Physical activity interventions for cancer survivors

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ABSTRACT

Obesity and a sedentary lifestyle are highly prevalent in cancer survivors, and a growing number of publications have shown statistically and clinically significant associations between low levels of physical activity, obesity and cancer recurrence and death. Adoption and maintenance of physical activity is a difficult challenge for healthy adults, and is likely to be even more difficult after a cancer diagnosis. More effective strategies to increase physical activity in cancer survivors should be explored.

The purpose of this paper is to (1) provide a rationale for physical activity interventions and programmes for cancer survivors, and (2) discuss successful approaches to adopting and maintaining physical activity to meet evidence based recommendations and ultimately improve cancer survival and overall survival. Since a majority of cancer survivors are not currently participating in recommended levels of physical activity, resulting in greater disease risk and health care costs, targeted exercise therapy has the potential to benefit a large number of cancer survivors. Cancer survivors should seek out the opportunities that exist towards being physically active, and oncologists should also become aware of the benefits of exercise, assist their patients by endorsing existing physical activity guidelines, and refer their patients to certified cancer exercise trainers.

RATIONAL FOR PHYSICAL ACTIVITY

INTERVENTIONS FOR CANCER SURVIVORS

Cancer diagnosis, surgery, treatment and side effects

Because of the continually improving survival rates, resulting in a large population of over 11 million cancer survivors in the USA alone, the psychological well-being and physical functioning of survivors is important from a public health standpoint. Furthermore, treatment advances, new chemotherapeutic agents, hormone treatments, and biologic therapy have, at least in part, altered the psychological impact of a diagnosis of cancer.

As a result of the cancer diagnosis, surgery, and adjuvant treatments, some cancer survivors experience fatigue, depression, anxiety, reduced overall quality of life, and weight gain. Increased weight is of particular concern because of negative effects of chemotherapy on the cardiovascular system and because of the observed association between weight gain and cancer mortality. As an example, in the American Cancer Society Cancer Prevention Study II, a longitudinal cohort study, obesity was strongly associated with increased risk of dying due to breast cancer. These data suggest that approximately 30–50% of breast cancer deaths among post-menopausal women in the USA can be attributable to being overweight. Similarly, in an analysis of obesity on breast cancer survival in premenopausal women, Daling and colleagues reported that women younger than 45 years of age who had invasive breast cancer and a body mass index (BMI) >25 kg/m² were 2.5 times as likely to die of their disease within 5 years of diagnosis compared with women with a BMI <21 kg/m². These findings of obesity and breast cancer death are apparent even after adjustment for stage at diagnosis and the adequacy of treatment.

Epidemiological studies have also shown that weight gain after a cancer diagnosis is associated with an increased risk for recurrence and death compared with maintaining normal weight after diagnosis. This is especially worrisome given the fact that, especially among women treated for breast cancer, a majority of them gain a significant amount of weight in the year following breast cancer diagnosis, and return to prediagnosis weight is rare. Analyses from the Nurses’ Health Study showed that weight gain after diagnosis (~5 to 10 lbs, 2.3–4.6 kg) was related to approximately 50% higher rates of breast cancer recurrence and death. The findings were especially apparent in women who never smoked, among women with earlier stage disease, or those who were normal weight before diagnosis.
While these findings are intriguing, not all studies have observed an association between obesity or weight gain and poor survival. Caan and colleagues did not observe an association between post-diagnosis weight gain and breast cancer recurrence risk in the first 5–7 years post-diagnosis.14 However, weight gain may still have adverse effects on risk of other new cancer and overall survival. Specifically, there is evidence that cancer survivors die of non-cancer causes at a higher rate than persons in the general population (deaths being primarily from cardiovascular disease and diabetes).13 Therefore, surviving cancer requires that patients not only treat the primary cancer, but also avoid second cancers for which they are at increased risk. To improve overall survival, it is critically important for cancer survivors to prevent obesity. One of the primary methods for preventing or treating obesity and weight gain is by increasing physical activity levels.5 Physical activity has therefore been presented as a therapeutic strategy to address both the psychological and physical concerns faced by cancer survivors.

