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REVIEW

The Future of Breast Cancer Research in the Survivorship Field

D. Soldato · L. Arecco · E. Agostinetto · M. A. Franzoi · E. Mariamidze · S. Begijanashvili · N. Brunetti · S. Spinaci · C. Solinas · I. Vaz-Luis · A. Di Meglio · M. Lambertini

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ABSTRACT

Prevalence of survivors of breast cancer has been steadily increasing in the last 20 years. Currently, more than 90% of women diagnosed with early-stage breast cancer are expected to be alive at 5 years from diagnosis thanks to early detection and breakthrough innovations in multimodal treatment strategies. Alongside this advancement in clinical outcomes, survivors of breast cancer might experience several specific challenges and present with unique needs. Survivorship trajectories after diagnosis and treatment of breast cancer can be significantly impacted by long-lasting and severe treatment-related side effects, including physical problems, psychological distress, fertility issues in young women, and impaired social and

D. Soldato · L. Arecco · M. Lambertini (✉)
Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genova, Genoa, Italy
e-mail: matteo.lambertini@unige.it

D. Soldato · L. Arecco · M. Lambertini
Department of Medical Oncology, U.O. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Largo Rosanna Benzi 10, 16132 Genoa, Italy

D. Soldato · M. A. Franzoi · I. Vaz-Luis · A. Di Meglio
Molecular Predictors and New Targets in Oncology, Institut National de la Sante et de la Recherche Medicale Unit 981, Gustave Roussy, Villejuif, France

D. Soldato · M. A. Franzoi · I. Vaz-Luis · A. Di Meglio
Breast Cancer Unit, Medical Oncology Department, Gustave Roussy, Villejuif, France

E. Agostinetto
Department of Medical Oncology, Institut Jules Bordet and Université Libre de Bruxelles (U.L.B.), Brussels, Belgium

E. Mariamidze
Department of Oncology and Hematology, Todua Clinic, Tbilisi, Georgia

S. Begijanashvili
Department of Clinical Oncology, American Hospital Tbilisi, Tbilisi, Georgia

N. Brunetti
Department of Experimental Medicine (DIMES), University of Genoa, Genoa, Italy

S. Spinaci
Division of Breast Surgery, Villa Scassi Hospital, Genoa, Italy

C. Solinas
Medical Oncology, AOU Cagliari, Policlinico Duilio Casula, Monserrato, Italy

work reintegration, which add up to patients' individual risk of cancer recurrence and second primary malignancies. Alongside cancer-specific *sequelae*, survivors still present with general health needs, including management of chronic preexisting or ensuing conditions. Survivorship care should implement high-quality, evidence-based strategies to promptly screen, identify, and address survivors' needs in a comprehensive way and minimize the impact of severe treatment *sequelae*, preexisting comorbidities, unhealthy lifestyles, and risk of recurrence on quality of life. This narrative review focuses on core areas of survivorship care and discuss the state of the art and future research perspectives in key domains including selected long-term side effects, surveillance for recurrences and second cancers, well-being promotion, and specific survivors' needs.

Keywords: Breast cancer; Survivorship; Supportive care

Key Summary Points

1. Prevalence of breast cancer survivors has been steadily increasing thanks to early detection and improvement of oncological outcomes.
2. Over the course of the survivorship trajectory, survivors of breast cancer face several challenges that can lead to quality-of-life deterioration.
3. Survivorship care is articulated in five main areas: management of physical and psychological *sequelae* of treatment, health promotion, management of chronic conditions, and surveillance for recurrences and second cancers.
4. To accelerate progress in the field and improve quality of survivorship care, future research in the field should aim at integrating high-quality data to better characterize determinants of long-term toxicities, deliver novel and effective interventions, and test novel models of care.

INTRODUCTION

Survivors of breast cancer (BC) are currently estimated at 4 millions in the USA [1] and 2 millions in Europe [2], and are expected to further increase in the next decades [3]. The progressive increase in prevalence of survivors is multifactorial, being linked, on the one hand, to increased prevalence of unhealthy lifestyles [4] and earlier detection due to implementation of mammographic screening [5], and on the other hand, to striking advances in the multimodal treatment of BC [6, 7].

Over the last 20 years, the treatment landscape of BC has been repeatedly revolutionized by novel agents that have radically modified patterns of care and significantly improved clinical outcomes [8]. However, novel agents can pose significant challenges for survivors of BC.

First, the use of novel treatments in the early setting has significantly extended the active treatment phase, requiring more frequent medical evaluations in the hospital setting [9–12]. Second, although pivotal studies and patient-reported outcomes (PROs) data suggest that most novel agents are tolerable and not associated with substantial deterioration in quality of life (QoL), adverse events and long-term physical and psychological effects might still place a significant burden on survivors in terms of interference with daily activities, potential need for medical care, and risk of long-lasting toxicities [13–15]. Third, the potential impact of novel agents on fundamental aspects of survivorship care, such as fertility issues in young women, long-term physical effects, psychological distress, and social and work reintegration, are still largely unknown.

Overall, following completion of primary treatment and along the survivorship trajectory, survivors of BC face several challenges and present different needs that have to be addressed in a comprehensive model of care rooted in an evidence-based framework [16]. Consequently, current guidelines for survivorship care recommend appropriate assessment and management of survivors' needs in five main areas:

physical and psychological *sequelae* of treatments, identification of recurrences and second cancers, general health promotion, and management of chronic conditions [16–18].

Recently, a consensus statement at the European level reinforced the need to promote high-quality survivorship care and research in the context of an evidence-based framework, underlying the need for better identification and management of survivors' needs [19]. A similar attention toward survivorship care has been raised by policymakers in the context of the Europe Beating Cancer Plan [20], with a specific flagship aimed at improving QoL in cancer survivors.

In this narrative review, we discuss state of the art and research perspectives (Fig. 1) in the field of survivorship care, focusing on selected issues including long-term side effects, surveillance protocols, well-being and general health promotion, and specific survivors' needs.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

LONG-TERM SIDE EFFECTS

Survivors of BC are at risk of developing a variety of physical effects whose appearance, severity, and persistence may be related to different treatment exposures and underlying risk factors.

Multimodal treatment of BC requires administration of different agents, each associated with a specific spectrum of physical effects that can appear during treatment and frequently persist afterward. The most common long-term physical symptoms reported by survivors of BC include, among others, fatigue, insomnia, musculoskeletal pain, vasomotor symptoms and sexual dysfunction, cognitive dysfunction, peripheral neuropathy, and weight gain. Treatment of BC also carries a risk of long-term physician-assessed conditions such as cardiotoxicity and loss of reproductive potential in young women.

