4 MET-hours/week per year) was associated with a significantly lower prostate cancer-specific mortality risk (HR: 0.56; 95% CI, 0.35-0.90; p value for trend = 0.01). Sustained recreational activity before and after diagnosis (>18-20 vs <7-8 MET-hours/week per year)

was associated with a lower risk of all-cause mortality (HR: 0.66; 95% CI, 0.49-0.88). Limitations included generalizability to healthier cases and an observational study design.

Conclusion

There is a positive association between PA after diagnosis, and reduction in the risk of recurrence and overall and specific mortality in patients with non-metastatic, breast (level of evidence B) and colon (level of evidence B). A similar benefit is seen in several prospective studies for prostate cancer (level of evidence C)[1]. No study has shown an unfavorable impact.

For colorectal and breast cancer, compared with the lowest levels of PA, both the highest levels of pre-diagnosis and post-diagnostic PA appear to have decreased risks of total mortality and cancer-specific mortality among survivors, with a significant relationship observed between PA (pre-diagnosis or post-diagnosis) and improved outcomes.

All these results underscore the need for more PA.

III. Other positive effects of physical activity in subjects with cancer

A cancer survivor is defined as anyone who has been diagnosed with cancer, from the time of diagnosis through the rest of their life. Given advances in early detection and treatment, the number of cancer survivors is growing steadily, so that approximately the five-year relative survival after cancer is currently 50%, all cancers combined, in France.

Analysis of randomized trials, reviews and meta-analyses demonstrated with a high level of evidence the beneficial role of PA during and after treatments on fatigue and quality of life (in the physical function, social function, and mental health domain), whether fatigue is diagnosed during or after treatments (2). Results reported in a Cochrane review indicate that physical activity may also have beneficial effects on body image and self-esteem, emotional well-being, sexuality, sleep disturbance, social functioning, anxiety, and pain at varying follow-up periods (29).

Peri- and postoperative complications

Preoperatively, PA would be associated with a reduction in perioperative complications, especially for lung cancer. For breast cancer, most studies highlight the benefit of specific rehabilitation programs postoperatively, during the radiotherapy treatment phase, on shoulder recovery and associated pain.

Lymphoedema and breast cancer

The risk of lymphedema after axillary lymph node dissection for breast cancer is a major concern. For a very long time, advice to prevent and manage lymphoedema was to prohibit carrying weights on the operated side and performing weight-lifting movements. Currently, the recommendations of the National Lymphoedema Network include a progressive PA (slowly progressive weight lifting) avoiding constriction of the limb (discomfort with venous or lymphatic return). The report published by the French INCA (34) concludes that "the practice of controlled movements of the upper limb homolateral to axillary dissection (aerobic exercises and muscle strengthening while avoiding the risky behaviors described by the National Lymphedema Network, for example) does not seem to show worsening of pre-existing lymphedema (35). If the PA has not yet demonstrated any real benefit in preventing the risk of developing lymphedema, the prohibition of patients from practicing

[1] This corresponds to classifications used by Scientific Societies and by the French High Authority for Health (HAS) with: A: Established scientific evidence, B: Scientific presumption, C: Low level of scientific evidence.

physical exercise with use of the upper limb on the side of the operated cancer after axillary dissection does not seems more appropriate".

Side effects of treatments

- Impact on possible adverse effects of hormone therapy

Hormonal therapies are essential in the two most common hormone-dependent cancers (prostate and breast cancers). For prostate cancer, the removal of endogenous testosterone reduces muscle mass, alters body composition, and accelerates age-related bone loss. The majority of randomized intervention studies show maintenance of muscle mass by PA including muscle strengthening exercises, and an increase in muscle mass in cases where the muscular activity was sufficient (36). For breast cancer in postmenopausal women, regular PA practice improves arthralgia associated with anti-aromatase treatment (37). In pre-menopausal women receiving tamoxifen, PA helps to reduce fat mass gain and improve muscle mass.

- Physical deconditioning

All the meta-analyzes of randomized controlled trials confirm that PA after completion of cancer treatment is associated with clear benefits in all physical functions and perception of physical condition (2). This improvements include both cardiorespiratory fitness (increased peak oxygen consumption, peak power output, distance walked in six minutes) and muscular fitness (bench and leg press weight, right handgrip strength) (2). The improvement in cardiorespiratory capacities has been shown whether the PA program is initiated at the start of chemotherapy, at the end of treatments, or at a distance from these, with moderate and high intensity programs. PA programs tailored to individual physical capabilities allow for an 8-12% improvement in maximum oxygen consumption in 6-8 weeks.

- *Positive impact on body composition*: in patients who have completed treatment for cancer, physical activity is associated with significantly reduced fat mass, body weight, BMI, and increase in muscle mass. These programs provide muscle gain when they include strength-training. PA programs that combine endurance and strength-training seem to be particularly effective in correcting body composition, especially when they start during treatments and are continued afterwards. In addition, incorporating muscle strengthening exercises into PA programs can improve strength production and muscle endurance capabilities.