**Benefits of physical activity after a cancer diagnosis**

**Psychosocial outcomes and cardiovascular fitness**

Recent systematic reviews and meta-analyses have reported clear benefits of physical activity for cardiovascular fitness among cancer survivors but generally modest outcomes with respect to reducing fatigue or improving mood or quality of life.2 14 A breast cancer specific meta-analysis found exercise to be associated with small but statistically significant improvements in quality of life, physical functioning, and fatigue.15

In one of the largest studies to date, Courneya and colleagues examined the effects of aerobic exercise alone, resistance exercise alone, or usual care, on fitness, muscular strength, body composition, and quality of life in 242 breast cancer survivors initiating chemotherapy.17 There were significant favourable effects of both aerobic and resistance exercise on multiple outcomes including self esteem, fitness, and body composition, as well as increased chemotherapy completion rates compared with usual care. Furthermore, no significant adverse events were reported; lymphoedema did not increase or was not exacerbated by aerobic or resistance exercise. Recently, other clinical trials of women with breast cancer have shown no increased risk for or exacerbation of lymphoedema from either aerobic and/or resistance exercise.18

Courneya and colleagues also completed a similar trial of aerobic exercise versus usual care in breast cancer survivors who had completed adjuvant treatment, and observed similar favourable effects of exercise on fitness and overall quality of life.19 Overall, these and other studies have demonstrated that exercise is safe in cancer survivors and produces beneficial effects on quality of life and cancer related symptoms with no adverse side effects.

**Cancer specific survival and overall survival**

A growing number of large observational studies have recently been published demonstrating that participation in moderate intensity recreational physical activity after diagnosis is associated with improved survival in women who develop breast cancer.6–8 These studies have demonstrated a 24–67% reduction in the risk of total deaths and 50–55% reduction in the risk of breast cancer deaths in women who are physically active after breast cancer diagnosis compared with women reporting no recreational physical activity after diagnosis. While any amount of recreational physical activity performed after diagnosis was associated with a decreased risk of death, the maximal benefit occurred in women who performed the equivalent of brisk walking 3 h per week. These studies also showed that the decreased risk of death associated with physical activity was observed in pre- and post-menopausal women, overweight and normal weight women, and women with stage I–III disease.

Given that women who are more physically active after diagnosis may have been similarly active before diagnosis, these studies cannot exclude the possibility that physically active individuals who develop breast cancer acquire tumours that are biologically less aggressive. Therefore, being physically active before diagnosis may have been associated with a later diagnosis of breast cancer or earlier disease stage. However, one study examined change in physical activity from before to after breast cancer diagnosis, with an observed increased risk of death associated with decreasing physical activity.9 This finding emphasises the importance of also participating in physical activity after a diagnosis of breast cancer to gain the maximum benefits of physical activity on survival. Lastly, one study examined whether the influence of physical activity on survival differs according to time since breast cancer diagnosis, with physical activity appearing to be beneficial in both early and late post-diagnostic time periods.7

Two large observational studies have also demonstrated that participation in 5 h per week of moderate intensity recreational physical activity after diagnosis is associated with a 59–59% reduction in the risk of colon cancer death and a 50–63% reduction in the risk of total deaths in men and women who are physically active after a colon cancer diagnosis, compared with inactive men and women.10,11 The inverse relations between post-diagnosis physical activity and colon cancer mortality remained largely unchanged across strata of sex, BMI, age, disease stage, or year of diagnosis.

These observational findings of post-diagnosis physical activity and improved survival suggest that exercise may confer additional improvements in breast cancer survival beyond surgery, radiation and chemotherapy. However, despite this growing body of observational evidence suggesting a strong link between physical activity and breast cancer survival, there is still the potential for confounding by unknown or poorly characterised variables. For example, physical activity may be a marker of overall health behaviours including adherence to adjuvant treatments. Thus, randomised controlled trials testing the effects of physical activity on cancer survival and/or surrogate/biological markers mediating the association between physical activity and survival are necessary and would provide critical information for men and women about whether and how much lifestyle change can affect their prognosis. While a trial of physical activity on cancer survival has yet to be done, a small number of randomised trials of exercise on surrogate/biological markers of survival have been published.