Long-term physical effects can be associated with a significant time-dependent deterioration of QoL [21], loss of physical and role function,

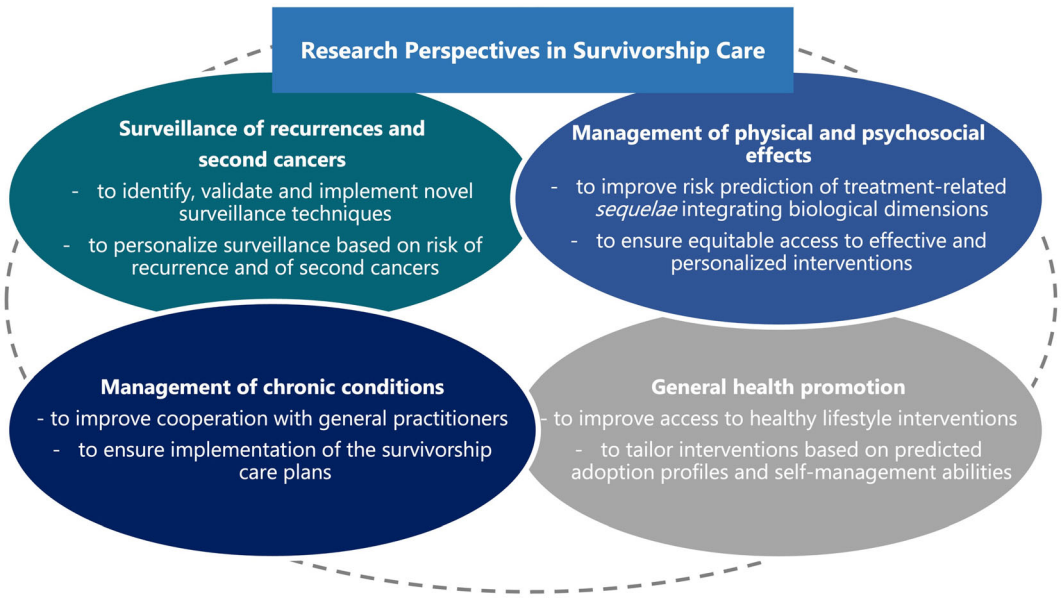

Fig.1 Future research perspectives in the four main areas of survivorship care

and with reduced adherence to adjuvant treatment as well, especially endocrine therapy [22].

Considering the broad spectrum of potential long-term physical effects, we selected some of the most prevalent and burdensome.

Fatigue

Cancer-related fatigue (CRF) is one of the most common and distressing long-term *sequela* among survivors of BC [23]. CRF is distinct from regular fatigue since it is less responsive to rest, is more intense and distressing [24–26], and has multidimensional manifestations involving the physical, emotional, and cognitive domains [23]. CRF can place a substantial burden on survivors and lead to deterioration in QoL due to physical, psychological, and socioeconomic repercussions [27].

The highest prevalence of CRF, around 60%, has been described during primary treatment and in the following year; however, up to 30% of survivors of BC report persistent fatigue up to 10 years after diagnosis and treatment for BC [27–30].

A complex interplay between several biobehavioral factors has been associated with the development of CRF. Previous data reported on significant associations between CRF and social (e.g., age, marital status, education, and income), psychological and cognitive (e.g., preexisting depression and fatigue), and medical (e.g. comorbidities and type of treatment) factors [27]. Furthermore, dysregulation of relevant biological pathways may play a significant role in the development of CRF. Higher levels of proinflammatory cytokines, alterations in the neuroendocrine system, and higher expression of aging biomarkers have been described in survivors reporting persistent and severe CRF [23, 31–36]. Additionally, preliminary data show a potential role of single nucleotide polymorphism on the risk of developing CRF after BC [37].

Current guidelines recommend a systematic screening of cancer survivors using PROs, aiming at prompt identification of CRF and concomitant symptoms (e.g., pain, emotional distress, and insomnia) that frequently cluster with it [17, 38, 39]. Despite these recommendations, the high prevalence, and the significant impact on survivors' lives, data show that CRF remains a largely under-addressed issue [23, 27].

Despite the fact that the mechanisms underlying development and persistence of CRF are not completely understood, different therapeutic approaches have been tested and are endorsed by guidelines [39]. Optimized management of underlying medical conditions (e.g., anemia, nutritional deficits) and of concomitant symptoms clustering with fatigue (e.g., insomnia, emotional distress) should always be considered in a global approach to CRF [39]. In addition, specific interventions are effective in mitigating CRF and should be proactively proposed. Initiation and/or maintenance of adequate physical activity (including both aerobic and resistance training) reduce CRF, probably through modulation of systemic inflammation [38, 40–43]. Psychosocial interventions including cognitive behavioral therapy, educational therapies, and mindfulness reduce CRF by regulating maladaptive thoughts [38, 44, 45]. Finally, data from randomized clinical trials support a potential role of acupuncture in relieving CRF [46–49]. Despite availability of interventions targeting CRF, several barriers, including limited awareness of healthcare professionals and lack of resources and reimbursement for supportive care interventions [50, 51], significantly hamper their implementation in routine clinical practice [52].

Recent data published using the CANTO (NCT01993498) cohort [53] shed new light on the evolution of CRF over time and on risk factors associated with reporting severe CRF. Using longitudinal self-reported PROs among 4173 patients, the authors identified clusters of patients at different risk for severe global CRF: one cluster of patients (high-risk group, 21%) with a consistently high risk at diagnosis and 4 years after, and a second cluster (deteriorating group, 19%) of patients with low risk at diagnosis but with a significant 64% risk 4 years after. Patients belonging to these two clusters were more frequently young, single, had more comorbidities, and higher body mass index (BMI), reporting symptoms at diagnosis and

receiving endocrine therapy. Interestingly, dimensions of CRF (i.e., physical, emotional, and cognitive) showed that different clustering patterns and specific risk factors could be identified, although emotional distress and endocrine therapy were common to all dimensions [54].

The same authors developed an online tool exploiting risk factors collected at diagnosis to predict the probability of reporting severe global fatigue at year 2 and year 4 after diagnosis. Specific risk factors for reporting severe fatigue at year 2 included presence of severe fatigue at baseline, younger age, higher BMI, current smoking behavior, and presence of anxiety, insomnia, and pain at diagnosis, while endocrine therapy and premenopausal status emerged as significant risk factors at year 4 after diagnosis [55].

Overall, these studies reinforce the notion that CRF should be addressed in the context of a patient-specific framework to systematically screen for CRF, with the overachieving goal of identifying both patients with severe fatigue at diagnosis to propose therapeutic interventions and patients at risk of developing severe fatigue over time to implement symptom monitoring and address modifiable risk factors.

Future research in the field should aim for better understanding the neurobiological mechanism underlying development and persistence of CRF to inform the design of novel therapeutic approaches for this prevalent symptom. Development of CRF is multifactorial and several risk factors identified in large cohorts are related to unhealthy behaviors that are, therefore, modifiable. Future interventions should evaluate whether early implementation of therapeutic approaches for CRF and targeting of modifiable risk factors is able to prevent development of severe fatigue in survivors at risk. Finally, considering that PROs represent the most reliable tool to adequately detect the subjective experience of CRF, integration in clinical practice of electronic solutions to periodically and remotely monitor survivors might offer the chance for early identification of patients with symptom deterioration to promptly offer supportive and therapeutic measures.

Infertility

A relevant number of young patients diagnosed with early BC receive gonadotoxic chemotherapy treatments [56], leading to a potential risk of premature ovarian insufficiency (POI) and consequent infertility [57].

International guidelines recommend adequate counseling on gonadotoxicity risk for patients diagnosed with cancer during their reproductive years, and treatment planning should guarantee access to fertility preservation techniques before treatment start for all of those are interested in these strategies [58, 59].