- *Cardiotoxicity*: Doxorubicin is an anthracycline antibiotic, used in the treatment of a broad spectrum of human cancers. Unfortunately, the clinical use of this highly efficacious anticancer drug is limited due to its toxicity. In its recent paper, Smuder (38) reviewed the abundance of reports indicating that exercise can protect against Doxorubicin toxicity, and reported that exercise training produces beneficial adaptations to multiple organ systems (heart, skeletal muscle, kidney, liver), suggesting potential mechanisms mediating the positive effects of exercise on each organ system (endogenous antioxidants, induction of heat shock protein (HSP) expression, multi-drug resistance proteins). It remains to determine a safe and effective exercise protocol for patients receiving Doxorubicin chemotherapy.

In the same way, as a result of the side effect of treatment they received (Trastuzumab [Herceptin®]), HER2+ breast cancer patients are particularly exposed to cardiac event during or after therapy. Trials that have been conducted are very heterogeneous but recent studies demonstrate benefits of practice of aerobic exercise on heart, provided that the program is adapted to each patient from the initiation but also and especially during treatment depending on their tolerability (for a revue see (39)).

IV. Mechanisms underpinning the effects of regular physical activity and decreasing sedentary behaviors

The mechanisms underpinning the effects of regular PA to prevent the occurrence and recurrence of cancers are multiple (for a review see (18,40)). The current working hypothesis, using in vivo preclinical studies, is that PA acts via alterations in the systemic (host) milieu as reflected in a reduction in the circulating bioavailability of numerous growth factors, hormones, and immune cell subsets (40) but also by acting locally in the tumor micro-environment (41). In humans, a recent review summarized the biological mechanisms linking physical inactivity, sedentary behavior and obesity with cancer risk (18). According to Friedenreich et al., "evidence suggests that promoting PA and reducing sedentary behaviors can lead to cancer-preventing health benefits through maintenance of healthy body weight, thereby reducing the risk of metabolic abnormalities, chronic low grade inflammation, and overstimulation of endogenous sex hormones. Furthermore, the accumulation of ectopic fat tissue is of particular concern since it can interfere with normal cellular and organ function."(18).

Considering the role of BMI on the physiopathology of cancers (being overweight or obese increases the risk of incidence of at least 13 types of cancer), PA is significantly associated with better weight/adiposity (subcutaneous and visceral fat mass) management. Reduced fat mass is associated with decreased production of leptin whose angiogenic effects make it a pro-tumor factor, and increased production of adiponectin, recognized as an anti-tumor factor. As reported by Friedenreich et al. (42) "adipose tissue is an immunologically and metabolically active endocrine organ that is a source of inflammatory cytokines, adipokines, oxidative stress, and notably, the primary source of sex hormones after menopause, which are proposed biomarkers for breast cancer risk". Regular PA also improves insulin sensitivity and inhibits IGF-BP production by the liver, therefore reducing the biologically active part of insulin-like growth factor-1 (IGF-1), (IGF-I, like insulin, is a potent mitogen and has anti-apoptotic and pro-angiogenic actions).

Other biological mechanisms have been proposed: PA may improve antioxidant capacity and protect against "oxidative DNA damage" (43), stimulate immunity (increase in natural killer cell cytotoxicity), decrease micro-inflammation (CRP) by the muscular production of anti-inflammatory cytokines.

For breast cancer, the role of regular PA could be explained by the decrease in endogenous estrogen production and by the increase in SHBG (sex hormone-binding globulin), whose hepatic production is inhibited by insulin and IGF-1 and boosted by estradiol and testosterone. SHBG binds these hormones and decreases their free - biologically active- fraction. However, it should be noticed that the effects of PA on SHBG also depend on food intake and are sometimes confused with the effects of exercise (44).

For colon cancer, in addition to the systemic effects of PA, a local effect has been proposed: PA is associated with increased gut motility, inducing a reduction in gastrointestinal transit time and therefore a decrease in the opportunity for carcinogenic factors to be in contact with the colon mucosa.

Emerging evidence also suggest a role of other additional biologic mechanisms: epigenetic alterations to chromosomes, DNA methylation, altered intestinal microbiome (for a review see (18)).

It is obvious that the beneficial effects of PA are dependent on multiple mechanisms entangled with each other. Research is still needed to better understand the cellular mechanisms that account for the effects of AP on the prevention and clinical course of each type of cancer.