**Biological/surrogate markers of survival**

The beneficial effects of physical activity on cancer survival may be mediated through a reduction in body fat, and beneficial changes in metabolic (for example, insulin) and sex hormones (for example, androgens and oestrogens), growth factors (for example, insulin-like growth factor (IGF)-1 and IGFBP-S), adipokines (for example, leptin, adiponectin), and/or inflammation (for example, C reactive protein).10 In a recent publication, moderate intensity aerobic exercise, such as brisk walking, performed for approximately 120 min per week, was associated with modest, yet favourable, changes in body fat in post-
menopausal breast cancer survivors. A dose–response effect was also observed with greater decreases in body fat occurring with higher doses of exercise per week. Another recent study investigated a resistance training programme on body composition and observed significant decreases in body fat (−1.15% for exercisers vs 0.23%, p = 0.023) with a twice weekly year long resistance training programme in pre- and post-menopausal breast cancer survivors. Their observed between-group effect sizes in body fat were similar to the effect sizes observed in the aerobic exercise study. Furthermore, both studies observed maintenance of bone mass or an attenuation of bone loss. This finding is clinically meaningful given that some of the hormonal therapies given to breast cancer survivors to improve their survival are associated with adverse side effects including bone loss, osteoporosis and increased risk of fractures.

A second strong surrogate or biological marker associated with breast cancer survival is insulin values. There has been increasing evidence that high insulin concentrations strongly increase the risk of breast cancer recurrence and death. Three recent studies have observed an approximate threefold risk of all cause mortality among women with high insulin values, measured approximately 2 years after diagnosis, relative to women with low insulin values. The strong association between fasting insulin values and breast cancer death has led a number of oncologists and scientists to consider the targeting of insulin as a therapeutic modality in breast cancer, particularly because insulin can be modified by lifestyle and pharmacologic interventions. Therapies to reduce insulin concentrations in breast cancer survivors could dramatically decrease cancer related deaths. A lowering of insulin concentrations by 25% may improve survival by 5%, the same order of magnitude as the beneficial effect of adjuvant chemotherapy. While pharmacologic interventions, for example, metformin, decreased insulin values, non-pharmacologic interventions including physical activity have been shown to have clinically meaningful effects on insulin concentrations.

Recently, Ligibel and colleagues observed a 28% reduction in insulin values in breast cancer survivors randomised to 4 months of twice weekly resistance training and 90 min per week of home based aerobic exercise compared to a 5% decrease in insulin values in breast cancer survivors randomised to control. Irwin and colleagues also demonstrated that moderate intensity aerobic exercise, such as brisk walking, performed on average for 120 min per week over 6 months was associated with a borderline statistically significant 21% between-group difference (that is, comparing women randomised to exercise vs usual care) in fasting insulin values (p = 0.089). Both studies observed reductions in insulin without concomitant decreases in body weight or fat.

Obesity and a high insulin value are also associated with a less favourable sex hormone profile. Sex steroid hormones have powerful mitogenic and proliferative influences and are strongly associated with the development of breast cancer. A number of clinical trials also show that oestrogen ablation increases survival following a diagnosis of breast cancer. Changes in sex hormones are perhaps the most consistently cited potential mechanism for the association between physical activity and breast cancer. The primary mechanism of physical activity influencing sex hormones in post-menopausal women is via decreased body fat, a substrate for oestrogen and testosterone production, which results in less tissue capable of aromatisation of the adrenal androgens to oestrogens. To date, only one randomised controlled exercise trial has been published examining the effect of exercise on sex hormone concentrations in healthy women. While an overall effect of exercise was significantly associated with decreased serum oestrogens and androgens, and increased sex hormone binding globulin resulted in lower amounts of free active oestrogens and androgens, in healthy post-menopausal women, a stronger effect was observed among women who lost body fat with exercise compared to women who did not lose body fat with exercise.

Physical activity levels in cancer survivors

Despite these and other well documented benefits of physical activity, a large proportion of cancer survivors do not perform regular physical activity. Similarly, many cancer survivors decrease their physical activity level after diagnosis, highlighting the need for intervention. Exercise adherence is a difficult challenge for healthy adults, and is likely to be even more difficult after a cancer diagnosis and during medical treatments, as evidenced by the decreases in exercise participation during cancer treatment. It has been reported that only 37% of colorectal cancer survivors and 28% of breast cancer survivors exercise regularly during treatment. Furthermore, only 32% of breast cancer survivors participated in recommended levels of physical activity defined as 150 min per week of moderate to vigorous intensity sports/recreational physical activity after completing treatment. Similarly and most recently, Blanchard and colleagues examined the prevalence of physical activity across six major cancer survivor groups (breast, prostate, colorectal, bladder, uterine, skin melanoma). A total of 9105 survivors completed a national cross-sectional survey that revealed only 30–47% of cancer survivors are meeting the physical activity recommendations.