Medical Gonadoprotection

Administration of a gonadotropin-releasing hormone agonist (GnRHa) during chemotherapy is not a fertility preservation technique per se, but should be proposed to premenopausal patients that wish to preserve ovarian function and following cryopreservation options in those concerned about risk of infertility [58]. Medical gonadoprotection using GnRHa should start at least 1 week before cytotoxic chemotherapy with the aim of reducing the risk of POI and its fertility and endocrine-related consequences [58].

A systematic review and meta-analysis of 14 randomized trials in premenopausal patients with BC demonstrated the efficacy of this strategy [60]. Efficacy was also confirmed in a patient-level meta-analysis showing that risk of POI was significantly reduced by concurrent GnRHa administration during chemotherapy (POI rates 30.9% versus 14.1%, adjusted OR 0.38; 95% CI 0.26–0.57; $P < 0.001$) [61].

While a proper counseling of patients on the risk of developing POI with the use of chemotherapy is possible, to date there are no data in humans on the gonadotoxicity of new targeted treatments and on the safety of pregnancy following their administration [62]. Evidence in this regard is urgently needed, especially considering that new treatments approved in early BC (e.g., immune checkpoint inhibitors and PARP inhibitors) have shown to reduce ovarian reserve and reproductive potential in animal models [63, 64].

Fertility Preservation Techniques

Cryopreservation of oocytes/embryos following controlled ovarian stimulation (COS) is the first fertility preservation technique. Ovarian tissue cryopreservation is an alternative that can be proposed to patients who cannot receive COS, who cannot delay gonadotoxic therapy because of disease aggressiveness, or in prepuberal girls [59, 65].

Increasingly reassuring data on the safety of these techniques are emerging. A recent meta-analysis by Arecco et al. showed the safety of COS before the start of cancer treatment among 3980 patients [66]. COS was not associated with inferior outcomes in terms of risk of recurrence (RR 0.58, 95% CI 0.46–0.73), event-free survival (EFS, HR 0.76, 95% CI 0.55–1.06), or death (RR 0.54, 95% CI 0.38–0.76), neither in the overall population nor in the hormone-receptor positive subtype (HR for EFS 0.36, 95% CI 0.20–0.65). Most of the efficacy and safety data on cryopreservation options in young women with BC derive from single-center retrospective studies with a limited sample size. Results from multicenter prospective studies, such as the ongoing Italian PREFER study [67], are awaited to provide more solid answers on this topic.

In recent years, several studies have shown that pregnancy following proper treatment and follow-up is safe for both the mother and the baby [68], including in the case of prior history of hormone-receptor positive BC [69, 70]. Recently, the POSITIVE trial (NCT02308085) has also shown, at short-term follow-up, no alarming signals for a temporary interruption of endocrine therapy for up to 2 years in order to become pregnant for women ($\leq$ 42 years) who completed at least 18 months of endocrine therapy [71–74]. Longer-term follow-up from this trial will be crucial before revolutionizing our approach to endocrine therapy in all patients seeking to become pregnant.

The oncofertility counseling of patients with hereditary breast and ovarian cancer syndrome (HBOC) syndromes is complex considering the additional issues that they have to face, including the indication for risk-reducing gynecological surgeries at a young age [75]. Moreover, as shown in preclinical studies, carriers of *BRCA1/2* pathogenic variants (PVs) might have an accelerated involution of the ovarian follicular reserve leading to POI, an increased risk of aneuploidies, and ultimately, earlier menopause [76, 77].

The biological mechanism underlying this negative effect on reproductive potential is potentially related to DNA damage in the primordial oocytes that can occur in the form of both single- and double-strand breaks (DSBs) [78]. DSBs are the most deleterious damage that can result in failed rearrangements and chromosomal instability [79]. The relevance of this damage is particularly high in the presence of *BRCA1/2* PVs since ATM-pathway repair system is defective and inevitably leads to cell cycle arrest and apoptosis [80], resulting in an early reduction of ovarian reserve. Preliminary evidence in young women with BC suggests that *BRCA* carriers have worse ovarian reserve (measured with the levels of anti-müllerian hormone, AMH) at breast cancer diagnosis than women without genetic defects [81].

This observation has raised concerns of a possible higher risk of treatment-induced gonadotoxicity in *BRCA1/2* carriers compared with non-carriers, but very limited data are available [82–84]. Similarly, in the specific cohort of patients with BC carrying *BRCA* PVs, data on the efficacy and safety of the available options for fertility and/or ovarian function preservation [85–92] and on the safety of pregnancy after BC [82, 93, 94] are very limited. Further research focused on fertility- and pregnancy-related issues in *BRCA* carriers with BC is needed. Moreover, evidence on how to properly counsel young women with BC harboring other high-to-moderate penetrance genes is warranted.

Sexual Dysfunction

Available options for adjuvant endocrine therapy in premenopausal women include ovarian function suppression (OFS) in combination with an aromatase inhibitor or tamoxifen, or tamoxifen alone. Treatment should be tailored on individual risk of recurrence and patients' characteristics [95–97]. Addition of OFS to endocrine therapy has proven effective in reducing risk of recurrence and death in

premenopausal women diagnosed with high-risk disease [98].

However, OFS leads to a significant increase in side effects including hot flashes, sexual dysfunction, weight gain, musculoskeletal symptoms, bone density loss, depression, cognitive dysfunction, and fatigue [99, 100].

Consequently, an accurate evaluation of the risk–benefit ratio, discussion with patients, and availability of a framework [101] to address endocrine therapy-related side effects are fundamental aspects to consider when proposing addition of OFS in women who are premenopausal.

Sexual concerns are highly prevalent among survivors of BC and include different symptoms such as poor body image, sexual inactivity, vulvovaginal symptoms, low sexual desire, and reduced sexual satisfaction. These symptoms can be temporary or permanent and have a negative impact on QoL [21, 102]. Risk factors for reporting sexual concerns include OFS-related side effects, coexistence of anxiety and depression, and partner satisfaction [103, 104]. Radical breast surgery is certainly associated with poorer body image, which might negatively affect sexual health, but evidence of its direct impact on it is less compelling [103–106]. In a recent meta-analysis, breast reconstruction was associated with improved body image or satisfaction compared with mastectomy, but no difference was observed for sexual health, although relevant heterogeneity was observed among included studies [107].

Despite their prevalence and relevance for survivors, these concerns remain largely unaddressed, and only a small percentage of survivors are referred to specific counseling [108], although several strategies, both pharmacological and non-pharmacological, have proven effective in treating these disorders [101].

Local treatments using vaginal lubricants (water-based formulations, polycarbophil, and hyaluronic acid moisturizers) can provide support to treat genitourinary symptoms [109, 110]. Lubricants reduce friction and discomfort during penetrative sexual activity, and their availability, low cost, and irrelevant side effects make them a valid first approach to all survivors reporting sexual dysfunction and vaginal symptoms.

