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[Review article]

Current status of research on sarcopenia in post-treatment cancer survivors in Japan : A narrative review

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Abstract

Sarcopenia is prevalent among 11–25% of adult cancer survivors, depending on the cancer type, although the available data on post-treatment survivors in Japan are limited. If cancer patients develop cachexia, they may experience sustained weight loss as a result, ultimately leading to sarcopenia. Conversely, some patients experience post-treatment weight gain, resulting in sarcopenic obesity. Both sarcopenia and obesity elevate the risk of cardiovascular diseases and mortality ; therefore, the importance of sarcopenia prevention and management is undeniable. The Guidelines for Exercise for Cancer Survivors recommend continued physical activity. Recent studies have reported the effectiveness of multimodal interventions, combining pharmacological, nutritional, and exercise approaches, necessitating multidisciplinary care for post-treatment sarcopenia. Innovative health interventions using mobile devices have also gained attention. However, studies on sarcopenia in post-treatment cancer survivors, especially those regarding exercise interventions, remain scarce in Japan, primarily due to limited insurance coverage for such post-treatment interventions and workforce challenges. It is clear that some cancer survivors have sarcopenia, which can lead to worse survival and secondary illness. While the benefits of exercise are clear, a comprehensive approach to sarcopenia is a further challenge for the future.

Keywords : sarcopenia, cancer survivors, type-specific prevalence, exercise therapy

Introduction

Sarcopenia is a syndrome characterized by progressive and systemic reduction in skeletal muscle mass, leading to decreased muscle strength and physical performance. It is associated with impaired physical function, reduced quality of life (QOL), and increased mortality risk[1)]. Its causes include multiple age-related factors, such as physical inactivity, malnutrition, inflammation, and reduced neuromuscular communication. Among cancer patients, sarcopenia is a commonly observed syndrome[2)]. In addition to age-related changes in skeletal muscles, cancer patients are also affected by alterations in skeletal muscle due to the cancer itself and its treatment (Figure 1). In Japan, the diagnosis of sarcopenia is based on criteria set by the Asian Working Group for Sarcopenia 2019 (AWGS2019), including assessment of skeletal muscle mass, muscle strength, and physical function[3)].

The prevalence of sarcopenia in cancer patients varies significantly, depending on cancer type, stage, and patient age. The prevalence of sarcopenia in all adult cancer patients ranges from 11% to 74%, with

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a tendency to increase with age[4]. Previous reports have indicated that, when examining prevalence by specific cancer type, it exceeds 50% in esophageal cancer, urothelial cancer, bile duct cancer, prostate cancer, sarcoma, and thyroid cancer, while it ranges from 14% to 45% in breast cancer[5-7]. With differences in prevalence by cancer type, sarcopenia is common in cancer patients. It can lead to adverse outcomes, including an increased risk of postoperative complications, prolonged hospital stays, reduced response to chemotherapy, and poorer survival rates[2,5,8]. Traditionally, performance status (PS) has been considered to be an indicator for treatment planning and prognosis. Recently, however, evaluation of sarcopenia in addition to PS has been shown to be potentially useful for prognostic estimation and clinical decision-making[9]. Sousa *et al.*[10] reported that poor PS was not an independent factor for mortality, but sarcopenia was a factor that increased mortality risk. Sarcopenia also elevates the risk of toxicity and adverse effects of cancer treatment[5,11]. In addition to affecting treatment outcomes as mentioned above and impacting QOL as it does in non-cancer patients, sarcopenia in cancer patients has been reported to be correlated with increased depressive symptoms[12-14] and a higher proportion of fatigue, which tends to worsen with the progression of sarcopenia[15,16]. Thus, proper interventions for, as well as prevention and early detection of, sarcopenia are especially important in cancer patients not only to optimize their treatment outcomes, but also, to improve their psychological and social well-being.