Not only are few cancer survivors exercising at recommended levels, a majority of them decrease their participation in physical activity after diagnosis, with a return to pre-diagnosis levels occurring in less than half of the survivors. Irwin and colleagues reported that, compared to physical activity levels reported in the year before diagnosis, breast cancer survivors, on average, decreased their total post-diagnosis physical activity levels by 2 h per week. Thus, while a cancer diagnosis has been referred to as a possible ‘teachable moment’ where survivors are likely to be motivated to make lifestyle changes to improve health outcomes, few are actually making these changes. Breast cancer survivors benefit from arguably the widest variety of support groups, networks, and resources of any cancer type, and yet they have largely failed to adopt recommended levels of physical activity levels even in the face of such a severe threat to their health and life. This highlights dramatically the need for further investigation of ways to promote adoption and maintenance of physical activity. Recently, several studies have indicated few differences in the prevalence of physical activity between cancer survivors and those without a history of cancer; thus, perhaps examining predictors and barriers to adoption and maintenance of physical activity in healthy populations may guide the promotion of physical activity in cancer survivors.

Why the high prevalence of physical inactivity in cancer survivors?

A question that remains is why are a majority of cancer survivors not physically active when it is known that physical activity programmes carry tremendous potential to affect length and quality of survival, as well as prevent or control morbidity associated with cancer or its treatment? One explanation may be that while survey studies have shown
that cancer survivors are highly motivated to become physically active and want to receive information about physical activity and cancer survivorship. Physical activity counselling has not traditionally been a part of the cancer treatment/survivorship plan. Perhaps, because clinical trial data are lacking to show that physical activity directly impacts cancer survival, physical activity is not a standard treatment recommendation for cancer survivors. Unfortunately, the result is a reluctance of oncologists to prescribe physical activity, a lack of prioritisation of lifestyle/behaviour change in health care systems, non-availability of insurance coverage for physical activity counselling, and confusion of patients on whether physical activity might improve their chances of survival. Therefore randomised clinical trials demonstrating that physical activity after a cancer diagnosis improves survival may lead to the widespread incorporation of physical activity into treatment recommendations for cancer survivors, as well as providing a mandate for the development of lifestyle programmes for cancer survivors, as are available for patients after myocardial infarction. However, until these studies are conducted, cancer survivors should seek out the growing number of opportunities that exist towards being physically active, and oncologists should also become aware of the benefits of being physically active after a cancer diagnosis, as well as existing referral networks (fig 1).

**APPRAOCHES TO INCREASING PHYSICAL ACTIVITY IN CANCER SURVIVORS**

**Oncologist based physical activity counselling and referrals**

Becoming physically active is a difficult challenge for healthy adults and is likely to be even more difficult after a cancer diagnosis and during medical treatments. In reviewing papers that examined predictors of physical activity adoption and maintenance in healthy men and women and cancer survivors, a physician’s recommendation to exercise has been shown to be a strong predictor. It has been recognised that physician based exercise counselling may have a number of distinct advantages over traditional methods of exercise delivery, such as exposure to a high percentage of the population and enhanced credibility regarding the recommendation of certain health practices.

Survey studies have shown that cancer survivors want to receive information about physical activity. Specifically, in a descriptive study, Jones and colleagues mailed a self administered survey to 311 survivors of prostate, breast, colorectal, or lung cancer. A total of 84% of the participants indicated that they would prefer to receive exercise counselling during their cancer experience. Yet, in their study, only 28% of cancer survivors reported that their oncologist initiated a discussion of exercise during their treatment consultation, and that 14% of participants said that they initiated a discussion about physical activity, as was revealed in their follow-up questionnaire.
activity. This finding is surprising given only 16% of the survivors in this study reported exercising at recommended levels. The rate of 28% oncologist initiated and 14% patient initiated (or 42% in total) discussions of the benefits of physical activity is comparable to those in other recent studies. Young-McCaughan and Sexton found that only 41% of breast cancer survivors said that their physician mentioned exercise to them as part of their rehabilitation. Segar and colleagues reported that 50% of breast cancer survivors had received a physician recommendation to exercise, and Demark-Wahnefried found that only 34% of breast cancer survivors and 36% of prostate cancer survivors reported receiving a recommendation to exercise from their physician.