Whenever other pharmacological or non-pharmacological hormonal-free approaches fail, use of local estrogen can be considered. Absorption of local treatments varies by the amount of active ingredient applied and by the product's formulation, and these agents can cause an elevation of serum estradiol concentrations [111], which might be reason of concern in women receiving adjuvant endocrine therapy for BC [112]. Recently, results of an observational cohort of women receiving local or systemic estrogens for endocrine-related genitourinary symptoms have been reported. With a median follow-up of 9.8 years for recurrences and 15.2 years for mortality, the authors did not observe an increased risk of events in the general population, neither with administration of systemic nor local estrogens; however, an increased risk of recurrence was found in patients receiving aromatase inhibitors [113]. More robust data from studies investigating these strategies are needed to definitely establish safety of local estrogen treatments [114].

Ospemifene is a systemic oral selective estrogen receptor modulator approved for the treatment of moderate/severe menopause-related dyspareunia and vaginal dryness; despite its efficacy in the general population, there are no safety data to support its use in survivors of BC [114].

Aqueous lidocaine compresses applied to the vulvar vestibule before vaginal penetration can effectively reduce dyspareunia and sexual distress in patients receiving endocrine therapy. Lidocaine might, therefore, be a useful temporary strategy for patients reporting insertion pain [115].

The effect of vaginal laser for genitourinary symptoms related to sexual dysfunction (such as vaginal dryness, dyspareunia, vaginal itching, and burning) remains a topic to be further investigated. Results of single-arm cohorts have reported improvement in vaginal atrophy and related symptoms [116–118]. However, in a recent randomized clinical trial, no significant improvement of overall vaginal symptoms after use of laser was observed [119]. Several

additional trials are ongoing and will help to better place the role of vaginal lasers in this setting.

Injections of autologous platelet-rich plasma have also been reported to improve vaginal atrophy and sexual distress in survivors; however, additional evidence is needed before this approach can be considered in clinical practice [120].

Several trials have evaluated the role of cognitive behavioral therapy in survivors facing sexual dysfunction, reporting improvements in overall sexual function, sexual desire, arousal, and vaginal lubrication, as well as improvement in sexual pleasure, discomfort during sex, and sexual distress [121]. Telephone counseling intervention or in-person 6-week sexual life reframing programs (including interventions not only on psychological but also on physical aspects of sexual health) have also shown to have a positive effect on sexual dysfunction [122, 123]. On the basis of available evidence, cognitive behavioral therapy should be highly encouraged for survivors facing sexual dysfunction. Dedicated and experienced counseling in this regard should be made available to all patients facing these side effects.

Considering that there are no clear data on the safety of locoregional hormonal treatments in patients reporting sexual dysfunction during endocrine therapy, non-hormonal approaches should always be the first option for the management of genitourinary symptoms. However, pharmacological strategies using temporary application of low-dose local estrogens may be considered in the case of severe and refractory symptoms after careful discussion with the patient about the risk–benefit ratio.

Future research and education in the field of sexual dysfunction is needed. First, determinants and risk factors should be further elucidated using data from prospective studies, particularly to assess the impact of different surgical and reconstructive techniques on long-term outcomes of sexual health. Second, the approval of novel agents in the adjuvant setting could potentially modify incidence and severity of this toxicity; therefore, clinical trials should collect high-quality data to allow for adequate counseling. Third, personal and cultural barriers of patients and physicians might hamper appropriate management of sexual dysfunction; additional education and awareness are needed to quickly capture sexual dysfunction onset to address causes and promptly treat patients or refer them to gynecologists or sexologists. Finally, additional data regarding the safety of local hormonal treatments for patients diagnosed with hormone receptor-positive (HR+)/HER2-negative (HER2−) are needed, considering their efficacy when non-hormonal therapies are ineffective.

WELL-BEING PROMOTION

Weight Management

Approximately 50% of patients are overweight at BC diagnosis, and over 25% experience substantial weight gain (≥ 5% of baseline) by year 4 post-diagnosis [124, 125].

Clinicobehavioral factors for weight gain after diagnosis include younger age at diagnosis, lower pretreatment body mass index (BMI), receipt of chemotherapy, chemotherapy-induced menopause, reduced energy expenditure, and excess caloric intake [126–128].

BC treatments may also alter body composition [129] and lead to metabolic (e.g., reduction of adiponectin and elevation of leptin and resistin) and inflammatory (e.g., elevation in CRP, IL6, IL2, TNFα) alterations that could trigger or accelerate weight gain [130]. A genetic predisposition may also play a role in the risk of gaining weight, as previous data showed a link between SNPs in fat mass and obesity-associated protein gene (FTO), adiponectin gene (ADIPOQ), and its receptor (ADIPOR1) with obesity and BC [131, 132].

Several studies demonstrated a link between excess weight at diagnosis, weight gain after BC treatment, and poorer outcomes among survivors of early-stage BC [133]. Moreover, obesity and weight gain increase risk of cardiovascular disease, severe treatment-related sequelae, deterioration of QOL [134], and impaired social reintegration [135].

Additionally, the prognostic impact of BMI has been identified in several studies and most

of them showed that being obese at any time (e.g., before, at, and after BC diagnosis) is associated with poorer prognosis in terms of recurrence rate, disease-specific, and overall survival [136–139].

The most extensive meta-analysis evaluated data from 82 studies and reported relative risks (RRs) of 1.41 (95% CI, 1.29–1.53) and 1.35 (95% CI, 1.24–1.47) for breast cancer-specific mortality and overall mortality, respectively, for patients who were obese at diagnosis compared with normal weight. Lower RRs were observed for patients who were overweight, who were still significantly at higher risk compared with those with normal weight. Furthermore, a linear relationship between BMI at diagnosis and outcomes was observed with RRs of 1.17 and 1.18 for total mortality and breast-cancer-specific mortality, respectively, for each 5-unit increment of baseline BMI. Similarly, weight gain after BC diagnosis was associated with higher risk of BC recurrence (HR 1.24, 95% CI, 1.00–1.53) and weight loss with lower risk (RR 0.67, 95% CI, 0.42–1.05), although these last data were not significant and not confirmed in other studies [140].

Overall, the role of intentional weight loss in overweight and obese survivors in improving oncological outcomes after BC diagnosis remains to be determined. The Breast cancer WEight Loss Study (BWEL, NCT02750826) is a clinical trial that randomized overweight and obese survivors of BC (baseline BMI $\geq$ 27 kg/m^2) to a telephone-based intervention versus a health educational control to test the effect of weight loss on invasive disease-free survival (iDFS); accrual has been completed and results of the study will provide more information on this specific aspect [141].

Similarly to BWEL, several studies investigated the role of weight loss interventions based on behavioral and lifestyle changes to improve energy balance by reducing caloric intake and increasing physical activity and energy expenditure [142, 143]. Multimodal behavioral interventions are associated with the most significant and sustained weight loss, while also improving health-related outcomes and QOL [144]. Data from the CANTO cohort also confirmed that obese survivors of BC losing weight after primary treatment had lower odds of reporting dyspnea, breast symptoms, and deterioration in physical functioning compared with survivors with stable or increasing weight [125].

Recently, several studies suggested that digitally-delivered weight loss interventions, including both self-managed and provider-based solutions, are effective and safe for survivors of BC [145]. Nevertheless, despite the proven efficacy of weight management interventions, several limitations to their implementation exist, including high heterogeneity in adoption of behavioral weight loss strategies, overtime adherence, and long-term post-intervention maintenance of lifestyle changes [143].