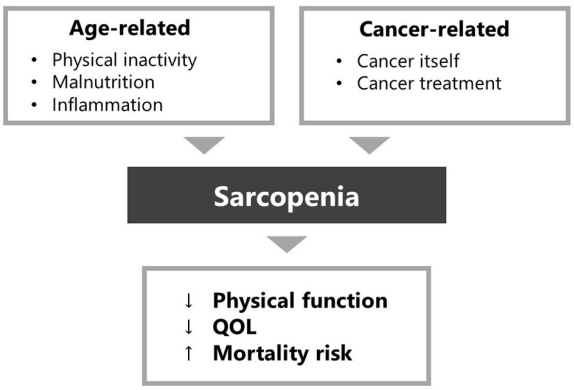

Fig. 1. Association between cancer and sarcopenia

Advances in treatment technologies have improved the 5-year survival rates of cancer patients, resulting in an increasing population of cancer survivors in Japan[17]. Cancer patients who exhibit sarcopenia during treatment are likely to continue experiencing this issue even after treatment. Exercise therapy and nutritional interventions have been reported as crucial in managing sarcopenia during cancer treatment[18-20]. Exercise therapy is also believed to improve immune function, making it an essential supportive therapy for cancer patients[21,22]. However, there are several unclear aspects for cancer survivors, including sarcopenia prevalence and the efficacy of exercise therapy. This review provides a comprehensive overview of sarcopenia in Japanese post-treatment cancer survivors, and compares Japanese findings with those from other countries.

Prevalence of Sarcopenia in Post-Treatment Cancer Survivors

Sarcopenia poses various challenges to cancer survivors not only during treatment but also after treatment. Cancer survivors may experience prolonged physical stress and persistent declines in skeletal muscle mass and physical function due to long-term cancer treatment. Table 1 shows the prevalence of sarcopenia among all cancer survivors after treatment and breakdown by cancer type in countries other than Japan, and Table 2 shows the prevalence of sarcopenia by cancer type in those countries.

According to reports from other countries, the overall prevalence of sarcopenia in adult cancer sur-

Table 1. Prevalence (%) of sarcopenia among all cancer survivors and breakdown by cancer type (in countries other than Japan)

Author (year)	All cancer	Prevalence (%) of all cancer survivors with sarcopenia by cancer type							
		Gastric	Liver	Colorectal	Cervical or Gynecologic	Breast	Lung	Thyroid	Genitourinary
Park YJ et al.[21] (2021)	10.9%	13.8%	8.0%	12.6%	13.8%	12.6%	11.5%		
Lee SJ et al.[22] (2017)	23.1%	15.8%	5.4%	9.8%	13.6%	14.1%	6.0%		
Aduse-Poku L et al.[23] (2023)	25.0%								
Kim EY et al.[24] (2017)	11.0%	38.2%		9.1%	0.0%	1.8%	10.9%	5.5%	18.2%
Lee SJ et al.[25] (2018)	23.1%								

vivors ranges from approximately 11% to 25%[23-27]. The breakdown by cancer type is : gastric 14-38%, liver 5-8%, colorectal 9-13%, cervical 14%, breast 2-14%, lung 6-12%, thyroid 6%, and genitourinary 18%[23,24,26]. A study by Kim *et al.*[26] reported that lung, genitourinary, and gastric cancer survivors are at higher risk of developing sarcopenia, and are influenced by male gender, low body mass index (BMI), and inadequate protein intake. The reported sarcopenia prevalence by cancer type is : gastric 17-21%, liver 37%, colorectal 8-24%, cervical 21%, lung 32-44%, thyroid 4.5%, and genitourinary 26%[24,26]. Sarcopenia has been investigated more extensively in breast cancer survivors than in survivors of other cancer types. Breast cancer survivor reports are more extensive than those of other cancer survivors, with a 1-24% prevalence and links to higher overall and cancer-specific mortality rates[24,26,28,29]. Among pediatric cancer survivors, approximately 25-27% are affected by sarcopenia, with the average onset age being around 33 years, and 51% of pediatric cancer survivors being diagnosed with cancer between the ages of 4 and 13 years. Previous studies have shown that pediatric central nervous system cancer survivors have a higher incidence of sarcopenia, and that survivors who have received cranial radiation therapy are at a higher risk of developing sarcopenia, compared with survivors of other types of pediatric cancer[30,31].