Furthermore, in the study by Jones and colleagues, of the 42% who reported discussing physical activity with their oncologist, only 14% were referred to a specialist for further exercise counselling. Most oncologists likely do not have the training or resources to develop individualised exercise prescriptions for cancer survivors, and the low number of referrals may have resulted from a lack of referral opportunities. Most recently, working together, the American Cancer Society and the American College of Sports Medicine developed a certification called “the certified cancer exercise trainer” for personal trainers, physical therapists, nurse practitioners or other health professionals to become certified in counselling and training cancer survivors in how to exercise safely and at recommended levels. These “certified cancer exercise trainers” are knowledgeable about the potential physical limitations associated with surgery and treatment, and have the skills and abilities to help cancer survivors overcome some of the recent and late effects of surgery and treatment (for more information, visit www.acsm.org). In the near future, it will be of interest to know if oncologists refer their patients to these certified cancer exercise trainers, and in turn whether physical activity levels improve in cancer survivors. We are optimistic that physicians may improve their exercise prescription rates. Using a national survey, Jones and colleagues interviewed 281 oncologists regarding physical activity after a cancer diagnosis. The majority of oncologists agreed that exercise was beneficial, important and safe for cancer survivors during and after treatment. Thus, oncologists appear to have a favourable attitude toward recommending exercise to cancer survivors, yet several barriers, such as not being aware of the benefits of exercise or referral opportunities, may prevent them from providing exercise advice.

We also hypothesise that an oncologist recommendation or referral may increase exercise behaviour in cancer survivors; in another study by Jones and colleagues, a randomised control trial designed to compare the effects of two oncologist based interventions (recommendation only and recommendation plus referral) versus usual care on self reported physical activity showed an improvement in physical activity. Specifically, a total of 450 breast cancer survivors were randomly assigned to these interventions or usual care. The recommendation groups reported higher physical activity levels, but only modest effects (~30 min moderate intensity physical activity per week compared to usual care). However, these findings indicate that an oncologist initiated discussion of exercise during treatment consultations may be a cost effective strategy for promoting exercise in cancer survivors, even if only associated with short term increases in moderate amounts of exercise among previously sedentary individuals.

Types of physical activity programmes preferred by cancer survivors
In the above mentioned survey study by Jones and colleagues, cancer survivors were asked about their physical activity levels, discussions with their oncologists, and physical activity programming preferences. Overall, some of the cancer survivors preferred face to face or “supervised” counselling, while others preferred “home based” telephone or mail based counselling. Some cancer survivors mentioned a preference to exercise alone, and others in a group setting. Some cancer survivors also mentioned a preference to begin an exercise programme immediately after diagnosis, while others preferred to wait until after completing chemotherapy and/or radiation. A majority preferred to participate in recreational activities such as brisk walking. In summary, this important study indicated that cancer survivors have unique and varied exercise counselling and programming preferences, yet they all want to receive exercise counselling.

In regards to when to initiate an exercise programme after diagnosis, some scientists and oncologists feel the timing of physical activity programmes may be critically important because the teachable moment may best be capitalised on if interventions are offered soon after diagnosis. In a survey study of 978 breast and prostate cancer survivors, Demark-Wahnefried and colleagues found that the most preferred lifestyle interventions were initiated at diagnosis or soon thereafter; however, interventions that were offered “anytime” also garnered high scores. Certainly issues such as concurrent demands of treatment are key concerns in the timing of programmes, and therefore appropriate balance is necessary in determining the optimal time at which the patient is both physically and psychologically ready to undertake behaviour change.

Furthermore, in regards to approaches or types of exercise programmes, a supervised programme may have advantages over a home based programme in that cancer survivors can be directly observed (which may decrease risk of injury and also improve adherence to exercise). However, home based programmes may result in better long term adoption and maintenance of exercise, especially if the patient finds cost effective ways to incorporate exercise into his/her daily routine. Another approach could involve an exercise intervention consisting of a combined home exercise and supervised programme. Cancer survivors may be taught exercise techniques and principles in an initial in-person visit at a local health club with the certified exercise trainer and then provided with a home based programme.