Current guidelines state that survivors of BC should aim at achieving and maintaining a healthy weight through increased physical activity and healthy dietary habits, adopting recommendations from cancer prevention programs [17, 18, 146].

Future research in the field should focus on improving prediction of weight gain risk after BC, as well as integrating biological data, on patients' stratification on the basis of adoption of weight loss interventions and on improving integration of digital solutions to deliver them and promote sustained behavioral change. Finally, the use of digital solutions may facilitate and accelerate research toward the use of body composition analysis, which might provide additional information on survival outcomes when compared with BMI evaluation [147].

Physical Activity

Survivors of BC should be encouraged and counseled toward adoption of a healthier lifestyle that includes at least 150 min per week of physical exercise including both aerobic and resistance training, with an ideal target of 300 min per week [18, 146, 148].

The beneficial effect of engaging in physical activity have been proven both during active treatment and over the course of the survivorship trajectory.

Active Treatment Phase

Exercise during active treatment is safe, although a medical evaluation could be considered to tailor training type and intensity based on individuals' characteristics [149].

Patients with BC engaging in higher level of physical activity during cancer treatment experience improvement in cardiorespiratory fitness [150], physical function [151], and quality of life [152], and less severe treatment-related side effects including fatigue [153], anxiety and depression [152]; conversely, conflicting evidence exists on the impact of exercise in facilitating chemotherapy completion and maintaining chemotherapy dose intensity [154, 155].

Survivorship Trajectory

Consistent evidence suggests that higher levels of physical activity before and after diagnosis of BC are associated with improved survival outcomes.

A recent meta-analysis showed that pre-diagnosis level of physical activity has an inverse dose–response relationship with both breast-cancer-specific and overall mortality. Specifically, a significant reduction in breast cancer (HR 0.86, 95% CI, 0.78–0.94) and overall mortality (HR 0.82, 95% CI, 0.76–0.87) was observed in survivors with the highest levels of physical activity compared with the lowest. Additionally, this relationship was observed both for recreational (i.e., physical activity undertaken for the sake of exercise) and total physical activity (i.e., including occupational, household, and transportation physical activity) [156].

A positive association between improved clinical outcomes and appropriate levels of physical activity has been observed post-diagnosis and along the survivorship trajectory, with a higher magnitude of risk reduction compared with pre-diagnosis physical activity.

Friedenreich et al. conducted a meta-analysis investigating associations between risk of death and physical activity in cancer survivors. Among survivors of BC, the meta-analysis showed a significant reduction in breast cancer-specific mortality (HR 0.63, 95% CI, 0.50–0.78) and overall mortality (HR 0.58, 95% CI, 0.52–0.65) for the most active survivors, irrespective of BMI at diagnosis. Levels of physical activity showed a positive dose–response relationship with survival outcomes and risk of death showed a significant decline starting from 10 metabolic equivalent (MET) hours per week, which corresponds to approximately 3 hours of light walking per week, consistent with current recommendations [156].

A meta-analysis by Lee et al. specifically explored the association between recommended levels of physical activity and prognosis. Results of the study showed that survivors adhering to recommendations experienced a risk reduction of 21% and 28% in breast cancer-specific and all-cause mortality, respectively [157].

Although adherence to recommendations confers the greatest benefit, another meta-analysis showed that even low amounts of physical activity are associated with reduced mortality (HR 0.60, 95% CI, 0.50–0.69), although only three studies looked specifically at survivors of BC [158].

Several studies investigated the effect of reducing physical activity and of sedentary behavior after BC diagnosis. One meta-analysis of two prospective studies found a significant increase in the risk of all-cause mortality for survivors of BC who decreased their levels of physical activity after diagnosis (RR 2.36, 95% CI, 1.09–5.12) [157]. In one prospective cohort study including more than 8000 cancer survivors, total sedentary time, evaluated through the use of accelerometers, was associated with increased risk of cancer mortality when comparing survivors in the third (HR 1.52, 95% CI, 1.01–2.27) and second tertile (1.45, 95% CI, 1.00–2.11) with those in the first [159]. Similarly, in a prospective cohort of more than 1500 cancer survivors, self-reported levels of physical inactivity were associated with worse survival outcomes. Survivors sitting for more than 8 h/day, compared with those sitting less than 4 h, had higher risk of all-cause (HR 1.81, 95% CI, 1.05–3.14) and cancer-specific mortality (HR 2.27, 95% CI, 1.08–4.79) [160]. Finally, recent data from the CANTO cohort suggested an inverse association between levels of physical activity and QOL deterioration among survivors of BC who received adjuvant chemotherapy.

Using data from more than 4000 survivors, patients were clustered in four distinct trajectories on the basis of self-reported QOL evaluated through the EORTC QLQ-C30 questionnaire: excellent (51.7%), very good (31.7%), deteriorating (10.0%), and poor (6.6%). Patients with deteriorating and poor QOL trajectories were more frequently non-adherent to physical activity recommendations and had reduced levels of physical activity over the survivorship trajectory [161].

Overall, considering the positive benefits associated with physical activity, survivors should be counseled on meeting current exercise recommendations and eventually referred to specific programs of adapted physical activity. Several limitations remain to be addressed in the field. The use of passively collected physical activity data through electronic devices (smartphones, smartwatches, and accelerometers) could improve reliability of findings compared with self-reported questionnaires on physical activity. Despite recommendations, the overall levels of physical activity in survivors of BC remain suboptimal. Data from the CANTO cohort showed that more than 30% of survivors were insufficiently active at years 1 and 2 after diagnosis [125], and several barriers explaining this low adherence to recommendations have been described [162, 163]. Future research should aim at designing tailored interventions that take into account patient preferences and individual characteristics as well as self-management solutions to improve adherence to recommendations.

SMOKING AND ALCOHOL CESSATION

Smoking Cessation

Patients diagnosed with BC as well as survivors of BC who have an active smoking habit should be advised to avoid smoking and eventually be referred to smoking-cessation programs [17].

Active smokers have a significantly lower overall and breast cancer-specific survival (HR 1.33, 95% CI: 1.12–1.58) compared with former and never smokers [164]. Appropriate screening of survivors with a former or active smoking habit is fundamental considering that smoke is one of the main risk factors for a number of malignancies, including lung, esophagus, and head and neck, and that survivors with heavy smoking history could be referred to specific screening programs for lung cancer [165].

In addition to inferior oncological outcomes, smoking confers higher risk of several treatment-related complications including higher symptom burden during adjuvant chemotherapy, increased rate of surgical complications, worse physical, social, and emotional functioning, cognitive deterioration, sleep and mood alterations, and accelerated aging [36, 166–170]. Active smoking habit at diagnosis was associated with increased odds of reporting poor QOL at diagnosis, at 2 years, and 4 years after in a cohort of survivors of BC receiving adjuvant chemotherapy compared with never smokers (OR 1.82, 95% CI 1.49–2.22) [161]. Similarly, being a current or former smoker at diagnosis conferred increased odds of reporting severe pre-treatment fatigue at diagnosis and persistent severe fatigue at 2 and 4 years thereafter compared with never smokers (OR 1.65, 95% CI 1.26–2.15); interestingly, smoking status emerged as a relevant risk factor not only for global fatigue, but also for the physical, emotional, and cognitive dimensions [54].