In Japan, investigations into sarcopenia in post-treatment cancer survivors are limited in number (Table 3). Takahashi *et al.*[32] conducted a study of elderly gastric cancer patients who had undergone gastrectomy, and reported an increase in sarcopenia prevalence from 6% before surgery to 20% and 22% at 6 months and 1 year after surgery, respectively, suggesting that sarcopenia persists for at least 1 year after surgery. At 6 months after surgery, the patients also showed decreases in body weight, serum albumin levels, dietary intake, grip strength, walking speed, visceral fat area, and skeletal muscle index, compared to pre-surgery measurements. When comparing measurements at 6 months and 1 year after surgery, body weight, dietary intake, and visceral fat area had increased by the 1-year follow-up after surgery, but skeletal muscle mass index had not ; in addition, an increase in the prevalence of visceral fat-type obesity was observed. Hijikata *et al.*[33] reported that 35.1% of esophageal cancer patients who underwent esophagectomy had sarcopenia at the 6-month follow up after surgery. The risk factors for sarcopenia in male esophageal cancer

Table 2. Prevalence (%) of sarcopenia by each cancer type (in countries other than Japan)

Author (year)	Gastric	Liver	Colorectal	Cervical or Gynecologic	Breast	Lung	Thyroid	Genito-urinary	Pediatric
Lee SJ et al.[22] (2017)	17.0%	37.0%	24.3%	20.8%	24.1%	44.0%			
Kim EY et al.[24] (2017)	21.4%		8.3%	0.0%	1.4%	31.6%	4.5%	26.3%	
Villaseñor A et al.[26] (2012)					16.0%				
Benavides-Rodríguez L et al.[27] (2017)					22.4%				
van Atteveld JE et al.[28] (2023)									24.5%
McCastlain K et al.[29] (2021)									27.0%

Table 3. Surveys on sarcopenia in cancer survivors in Japan

Author (year)	cancer type	Summary
Takahashi S et al.[30] (2019)	Elderly gastric cancer patient undergoing laparoscopy-assisted distal gastrectomy	・The prevalence of sarcopenia was 6% preoperatively, 20% at 6 months postoperatively, and 22% at 1 year postoperatively. ・No increase in skeletal muscle mass at 1 year postoperatively.
Hijikata N et al.[31] (2022)	Esophageal cancer patients undergoing esophagectomy	・35.1% had sarcopenia at 6 months postoperatively. ・Risk factors for sarcopenia are preoperative BMI, postoperative grip strength, and tube feeding use at discharge.
Nakayama H et al.[32] (2021)	Childhood leukemia and lymphoma	・The prevalence of sarcopenia was 11%. ・Hematopoietic stem cell transplantation is a factor that increases the risk of sarcopenia, and patients who undergo total body irradiation have a higher rate of sarcopenia.

survivors included preoperative BMI, grip strength measured 6 months after surgery, and the use of enteral nutrition at discharge. Nakayama *et al.*[34] reported that 11% of survivors of childhood leukemia and lymphoma had sarcopenia. Of the survivors, sarcopenia was observed in 21% of those who had received hematopoietic stem cell transplantation (HSCT) but in only 4% of those who had not, indicating that HSCT was a risk factor for sarcopenia. Among those who had undergone total body irradiation as a preconditioning regimen of HSCT, 33% were diagnosed with sarcopenia, while no such diagnosis was made in those who had not received total body irradiation.

Thus, it is clear that some post-treatment cancer survivors experience sarcopenia. However, there are few long-term studies that have investigated whether sarcopenia typically occurs during or after treatment. In the future, it is necessary to investigate the long-term progression of sarcopenia, starting before cancer treatment and continuing after.

