INTRODUCTION

The human circadian timing system temporally organizes myriad physiological parameters across 24 hours (‘circa diem’ from Latin meaning ‘about a day’) from the highs and lows observed in gene expression in cells to the highs and lows in physical and cognitive performance, and much more in between [1,2]. With particular relevance to cancer treatment wherein anticancer drugs can have aggressive, cell damaging, side effects, there are circadian highs and lows in cellular growth, DNA repair, and metabolism [2-5]. Indeed, differentially timed administration of anticancer drugs can elicit differential trade-offs between efficacy and side effects [6,7]. Consideration of circadian timing in anticancer drug administration is commonly referred to as cancer chronotherapy. Of course, cancer, its treatments, and hospitalization may also disrupt the circadian timing system and sleep of the patient [6,8-10]. If treatment efficacy and tolerability depends on the patient’s circadian/internal time, disruptions to circadian timing or misalignment of circadian rhythms should be avoided. The goal must be to optimize circadian alignment in the patient to potentiate timed treatment and attenuate side effects. To this end, timed exercise may represent a valid and valuable, adjunctive, therapeutic strategy. Exercise is already encouraged as part of the treatment process and specified timing may, inter alia, exert chronobiological or diurnal effects that could aid cancer chronotherapy [11-15]. Herein, we briefly overview cancer chronotherapy and exercise medicine in oncology, highlight potential benefit of timed exercise in cancer treatment, and discuss research opportunities to assess these potential benefits.

CANCER CHRONOTHERAPY

Cancer chronotherapy involves specifically timed administration of anticancer drugs according to the individual’s circadian/in-
ternal time to improve treatment tolerance and efficacy [6,16,17].
That is to say, there will be an optimum time of day when trade-off
between efficacy and side-effects are best based on whether partic-
ular circadian rhythms (for instance, cell growth, DNA repair, and
metabolism [2-5]) are closer to their peaks or troughs in different
tissues. In return for better-timed treatment, better treatment tol-
erability may lessen circadian disruptive effects of cancer, treat-
ment, and hospitalization [6,8-10]. Furthermore, increased tolera-
ability can facilitate further drug administration [7,16]. Based on
experimental models, the chemotherapy tolerability can vary 2- to
10-fold depending on the circadian timing of administration [16].
As of 2010, this pattern exists for at least 40 anticancer drugs; there
are likely to be more in the meantime [16]. Evidently, timing can
be important. Although the current application of cancerchrono-
therapy is limited, there have been promising findings from clini-
cal trials. For instance, a meta-analysis of metastatic cancer pa-
ients receiving 5-fluorouracil, leucovorin, and oxaliplatin in
chronomodulated infusions revealed significantly improved sur-

vival (median overall survival: 20.8 months) compared to those
receiving conventional infusions (median overall survival: 17.5
months, p-value for difference=0.009) [18].

Clearly, cancer chronotherapies are focused on the internal
time of the individual, and rightly so. But as cancer, its treatment,
and hospitalization can have detrimental effects on a patient's
sleep and circadian timing system, other factors that improve
circadian rhythm alignment or lessen circadian disruption expe-
rienced by the patient may provide added benefit when combi-
ned with cancer chronotherapy.

EXERCISE MEDICINE IN ONCOLOGY

Exercise is a subset of physical activity that is planned, struc-
tured and repetitive with a purpose to improve health [19]. Re-
cently, a consensus report called for increased exercise prescription
in oncology and urged healthcare providers to actively promote
and provide advice on physical activity, exercise, and appropriate
exercise programs for cancer patients and survivors [11]. A body
of literature supports the hypothesis that exercise can improve
cancer treatment outcomes, quality of life and decrease risk of re-
currence in cancer survivors [11]. To date, there have been ap-
proximately 700 exercise intervention studies conducted in the
cancer survivor population [11,20]. Studies conducted in a mixed
population, including cancer patients who were either receiving
active treatment or have completed treatment, found physical ac-
tivity/exercise improved survival among patients with malignant,
 recurrent glioma [21] and breast cancer [22].