Emerging evidence linking sedentary behaviors to cancer risks

There is a growing body of research evidence that links sedentary behavior with cancer risk (45). Sedentary behavior, often assessed as a self-reported estimate of overall daily sitting or television viewing time in epidemiologic studies, has been associated with an increased risk of ovarian, colorectal and endometrial cancers but not with an increased risk of breast cancer. Several prospective cohort studies have demonstrated a statistically significant association of sedentary behavior with overall cancer mortality (46,47) and the existing epidemiological relationships between the incidence of site-specific cancers and the time spent in sedentary behaviors. The largest analysis covered 43 observational studies including a total of 68,936 cases of cancer. Comparing the highest vs lowest levels of sedentary time, the relative risks for colon cancer were 1.54 (95% CI = 1.19 to 1.98) for TV viewing time, 1.24 (95% CI = 1.09 to 1.41) for occupational sitting time, and 1.24 (95% CI

= 1.03 to 1.50) for total sitting time. For endometrial cancer, the relative risks were 1.66 (95% CI = 1.21 to 2.28) for TV viewing time and 1.32 (95% CI = 1.08 to 1.61) for total sitting time (47). A positive association with overall sedentary behavior was also noted for lung cancer (RR = 1.21; 95% CI = 1.03 to 1.43). Sedentary behavior was unrelated to cancers of the breast, rectum, ovaries, prostate, stomach, esophagus, testes, renal cell, and non-Hodgkin lymphoma. Any two hours increase in sedentary time per day is associated with a significant statistical increase of 8% in the risk of colon cancer and 10% in the risk of endometrial cancer. These associations persisted after adjustment for BMI and PA, which means that the recommendations for the prevention of the risk of cancer must relate both to PA but also to the reduction of sedentary time.
Two recently published reviews corroborated these findings (48, 49) showing that high vs low levels of sedentary time were consistently associated with a range in relative risks of 1.28-1.44 for colon cancer, 1.28-1.36 for endometrial cancer, and 1.21-1.27 for lung cancer, with limited evidence for dose-response effect (18).

VI- Physical activity recommendations and limitation of time spent sedentarily for prevention of cancer

For both cancer prevention and prevention of cancer recurrence, the recommendations are the same as for the general population.

PA characteristics in cancer patients
Both in primary prevention but also during and after cancer, adults who are able, should do at least 150 minutes (2 hours and 30 minutes) to 300 minutes (5 hours) a week of moderate-intensity (minimal values), or 75 minutes (1 hour and 15 minutes) to 150 minutes (2 hours and 30 minutes) a week of vigorous-intensity aerobic physical activity (minimal values), or an equivalent combination of moderate- and vigorous-intensity aerobic activity. Preferably, aerobic activity should be spread throughout the week. Muscle-strengthening activities of moderate or greater intensity that involve all major muscle groups on 2 or more days a week, should be added as these activities provide additional health benefits.
In addition, it is important to limit the total time spent sitting, and to break the sedentary times every hour or every 90 minutes (improving patterns of sedentary time could be targeted by increasing the frequency and duration of (light) activity breaks specifically during long bouts of sedentary time).
In all cases, the PA must be adapted to the usual level of PA, to the preferences/motivations of the patient as well as to its obstacles to practice, to its physical capacities, personalized and progressive.
Two major elements should be acknowledged:
- any physical activity is better than none,
- According to WHO “Physical activity can and should be integrated into the settings in which people live, work and play” (50). Physical activity should be integrated into multiple daily settings.

Finally, a regular practice of PA throughout life is currently recommended, studies have not been able to define an optimal period of PA practice maximizing its protective effect.

Future directions
In most of the studies included in the meta-analyses and systematic reviews, PA was measured through self-report, with different types of validated physical activity questionnaires. Collecting data with device-based measures of activity will be important, as will determine precise measures of dose of activity. Recent research into PA has expanded to include the role of light PA in health. It remains to determine its relationship with primary prevention of cancer, particularly for older adults (age >65 years), who are at the highest risk of cancer and for cancer survivors, people whole PA is mainly of

light intensity. Finally, acknowledging the quantity of time spent sedentary and the patterns of sedentary times (sedentary accumulation patterns) future studies will have to determine the effects of shifting time spent sitting to PA (i.e. 1h per day) to moderate or light PA to cancer prevention or recurrence. The exercise “dose” associated with reductions in either the primary incidence of, or relapse of and by type of cancer has to be determined. Another key limitation in this area is the difficulty to maintain PA on the long term (how to promote PA throughout life?).

In conclusion, these data highlight the important role of PA and limitation of sitting time in primary and tertiary cancer prevention. The role of PA and limitation of sitting time now appears to be of great importance in the management of patients during and after cancer. It remains to define the best management modulations to promote the maintenance of PA throughout life, and if certain periods of life are optimal to optimize the protective effect of PA.

Highlights

- Physical activity decreases breast, colon and endometrial cancer risks by 25%, independently of nutrition
- Post-diagnosis physical activity decreases total and specific cancer (breast, colon, prostate) mortality by 40%
- In cancer survivors physical activity increases quality of life and decreases fatigue and toxicity of treatments
- Emerging evidence link sedentary behaviors to cancer risks

Declaration of interest

Mr. Duclos declares occasional interventions for MSD, Mylan, Biogaran, Sanofi and Asdia and having been taken care of during congresses by MSD.

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