Despite the existence of public policy in place to reduce smoking in the general population and of specific recommendations regarding smoking cessation in survivors of BC, approximately 15–20% of patients are active smokers at diagnosis and around 10% of them maintain this unhealthy habit along the survivorship trajectory [125, 171, 172]. Furthermore, when looking specifically at smoking discontinuation rates after BC diagnosis, the available evidence consistently identifies a proportion of survivors who continue smoking, and some studies reported higher prevalence of smoking habits at longer follow-up [172]. Increased awareness among oncologists and primary care physicians in referring patients to smoking-cessation programs are needed.

Alcohol Cessation

The latest World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) summary report identified alcohol consumption as a significant risk factor for BC development, in both pre- and post-menopausal women, and a significant dose–response association was identified [173]. Current dietary recommendations for survivors of BC suggest that, similarly to what is recommended for cancer prevention, alcohol consumption should be avoided or at least limited [146].

Evidence regarding the association between alcohol intake and BC outcomes is inconsistent. Higher pre-diagnosis alcohol consumption was associated with increased risk of BC recurrences in two studies [174]. Only one study reported an association between higher post-diagnosis intake (≥ 6 g/day versus no consumption) and recurrence rate (HR 1.35, 95% CI, 1.00–1.83) [175]. After pooling results from two other studies, no association between consumption ≥ 6 g/day and recurrence was observed in the overall population, but a significant risk increase was observed among women who were postmenopausal (HR 1.19, 95% CI, 1.01–1.40) [174]. When looking specifically at the risk of late recurrences (i.e., ≥ 5 years from diagnosis) an increased risk of recurrence was observed among women consuming at least one drink per day compared with non-drinkers (HR 1.28, 95% CI, 1.01–1.62) [136]. No significant association between higher alcohol intake and overall mortality was observed [136, 176].

Unhealthy alcohol consumption appears to be prevalent in survivors of BC, reported by approximately 10% of patients at diagnosis and persisting in the vast majority of them along the survivorship trajectory [125, 177]. Factors associated with persistent unhealthy behavior include older age, depression, higher education, and partnered status [125].

Frequent alcohol consumption has been linked with increased risk of developing second non-breast cancers [173] as well as higher incidence of cardiometabolic diseases and obesity [178], osteoporosis [179], vasomotor symptoms, and poor sleep quality [180]. Furthermore, higher alcohol consumption frequently clusters with other unhealthy behaviors, including smoking habits [181], suggesting the need for additional health education in a subset of patients persisting in multiple unhealthy behaviors that might negatively impact outcomes over the survivorship trajectory.

SURVEILLANCE FOR RECURRENCES

Survivors of BC are at risk of developing local, regional, and distant recurrences as well as second primary cancers. Consequently, surveillance for early diagnosis and treatment of these recurrence events is a fundamental domain of survivorship care.

Current guidelines recommend a follow-up protocol based on physical examination, yearly mammograms, and additional tests based on previous and ongoing medical treatments (e.g., echocardiogram for previous anthracycline-based chemotherapy and/or anti-HER2 therapy exposure or laboratory tests to monitor endocrine therapy side effects). Imaging tests are indicated only to investigate symptoms potentially related to recurrence [56, 182]. This approach is supported by trials and meta-analyses that demonstrated no survival benefit from systematic imaging testing to identify recurrences in survivors of BC [183]. A recent study showed that asymptomatic imaging positively impact on BC death only in the HER2+ and triple-negative subtypes, while no benefit was seen in the HR+ subgroup [184]. Patterns of relapse over time vary significantly according to BC subtype and for the HR+ subtype it is constant over time with late relapses occurring up to 20 years from diagnosis [185].

New surveillance strategies to identify recurrences while reducing radiation exposure are needed to improve outcomes of BC survivors.

ctDNA

Recently, detection of circulating tumor DNA (ctDNA) has emerged as a potential tool to personalize adjuvant treatments and surveillance strategies. ctDNA refers to the part of circulating cell-free DNA (cfDNA) originating from tumor tissue that can be identified in several

biological fluids, although the most used is blood [186].

Currently, administration of adjuvant treatment after surgery is based on tumor–node–metastasis (TNM) staging, additional histopathological risk factors and results of genomic signatures. Identification of ctDNA after surgery (frequently referred to as molecular residual disease, MRD) might help stratify patients according to the expected risk of recurrence and thus potentially allow for the personalization of adjuvant therapies using (de)-escalation approaches. This approach was recently tested in a randomized clinical trial in stage II colon cancer and showed safety of a ctDNA-based approach to guide decision in adjuvant treatment without increasing risk of recurrence [187].

In early BC, detection of ctDNA after surgery has shown ability to predict risk of relapse and survival outcomes after surgery and (neo)adjuvant chemotherapy, both using a single timepoint and with serial monitoring [188–192]. Interestingly, ctDNA identification appears to retain predictive value for late recurrences as well. In a recent study, patients with HR+ stage II–III BC free from recurrence at least 5 years from diagnosis underwent serial evaluation of ctDNA with a personalized assay based on the genomic landscape of the primary tumor. The study demonstrated that detection of MRD predicted development of distant metastasis with a median diagnostic anticipation of 1 year [193].

Recently, results of the phase II multicenter c-TRAK-TN (NCT03145961) study have been reported. The study enrolled 208 patients who completed treatment for triple-negative breast cancer and started thrice monthly ctDNA-based surveillance. Rate of MRD at 12 months, the primary endpoint of the study, was 27.3%, and 72% of the patients already had metastatic disease at time of ctDNA positivity [194]. These results will be fundamental to design future studies, considering that several clinical trials (Table 1) are evaluating the use of ctDNA to inform surveillance protocols and de-escalating or escalating adjuvant treatments on the basis of MRD identification.

Brain Metastases

Brain metastases negatively impact the prognosis of BC: expected survival ranges from 6–36 months, depending on several prognostic factors including age, performance status, number of brain metastases, molecular subtype, and presence of concomitant extra-cranial disease [195, 196].

Despite the prognostic implications, the high risk of their development in specific subgroups, and the current availability of effective local and systemic treatments, imaging to detect brain metastasis is recommended only in the presence of symptoms suggestive of central nervous system (CNS) involvement, both at staging and during surveillance [56, 182].

Main factors associated with the risk of developing brain metastasis include disease stage and type of metastatic involvement, molecular subtype, and age. In metastatic BC, 15% of patients present with brain metastases at diagnosis; in patients without CNS involvement at diagnosis, 25% will subsequently develop brain metastases after a median of 2–3 years; conversely, in early BC, the estimated incidence of brain metastases is around 3% [197, 198]. Subtype is a major risk factor for brain metastasis development. In a cohort of 1434 patients treated with curative intent, brain metastases were observed in 2.5% of patients overall; however, the risk of brain metastasis at 10 years was highly dependent on BC subtype, ranging from 0.7% in low-intermediate grade HR+/HER2− to 7% in HR−/HER2− and 12% in the HR−/HER2+ subtypes [199]. Similar results are observed in advanced disease where 15%, 30%, and 50% of patients with HR+ , HR−/HER2−, and HR−/HER2+ subtypes are expected to develop brain metastases, respectively [200].