In contrast, and despite growing evidence in support of the ben-
efits of exercise in cancer survivors, few interventions have exam-
ined the effect of exercise on anticancer drug treatment tolerance
and efficacy. There is promising data from animal studies indicat-
ing exercise may improve anticancer drug efficacies. Compared to
mice treated with chemotherapy alone, mice treated with exercise
plus chemotherapy presented with delayed tumor growth in mod-
els of breast [23], melanoma [24], and pancreatic [24] cancers. A
similar beneficial effect of exercise was observed to improve
tamoxifen treatment in a mouse model of breast cancer [25]. In
human studies, inconsistent results are reported: some indicate
improvements [21,26-28], others indicate null findings [29-34].

Overall, several studies exploring adjunctive exercise interven-
tions and treatment efficacy outcomes among cancer survivors
indicate no adverse effect on treatment efficacy [28,29,33-35].

EXERCISE TIMING AND CANCER TREATMENT

The timing of exercise can affect peak performance levels, ho-
meostatic responses to the activity, and potentially even the cir-
dadian timing of the individual [12-15,36-38]. As examples: 1)
There is a diurnal rhythm to maximum achievable exercise per-
formance levels with peaks typically observed in the afternoon
and evening [36,37]; 2) Differential metabolic substrate utiliza-
 tion in response to exercise may occur depending on timing of
exercise in relation to other exposures (such as feeding or fasting
states) and/or concerning circadian/internal time [12,13,38]; 3)
There is evidence in humans that exercise can phase shift circad-
ian rhythm [14,15]. Conceivably, all three facets of timed exercise
effects may be of benefit to the cancer patient. For instance,
timed exercise may enhance circadian rhythm alignment in the
cancer patient, which may lead to improved tolerability and effi-
cacy of appropriately timed anticancer drugs (Figure 1). Wherein
there is difficulty in performing exercise more generally, ac-
counting for the time of day of the peak in performance may in-
crease the exercise capability of the patient. Differential homeo-
static responses to exercise depending on time of day and/or in
relation to other exposures and homeostatic states (e.g., meta-
 bolic substrate utilization) may be useful in constructing strate-
gies against e.g., cancer-induced cachexia [12,39].

OPPORTUNITIES FOR RESEARCH

Given the large and increasing burden of cancer, investigation of
the different facets of timed exercise as adjunctive therapeutic strat-
egies are warranted. To this end, we provide recommendations:
Firstly, exercise interventions in cancer co-treatment should include
using parameters of treatment efficacy as primary endpoints such as
tumor response [Response Evaluation Criteria in Solid Tumors
(RECIST)] in solid tumors, CT tumor density for tumors treated
with molecular targeting agent, and immune-checkpoint blockade
and atypical response patterns for cancer immunotherapy, etc [40].
Secondly, both observational and interventional studies should
 capture the circadian timing (or at least time of day) of exercise in
addition to individual chronotype information (indicative of
whether peaks/troughs in rhythms are likely to occur earlier or later
in the day). Ideally, this will be done using wearable accelerometers.
Indeed, wearables such as Actigraph (Pensacola, FL, USA) [41],
GENEActiv (Cambridge, UK) [42], and Axivity (Newcastle, UK)
can be used to capture data related to intensity, frequency, duration, and timing of physical activity (Figure 2). It is expected that detailed drug treatment data including dose, frequency, time of administration, completion rate, dose reductions, side effects, specific treatment responses, and patient-reported outcomes should also be collected. Whether observational or interventional in design, such studies would add to the knowledge base on whether specifically timed exercise could be a viable and valuable adjunctive therapeutic strategy against cancer. Thirdly, it would be beneficial for studies investigating the circadian-associated effects of exercise on cancer treatment to collect biological samples. Biological samples will provide opportunities to study pathways associated with physiological responses of the human body to specifically timed exercise during cancer treatments.

Additionally, existing studies that have collected accelerometer data among cancer survivors or patients undergoing cancer treatment could potentially be revisited to generate parameters that facilitate exploratory analyses. Finally, beyond exercise but in a similar vein, studies involving the timing of food may be warranted given that food timing may also affect the circadian system and circadian rhythm may also affect the homeostatic response to food (i.e., the fate nutrients) [44,45].
CONCLUSION

Research activities in exercise oncology recently began to investigate the effect of exercise on cancer treatment efficacy. Given that timing of exercise can have a diverse array of potential effects with relevance to cancer patients, studies that incorporate timing are warranted and may lead to innovative strategies in the fight against cancer.

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Conflicts of Interest
The authors have no potential conflicts of interest to disclose.

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