Problems related to Sarcopenia in Cancer Survivors

Sarcopenic obesity

Increased risk of cardiovascular disease (CVD) and death has been reported in cancer survivors with sarcopenia or obesity[35,36]. Sarcopenic obesity is a condition in which sarcopenia is accompanied by increased adipose tissue and weight gain, which is generally associated with a higher risk of insulin resistance and atherosclerosis, as well as an increased risk of death, compared to simple obesity[37-40]. It has been reported that disease-free survival and overall survival are significantly lower when sarcopenic obesity is present prior to cancer treatment[41]. Among cancer survivors, there is often an increase in dietary intake following cancer treatment, resulting in a regain of weight that had been lost during therapy. In breast cancer patients, weight gain is also frequently induced by hormone therapy ; thus, sarcopenic obesity typically results from increased adipose tissue rather than from decreased skeletal muscle mass.

Reports have suggested that sarcopenic obesity affects 12-33% of all adult cancer survivors. The prevalence rates by cancer type are : gastric 17.3%, liver 4%, colorectal 1.2%, cervical 13.3%, and lung 3.1%[23-26]. As in the case of sarcopenia research, research specifically into sarcopenic obesity in breast cancer has been done extensively worldwide, with documented rates of sarcopenic obesity varying from 15% to 38%[24,26,28,29].

Although research on sarcopenic obesity in cancer survivors is notably limited in Japan, Nakayama *et al.*[34] reported that approximately 12% of pediatric cancer survivors in their study were obese, yet no cases of sarcopenic obesity were observed. In studies targeting pediatric cancer survivors of acute lymphoblastic leukemia in other countries, approximately 22% were reported to be obese, with 14-43% classified as having sarcopenic obesity[42,43], although it is plausible that obesity itself is more prevalent in these countries than in Japan. Preventing and addressing sarcopenic obesity is of significant importance for secondary disease prevention and reduction of mortality risk in cancer survivors ; thus, this area should be further investigated in the future.

Cardiovascular disease risk

There are several treatments available for cancer patients, including anthracycline-based chemotherapy, radiotherapy, and monoclonal antibody therapies such as trastuzumab and bevacizumab. These treatments may cause cardiac dysfunction, including hypertension[44-47]. The risk of CVD remains high, even in patients who have successfully navigated cancer and entered the survivorship phase, compared to the risk in individuals without a history of cancer. Some reports have suggested that approximately one in four survivors has a cardiovascular condition[48,49]. While it has been acknowledged that both cardiovascular and pulmonary function typically experience a natural decline of around 10% per decade with advancing age, the use of chemotherapeutic agents may result in a more substantial decrease of up to 25% in cardiac and pulmonary function[50]. Lee[51] reported that the 10-year risk of CVD in cancer survivors is higher by about 10% in comparison to that in individuals without cancer. When cancer survivors have sarcopenic obesity, CVD risks become even greater. A Korean study[27] reported that cancer survivors with sarcopenia exhibited higher levels of BMI, blood pressure, and fasting glucose level, along with larger waist circumference and lower high-density lipoprotein levels, compared to survivors without sarcopenia. Additionally, a significant association between sarcopenia in cancer survivors and Framingham Risk Score, a metric indicative of CVD risk, was observed among male subjects. Sarcopenia, characterized by reduced skeletal muscle mass and diminished physical function, often conjures an image of a lean body

composition. However, it is essential to recognize that many survivors also exhibit concurrent obesity, particularly because such comorbidity may escalate the risk of CVD. Although the link between CVD risk and sarcopenia has been reported in several studies, the influence of other factors, such as age, gender, and cancer type, in elevating CVD risk remain elusive. Cancer and CVD share common risk factors[52]. It may be crucial to explore this association by considering the treatment regimens and medical histories experienced by cancer survivors, as well as whether they developed sarcopenia or obesity.