In the HER2+ subtype, brain metastases frequently represent the first site of relapse, even in the absence of extracranial metastases. Among 3400 women randomized in the HERA trial to receive adjuvant trastuzumab or no anti-HER2 therapy [201], CNS involvement as first site of recurrence was around 2% in both treatment arms at 4 years of follow-up [202]. The KATHERINE trial in patients with residual disease after neoadjuvant chemotherapy

Table 1 Ongoing clinical studies testing ctDNA-based surveillance and treatment strategies in early-stage breast cancer

Trial number	No. of patients	Setting	Timing of ctDNA test	Primary endpoint	Study intervention/objective
NCT05058183	400	Adjuvant—Stage I HER2+ and TNBC	Before and after surgery	Incidence of pts with positive ctDNA after surgery	Chemotherapy de-escalation in case of negative ctDNA
NCT04768426	25	Adjuvant—TNBC receiving adjuvant capecitabine	Baseline and 6 months	Detection of ctDNA at baseline and 6 months	Identification of patients not benefiting from capecitabine
NCT04530890	1000[a]	Adjuvant and neoadjuvant	Start of treatment, during treatment, at progression	Prognostic impact of ctDNA on mortality	Evaluation of the prognostic role of ctDNA on risk of death
NCT04567420	100	Adjuvant—Stage II–III HR+/HER2− BC at high risk of relapse	Every 4/6 months concomitant to follow-up visits	ctDNA positivity and RFS	Patients receiving adjuvant endocrine treatment with ctDNA positivity will be randomized to fulvestrant and palbociclib or to continue standard of care treatment
NCT03357120	180	Surveillance after neoadjuvant chemotherapy	After surgery and every 6 months thereafter for 5 years	Prognostic impact on RFI at 3 years	NA
NCT04985266 (TRAK-ER)	1100	Adjuvant—HR+/HER2− at high risk of relapse	Every 3 months for up to 3 years	Incidence of ctDNA detection during surveillance and RFS	Patients with ctDNA detection under endocrine therapy and without evidence of metastasis will be randomized to fulvestrant and palbociclib or standard endocrine therapy
NCT04501523 (Apollo)	460	Adjuvant—TNBC with and without RD	Baseline, after NACT, and after surgery	5-year DFS	Patients with ctDNA detection will be randomized to adjuvant therapy with capecitabine ± tislelizumab
NCT04849364 (PERSEVERE)	197	Adjuvant—TNBC with RD	After surgery	2-year DFS	Patients with residual disease after neoadjuvant chemotherapy and with ctDNA detection will be randomized to different treatments on the basis of identification of genomic targets

Table 1 continued

Trial number	No. of patients	Setting	Timing of ctDNA test	Primary endpoint	Study intervention/objective
NCT05512364 (EORTC – Treat ctDNA)	220	Adjuvant—Stage IIB and III HR+/ HER2−	Baseline and every 6 months for up to 3 years	DMFS	Patients with ctDNA detection under endocrine therapy and without evidence of metastasis will be randomized to elacestrant or standard endocrine therapy
NCT03709134	100	Neoadjuvant	NA	pCR	Determination of the prognostic and predictive role of genomic markers
NCT04803539 (Artemis)	260	Adjuvant—TNBC	After surgery and/or adjuvant chemotherapy	iDFS	Patients with positive ctDNA will be randomized to capecitabine ± camrelizumab + apatinib
NCT05433753 (Harmony)	60	Surveillance—Stage IIA–IIIC HER2+	NA	iDFS	Identify a relation between ctDNA detection and recurrence
NCT03285412 (Leader)	120	Adjuvant—HR+/ HER2−	Baseline	ctDNA clearance	Patients with ctDNA detection will receive ribociclib in addition to standard adjuvant endocrine therapy
NCT04915755 (ZEST)	800	Adjuvant—TNBC and HER2− BC with BRCA 1/2 mutations	Longitudinal monitoring of ctDNA after surgery or adjuvant treatment	DFS	Patients with ctDNA detection will be randomized to treatment with niraparib for 3 years or placebo
NCT05388149	15	Adjuvant—Stage I–III HER2+	After 2–6 cycles of T-DM1	ctDNA clearance	Patients with ctDNA detection will receive adjuvant neratinib and T-DM1
NCT04434040 (ASPRIA)	40	Adjuvant—TNBC with residual disease	After completion of all local and neoadjuvant therapies	ctDNA clearance after 18 weeks	Patients with ctDNA detection will receive adjuvant atezolizumab and sacituzumab govitecan

ctDNA circulating tumor DNA, *TNBC* triple-negative breast cancer, *pCR* pathological complete response, *RFS* relapse-free survival, *RFI* relapse-free interval, *RD* residual disease, *NACT* neoadjuvant chemotherapy, *DFS* disease-free survival, *DMFS* distant metastasis-free survival, *iDFS* invasive disease-free survival

[a]Including patients with digestive and gynecological malignancies as well

demonstrated no differences in brain metastasis rate between patients receiving trastuzumab or T-DM1 (~ 5% in both arms); CNS was the only site of recurrence in 4.8% of patients in the T-DM1 arm versus 2.8% with trastuzumab [203].

Whether the increased risk of brain metastases in patients with HER2+ is due to improved disease control leading to increased survival, to a biological predisposition of HER2+ clones for the brain, or to poor penetration of monoclonal antibodies across the blood–brain barriers is still a matter of debate [204].

Molecular structure of tyrosine-kinase inhibitors (TKI) allows for better penetration in the CNS. However, in the ALTTO trial, investigating the addition of lapatinib to trastuzumab as adjuvant treatment for HER2+ disease, CNS involvement as first site of relapse (~ 2%) was identical between patients treated with lapatinib plus trastuzumab or trastuzumab alone [205].

The ExteNET trial evaluated the role of adjuvant neratinib after adjuvant chemotherapy and trastuzumab. At the final report with a median 8 years of follow-up, incidence of brain metastases was slightly lower in the neratinib arm (1.3%) compared with the placebo (1.8%) [206].

Risk of CNS involvement for patients diagnosed with HR−/HER2− BC is highly dependent on stage at diagnosis. Approximately 3%, 5%, and 10% of patients diagnosed with stage I, II, and III, respectively, will develop brain metastases as first site of recurrence at 5 years from diagnosis, and the cumulative incidence of brain metastases over the natural history ranges between 25% and 45% [199]. Interestingly, in the TNBC subtype, occurrence of brain metastases is usually associated with systemic disease progression [207].

TNBC is frequently associated with germline pathogenic variants (PVs) in the BRCA genes; however, whether harboring a PV increases risk of brain metastasis is debated as conflicting results have been reported in the literature, mainly from retrospective cohorts [208–210]. Recently, the PARP inhibitor olaparib has been approved in TNBC and HR+/HER2− breast cancer as adjuvant treatment for BRCA carriers with high-risk disease after (neo-)adjuvant chemotherapy. Olaparib significantly improved DFS and OS in the intention-to-treat population, and a lower rate of brain metastases as first site of recurrence was observed in patients treated with olaparib (2.6%) compared with placebo (4.2%) [10, 211].