Most recently, Vallance and colleagues examined the effects of a non-intensive “home based” exercise programme using breast cancer specific print materials and step pedometers on physical activity in 377 women diagnosed with breast cancer. A combination of print material and step pedometers was associated with an approximate 60 min per week increase in moderate to vigorous intensity physical activity compared with usual care group. This study shows that a distance based approach or a low cost, non-supervised, home based approach encouraged patients to increase weekly physical activity. Future studies and physical activity programmes should explore the use of pedometers and information based (that is, print, telephone, and/web based) programmes on improving physical activity levels in cancer survivors.

In summary, whether a home based or supervised exercise programme is implemented soon after a cancer diagnosis or years after a diagnosis, the high level of interest in physical
activity counselling creates a strong rationale for providing physical activity counselling services as part of the standard of care in comprehensive cancer centres (fig 1). Thus, oncologists should discuss with their patients the benefits of physical activity after a diagnosis of cancer, reassure them that exercise is safe and associated with improved overall survival and quality of life, and to refer them to a certified cancer exercise trainer who will prescribe an exercise programme that is tailored to them. The oncologist and certified exercise trainer should also consider any pre-existing conditions and adverse effects of treatment. Patients should be screened for osteoporosis, bone metastasis, cardiac toxicities, and lymphoedema.

CONCLUSIONS

One of the most common questions cancer survivors ask is: “What can I do to improve my survival?” Physical activity is a modifiable behaviour with a multitude of health benefits. A growing number of publications show a strong relationship between physical activity and cancer survival. Numerous observational studies have also demonstrated that obesity and weight gain adversely affect cancer prognosis, adding further evidence to the hypothesis that physical activity—one of the critical components of obesity and weight gain—influences cancer survival.

Furthermore, many existing cancer therapies are costly and have significant side effects that can result in long term morbidity. Therefore, non-pharmacologic methods, such as participating in physical activity to lower the risk of cancer mortality, especially methods that are also associated with improvements in quality of life and other chronic diseases, may offer an attractive addition to the currently available treatment options. Thus, oncologists and primary care physicians should be encouraged to counsel their patients proactively about physical activity.

In summary, there are, clearly, many questions to be answered concerning who, in terms of cancer survival, would benefit from increasing physical activity, when physical activity would be most beneficial, and how much physical activity would be optimal. Given the high level of physical inactivity in the population, and the heavy burden that cancer creates for the individual and for society, the need for well designed trials of exercise on cancer survival, and programmes available to cancer survivors, are an urgent public health priority. More studies are needed to determine what types of interventions work best at various times after diagnosis and how to encourage adoption and maintenance of physical activity.

Future research might also benefit from specifically targeting those survivors who are experiencing psychosocial impairment or reduced quality of life. This could be accomplished by screening all potential participants for psychosocial functioning and enrolling those who fall below a certain cut-off. Another strategy is to target exercise trials towards specific subgroups of survivors. Despite overall improvements in the health and well-being of cancer survivors, quality of life remains a major concern for certain subgroups of survivors, including young survivors, survivors with a lower level of education, survivors who are diagnosed with later stage cancer, and those who undergo chemotherapy, hormone therapy, or extensive and debilitating treatment regimens. These survivors, who are at risk of greater quality of life impairment, constitute an appropriate and interesting target for future interventions aiming to improve well-being via physical activity. Improved understanding in these research areas will pave the way for physical activity interventions/programmes to become a routine component of cancer treatment and recovery, and will hopefully provide the necessary evidence to convince policymakers for the inclusion of exercise counselling in cancer management, and second party payers in reimbursing cancer survivors for receipt of their exercise counselling.

However, until these studies are conducted, cancer survivors should seek out the opportunities that exist towards being physically active, and oncologists should also become aware of the benefits of exercise, assist their patients by endorsing existing physical activity guidelines, and refer their patients to certified cancer exercise trainers. The simplest, evidence based recommendation at present would be to undertake 30 min of moderate intensity recreational physical activity, such as brisk walking, five times per week. Since a majority of cancer survivors are not currently participating in recommended levels of physical activity, resulting in greater disease risk and health care costs, this targeted therapy has the potential to benefit a large number of cancer survivors.

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REFERENCES

Review