Cancer cachexia

Cancer cachexia is reported to occur in 50–80% of cancer patients, and is characterized by symptoms such as weight loss, loss of appetite, and fatigue, leading to decreased QOL[53]. The Asian Working Group for Cachexia (AWGC) published a consensus report on the diagnosis and clinical outcomes of cancer cachexia in Asians[54]. The diagnosis requires the presence of specific diseases underlying the cachexia, as well as weight loss and low BMI. In addition, the patient must have anorexia, decreased grip strength, or elevated C-reactive protein. While mechanisms of cancer cachexia are not fully understood, the involvement of glucocorticoids, tumor necrosis factor-alpha, interleukin-6, growth differentiation factor-15, GDF-11, and parathyroid hormone-related protein have been reported. These factors contribute to increased protein degradation and reduced synthesis in skeletal muscles, resulting in muscle wasting. Moreover, the emergence of symptoms such as appetite loss and fatigue can lead to further reduction of physical activity, raising concerns of sarcopenia. An investigation targeting advanced non-small cell lung cancer patients found sarcopenia in 68.5% and 66.7% of pre-cachectic and cachectic patients, respectively[55]. Furthermore, Dunne *et al*[56]. reported weight loss accompanied by sarcopenia in 48% of the elderly cancer patients enrolled in their study. Many cancer cachexia studies focus on patients undergoing cancer treatment, leaving the extent of its impact on post-treatment cancer survivors unclear. However, a higher rate of weight loss over one year has been associated with shorter survival in cancer patients[57]. suggesting a likelihood of sustained sarcopenia after treatment. Weight loss also affects not only physical function but also QOL, according to Japanese studies[57,58]. AWGC also considers mortality, QOL, and functional status as important clinical outcomes for Asian patients with cachexia[54]. For assessment of QOL in cancer survivors, the use of the EuroQol 5 Dimension, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30, EORTC-QOL-CAX24, and Functional Assessment of Anorexia/Cachexia Therapy, is recommended. Regarding patients' functional status, Clinical Frailty Scale, Barthel Index, Katz Index, Lawton scale, and 6-minute walking distance are considered important indicators. Cancer cachexia, characterized by weight loss, is closely associated with sarcopenia. Therefore, it is necessary to conduct intervention studies that focus on cancer cachexia, and perform interventions aimed to prevent sarcopenia from the start of cancer treatment.

Exercise Therapy for Post-Treatment Cancer Survivors with Sarcopenia

Recommended exercise therapy for cancer survivors

Exercise therapy is recommended for cancer patients, and has been reported to provide various benefits, such as improvements in physical function, QOL, and psychological well-being for cancer survivors after treatment (Figure 2)[59-61]. The exercise guidelines proposed by Campbell *et al.*[60] state that engaging in exercise is safe for cancer survivors, and that inactivity should be avoided. Aerobic exercise and resistance training have been reported to contribute not only to improved physical function but also to the amelioration of anxiety, depression, fatigue, and health-related QOL in cancer survivors. In addition to the aforementioned physical benefits, the guidelines also address the potential benefits of exercise for treatment-related problems such as cardiotoxicity, peripheral neuropathy, cognitive dysfunction, nausea, and sexual dysfunction. Although the evidence is insufficient regarding the effectiveness of exercises for treatment-related problems, Campbell *et al.*[60] recommend that inactivity should be reduced as much as possible. According to these guidelines, cancer survivors should engage in moderate-intensity activity for 150-300 minutes per week or high-intensity activity for 75-150 minutes per week. In addition, resistance training at least twice a week is recommended. The guidelines emphasize the importance of performing optimal exercises according to individual conditions and circumstances based on consultation with medical professionals before starting an exercise regimen. A study of adult cancer survi-