Overall, future research in this field should be focused on refined identifications of patients at risk of developing brain metastases, development of personalized surveillance protocols, identification and integration of novel biomarkers for CNS disease, and assessment of the potential protective role of novel agents that reported high efficacy data on CNS involvement in the metastatic setting (e.g., tucatinib and trastuzumab deruxtecan in the HER2+ setting).

Hereditary Cancer Syndromes

Approximately 10% of all diagnosed BC cases are related to HBOC, defined by the presence of a suggestive family history and identification of germline PVs in genes that increase the risk of developing breast and/or ovarian cancer [75, 212, 213]. According to the increased risk of tumor development, high- (e.g., *BRCA1*, *BRCA2*, *PALB2*, *TP53*) and moderate- (e.g., *ATM*, *CHECK2*, *RAD51C*, *RAD51D*) risk genes have been identified [214, 215].

Identification of PVs associated with HBOC holds several medical and psychological implications for patients, survivors, and unaffected relatives. The main aspects related to identification of HBOC include: tailored medical treatments in *BRCA1/2* carriers and risk management of breast and ovarian cancer as well as of other malignancies based on the identified PV, management of estrogen-deprivation associated sequelae after risk-reducing bilateral salpingo-oophorectomy (RRBSO), fertility, and psychological issues [75].

Risk management strategies for BC in PV carriers include bilateral risk-reducing mastectomy (BRRM), risk-reducing medications, and intensified screening [75]. Adequate counseling for PV carriers is fundamental when HBOC is identified, and should include appropriate

discussion regarding individualized risk and physical, psychological, and social consequences of each risk-reducing strategy [75].

The most effective strategy for BC risk management is represented by BRRM [216]. Radical risk-reducing surgery can be proposed to all carriers of PVs in high-risk genes, although individual risk assessment should be carefully weighed against the risk and complications to assure informed decision-making [217, 218]. The only effective strategy available for risk management of ovarian cancer is RRBSO [219, 220]. There is no effective screening strategy for ovarian cancer in PV carriers, although current guidelines recommend transvaginal ultrasound and Ca125 testing every 6 months in patients not receiving RRBSO [75].

Intensified screening has been evaluated in the context of retrospective studies that proved its efficacy in early identification of BC, improved outcomes [221], and cost-effectiveness [222].

Adequate planning of intensified screening should include: age of screening onset (based on age at diagnosis in the youngest affected family member), screening intervals (based on the HBOC gene identified), and imaging modality [75].

All international guidelines indicate that surveillance of carriers harboring PVs in high-risk genes should include magnetic resonance imaging (MRI) [223, 224], but screening intervals and duration vary significantly across guidelines [75, 225, 226]. Annual MRI among carriers of high-risk PVs between 30 and 49 years of age is recommended by all guidelines [75, 225, 226]. Extension of MRI screening after 50 years is more debated as some guidelines indicate that annual mammography could be sufficient as surveillance technique with the exclusion of carriers with dense breast tissue [225], while others indicate the need for continued annual MRI surveillance as long as carriers are in good health status [227], since breast density is not the only determinant of lower sensitivity of imaging techniques [75, 226].

Recent data suggest the potential interest of further intensifying surveillance in *BRCA1* carriers using MRI every 6 months [228] considering the aggressive biology and rapid growth rates of BC associated with PVs in this gene.

Future research in this field should be directed toward improved and individualized risk definition, potentially using single nucleotide polymorphisms (SNPs) in the context of polygenic risk scores (PRS) to further refine surveillance and risk-reducing strategies [229, 230]. Application of liquid biopsy in patients with PVs might be highly relevant for early detection of malignancies that are diagnosed in advanced stage in the interval between screening exams (e.g., pancreatic cancer) or without reliable screening strategies (e.g., ovarian cancer). However, the diagnostic accuracy of these techniques is not optimal, false positives are common, and these strategies should be further validated before introduction in clinical practice [231].

DISCUSSION AND FUTURE PERSPECTIVES

Long-term prognosis of BC has significantly improved in the last 40 years. However, alongside the striking improvement in clinical outcomes, treatments for BC have a substantial risk of long-term physical and psychosocial sequelae that negatively impact QoL.

Several barriers to delivering high-quality survivorship care exist, including lack of awareness among physicians on the long-term consequences of BC treatments and their management, shortage of human and financial resources to refer survivors toward supportive care and behavioral interventions, and lack of a comprehensive and multidisciplinary approach.

Future research should aim at upfront identification of the multifactorial and multidimensional determinants of long-term *sequelae* to move toward more personalized surveillance and management strategies. Lack of high-quality, multimodal, and prospective data still represent a significant limitation in the field and reinforce the need for a collaborative research effort to improve the quality of survivorship research, particularly in the strengthening of methodological quality and analytic standards

for QoL studies, but also in collecting high-quality, multimodal data that integrate multiple sources and intersect biology data with clinical and patient-reported ones. Contemporary longitudinal cohorts of survivors of BC such as CANTO (NCT01993498) [53] and the Young Women's Breast Cancer Study (YWS, NCT01468246) are examples of real-world efforts that integrate biological, clinical, and patient-reported data to address these limitations.

Understanding determinants of long-term *sequelae* could also help accelerate interventional research in the field by developing novel approaches for long-lasting toxicities with more limited management options such as cognitive dysfunction and neuropathy.

Additionally, interventional research in the field should be focused on evaluating the efficacy of lifestyle interventions on the basis of behavioral change in mitigating long-term sequelae of BC treatment in underrepresented populations, including carriers of PVs, and on implementing coordinated research efforts to test in a reliable and high-quality framework the potential benefit of non-pharmacological strategies, including complementary and alternative medicine solutions.

Research in the field should also focus on determining the feasibility, acceptability, and efficacy of different models of delivering survivorship care on the basis of patients' individual needs and ability to self-manage. Self-management involves behavioral change and ability to apply different tasks that pertain to medical, emotional, and role management, and is an essential pillar in the management of several chronic diseases [232, 233]; it could be appropriate for cancer survivors as well, although less evidence on the topic is available in this setting [145]. Testing the implementation of novel models of care in empowering cancer survivors to self-manage the consequences of treatments over the course of the survivorship trajectory could improve health outcomes and optimize the use of resources [234]. However, ability to self-manage is strictly dependent on self-efficacy, defined as the patient belief in their capacity to self-manage, and on health literacy. Future study should stratify patients on the basis of these characteristics to assess whether personalized models of care can be implemented in clinical practice.

Development of digital health solutions has increased steadily in recent years and some of these solutions have also been evaluated in survivors of BC [235], proving effective in the management of several symptoms including fatigue, menopausal symptoms, sexual dysfunction, weight gain, cognitive dysfunction, and emotional distress [121, 236–241]. Digital health solutions could allow continuous assessment over time, intercepting patients with deteriorating symptoms or quality of life that could then be referred to digitally delivered self-management interventions, in-person interventions, or to a medical evaluation, on the basis of severity of deterioration.

CONCLUSIONS

Future research in the survivorship field should aim at better defining the needs and psychosocial profile of cancer survivors in terms of risk of long-term toxicities, adoption of behavioral and digital interventions, self-efficacy in managing consequences of cancer care, and health literacy. These research efforts would ultimately allow for the development and implementation of personalized care models able to simultaneously tackle consequences of cancer care and optimize resources by providing the best framework and tools based on survivors' characteristics.

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