Fig. 2. Benefits associated with exercise for cancer survivors

vors reported that the percentage of those who met the recommended amount of physical activity ranged from 20% to 34%, and the percentage of those who adhered to resistance training two days per week was 12%[62,63]. In a study of breast cancer patients, 26% were engaged in guideline-equivalent activities 3 years after diagnosis[64]. However, many of the reports demonstrating the effects of exercise therapy targeted patients undergoing cancer treatment and cancer survivors without sarcopenia ; there is a significant lack of studies focusing on survivors with sarcopenia following cancer treatment, both domestically and internationally. Therefore, the effect of adherence to exercise on cancer survivors with sarcopenia is unclear. However, in a report of hematologic malignancy patients undergoing chemotherapy, resistance training and aerobic exercise at an intensity equivalent to the Borg scale 13 at a frequency of once a day six times a week, resulted in a 95% adherence rate, even among patients with sarcopenia[65]. Moreover, in a study of cancer patients before surgery or during chemotherapy, whose population includes sarcopenic patients, resistance training and aerobic exercise improve physical function and skeletal muscle mass. In addition, the percentage of sarcopenia reversal has been reported to be approximately 20-30%. Furthermore, adherence to exercise has been reported to be around 50-85%[66]. Thus, high adherence to exercise has been reported even during periods when treatment-related adverse events are likely to occur, and similar or better exercise feasibility is expected in cancer survivors who have completed treatment. A report on exercise for breast cancer survivors, some of whom had sarcopenia obesity, reported an exercise adherence of 95%, resulting in improvement of body composition[67]. However, there are few studies on cancer survivors with sarcopenia, and the effects of exercise on such individuals have yet to be elucidated. Although increased exercise and physical activity are recommended, the existence of inadequate evidence between treatment-related side effects and the benefits of exercise is an issue that should be investigated by future studies.

A Multimodal approach for cancer survivors

It is considered important to improve sarcopenia through nutritional therapy, exercise therapy, and physical activity[66]. In Japan, an oral ghrelin mimetic agent, anamorelin, has been developed as a therapeutic drug for cancer cachexia. This drug has been shown to prevent weight loss in patients with lung or gastrointestinal cancers[68,69]. Reports from Japan and other countries have suggested that a multimodal approach combining this medication with exercise, physical activity, and nutritional therapy maintains and improves body composition, physical function, and QOL[70-73]. Seemingly, this multimodal intervention requires multidisciplinary collaboration, and may raise concerns about feasibility and compliance. However, Naito *et al*[71]. reported that both nutritional and exercise interventions in elderly patients with advanced pancreatic and non-small-cell lung cancer showed high feasibility (> 90%) and no

serious adverse events. Additionally, Liu *et al.*[74] reported, in their study on elderly cancer survivors, that combining dietary guidance with exercise is effective for improving physical function ; however, they concluded that further investigation is necessary to determine its impact on sarcopenia. A Cochrane review in 2014 that investigated exercise interventions for cancer cachexia patients reported that there was a lack of evidence to determine the safety and effectiveness of exercise, because no randomized controlled trials (RCTs) had met the inclusion criteria[75]. However, another Cochrane review in 2021 reported on four RCTs for head and neck cancer and lung cancer[76]. It is highly possible that these reports may be biased by factors such as masking of participants, personnel, and outcome assessors ; thus, the efficacy, tolerability, and safety of exercise for cancer cachexia patients are still unclear, warranting more high-quality, well-designed RCTs in the future. While studies on multimodal interventions during cancer treatment have demonstrated the importance of sarcopenia prevention, reports incorporating medications and exercise remain limited, warranting further research development in the future.

Trial of exercise intervention for cancer survivors

In recent years, there has been an increase in reports on high-intensity interval training (HIIT) for cancer survivors. A study implementing high-intensity training for postoperative lung cancer survivors demonstrated improvements not only in physical function but also in muscle mass and QOL compared to patients receiving standard postoperative care only. In the present study, patients aged ≤ 80 years exercised for 60 minutes per session at a frequency of 3 days per week, for 20 weeks. Intensity was set at 80-95% of maximal heart rate for endurance training and 6-12 repetition maximum for resistance training, with a reported exercise retention rate of approximately 88% for 20 weeks[77]. In Japan, HIIT using smartphone-based support was conducted for breast cancer survivors, resulting in improvements in cardiorespiratory function and lower limb muscle strength[78,79]. This home-based program, indicated for breast cancer survivors aged 20–59 years, did not show significant improvement in QOL, but it achieved an adherence rate of 86% and did not result in serious side effects. The exercise program consisted of 6 weeks' home exercise support using exercise counseling plus exercise instruction (six sessions per week, 30 minutes per session), 12 weeks of ICT intervention using personalized emails (one session per week) and an exercise application. Participants were encouraged to perform high-intensity body weight exercises set to increase in intensity each week, with one 10-minute training session three times per week for 12 weeks. The specific intensity was set at three levels of load according to cardiorespiratory fitness (VO2peak) at week 0, and was set to progressively increase fitness according to the individual's fitness levels. The findings in these studies suggest that although consistent data on its effects on cancer survivors are not yet available, HIIT may provide both physical benefits and improved QOL to cancer survivors after treatment, and its continuation rates are noteworthy. Nevertheless, it should be noted that engaging in high-intensity workouts poses a potential risk of excessive exercise. It is important to remember that, to the best of our knowledge, no serious side effects associated with exercise interventions provided have been reported. In particular, if a study focuses on patients with reduced physical function, such as those with sarcopenia, it is even more important to receive expert advice regarding exercise load and physical condition management.

The use of smartphones to support intervention methods, as illustrated in the aforementioned HIIT, has been gaining in popularity. Interventions such as these using smartphones and other devices are referred to as mHealth. mHealth is a health and medical service that utilizes cell phones, applications, wearable monitoring devices, and other devices that can communicate and collaborate with each other. Onyeaka *et al.*[80] found that cancer survivors use mHealth, via the use of health applications and wearable devices, at a similar rate to non-cancer patients (health applications, about 50% ; wearable devices, 22%). Many cancer survivors have reported a desire to share information with their health care providers via mHealth. In addition, survivors who use health applications are more likely to meet the recommended vegetable intake and exercise regularly. They also reported that using mHealth not only improves physical function and physical activity, but also helps improve QOL, cognitive function, and fatigue[81-83]. Furthermore, combining mHealth with rehabilitation has been shown to increase the benefits of exercise[82,83]. Thus, mHealth could offer benefits to individuals recovering from sarcopenia, as it helps the management of both exercise and dietary habits, which are two key components in the effective treatment of this disorder. Such reports on mHealth have been reported in the U.S. and Spain, not only for middle-age can-

cer survivors but also for those aged ≥ 65 years. However, there are also concerns regarding the challenges of low adaptation of applications and wearable devices in the older population[80-83].

Although none of the studies mentioned in this section involved post-treatment cancer survivors with sarcopenia, programs to improve skeletal muscle mass and physical function in cancer survivors have been reported, and innovative programs to prevent and improve sarcopenia should be explored in the future.

Problems and exercises related to sarcopenia

The effectiveness of exercise therapy has been reported with regard to issues related to sarcopenia, such as obesity and CVD risk. A study investigating exercise intervention targeting post-treatment breast cancer patients with obesity (including sarcopenic obesity) reported an increase in skeletal muscle mass over a 16-week period through aerobic exercise and resistance training, as well as improvements in biomarkers such as insulin, IGF-1, leptin, and adiponectin[67]. A study on obese breast cancer survivors also reported extensive benefits of exercise, which encompass improvements in physical function, bone health, QOL, cardiorespiratory function, and muscle strength[84]. Regarding CVD risks, the American Heart Association has introduced the concept of 'cardio-oncology rehabilitation' (CORE). By integrating elements of cardiac rehabilitation into cancer rehabilitation, CORE aims to enhance cardiorespiratory function and reduce CVD risks in cancer survivors. Reports from various countries have indicated that exercise therapy for cancer survivors leads to improved cardiorespiratory function [85-88], suggesting that exercise therapy may potentially mitigate CVD risk. Although exercises such as resistance training, aerobic exercise, and inspiratory muscle training have been reported to result in such risk-reducing effects[89]. there is no clear consensus on which type of exercise is most effective. Furthermore, to what extent sarcopenia affects CVD risk has not yet been definitively established. Most reports on the relationship between obesity and CVD risk come from overseas studies, and research into these aspects has been limited in Japan.

Sarcopenia has been shown to be clearly detrimental to cancer survivors during and after treatment ; in a study of resected non-small cell lung cancer patients in Japan, Kawaguchi *et al.* reported that patients with sarcopenia had a higher recurrence rate than those without sarcopenia[90]. Although exercise therapy for cancer survivors is recommended and clearly provides a variety of health benefits, there is still a lack of research on sarcopenic cancer survivors. Recently, it has been suggested that skeletal muscle is involved not only in sarcopenia, but also in immune function, and that exercise and physical activity both support immune function and improve neurotrophic function, NK-cell cytotoxicity, and vaccine responses[91]. It has also become clear that exercise therapy has a positive effect on the immune system in cancer survivors, in addition to the improvement of physical function and the aforementioned effects. Specifically, it has been shown that exercise therapy in cancer patients reduces inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α, which may lead to a reduction in fatigue[92-94].

It is clear that further investigation should be conducted to determine the outcome of cancer survivors with sarcopenia after exercise therapy. While there are few overseas studies on exercise therapy for post-treatment cancer survivors, Japanese research significantly lags in this area. As the number of post-treatment cancer survivors is increasing in Japan, further research on the subject is essential and urgent.

Conclusions

Investigations into sarcopenia among cancer survivors remain limited globally. In Japan, research on this topic is even more scarce, and advancements in intervention studies, including post-treatment exercise therapy, are warranted.

An investigation into the recommended physical activity guidelines for breast cancer survivors in Japan revealed that only 20% of cancer survivors were familiar with the prescribed regimen. Similarly, the proportion of those regularly receiving information on physical activity was also around 20%[95]. Furthermore, Okubo *et al.*[96] reported that, while the Japanese guidelines did address issues concerning cancer survivorship, such as cancer recurrence and secondary tumors, no insight was provided regarding care coordination, potential effects of medical interventions, or involvement of family members. These reports illuminate the scarcity of research on the health and physical functionality of post-treatment cancer survivors in Japan, particularly in the context of sarcopenia[95,96]. Based on the important outcomes presented by the AWGC regarding cancer cachexia, early detection of cachexia may contribute to the prevention of weight loss and

sarcopenia during cancer treatment. A multidisciplinary approach that includes exercise, nutrition, and drug therapies is important for this purpose. Although advancements in drug development continue to be made in Japan, the evidence remains inconclusive. It is therefore imperative to conduct follow-up studies beyond the cancer treatment phase to include the post-treatment period as well. However, barriers exist with regard to conducting studies on sarcopenia after cancer treatment in Japan, because cancer rehabilitation in Japan for outpatients is not yet covered by the Japanese health insurance system. As a result, there is a current lack of professionals involved in rehabilitation, such as physical or occupational therapists. In a study by Fukushima *et al.*[97], it was found that only 39% of nationally designated cancer care hospitals in Japan offered outpatient cancer rehabilitation services. Among these hospitals, more than 80% perceived the rehabilitation services as insufficient. Factors contributing to this insufficiency include ineligibility for reimbursement of medical fees, a lack of human resources, insufficient awareness regarding the importance of rehabilitation, and an inadequate educational framework. To foster advancement in research focused on post-treatment cancer survivors in Japan, securing insurance coverage for outpatient cancer rehabilitation and necessary human resources is crucial. Simultaneously, it is also important to promote further exploration into sarcopenia and related issues, as well as enhance the education of medical staff on the post-treatment health of cancer survivors. If consistent intervention for sarcopenia during and after cancer treatment becomes possible, significant improvement of QOL in cancer patients during and after treatment can be anticipated. Therefore, more extensive research on cancer survivors is urgently needed to implement multimodal, evidence-based post-treatment care in rapidly aging Japan.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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