BIOCELL
2022 46(10): 2221-2223

Tech Science Press

Biomarkers for targeted rehabilitation strategies after breast cancer: Proposal for the next-generation management of survivorship issues

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Key words: Breast cancer, Biomarkers, Survivorship, Rehabilitation, Precision medicine

Breast cancer (BC) is the most common malignant tumor and one of the top causes of cancer-related death worldwide (Sung *et al.*, 2021). The recent advances in early tumor diagnosis coupled with more effective treatment strategies resulted in a steady increase of long-term survivors (Nardin *et al.*, 2020; Invernizzi *et al.*, 2022). These improved survival rates led to a significantly higher incidence of disabling complications related to breast cancer and/or its treatment (Invernizzi *et al.*, 2020a; D'Egidio *et al.*, 2017; Zhong *et al.*, 2020). These conditions have detrimental effects on patients' health status, leading to a high burden of psychological suffering, functional impairment, and reduced health-related quality of life (HRQoL) (Sunilkumar *et al.*, 2021). Not dissimilarly from the tumor, the diagnosis and treatment of survivorship issues require a precision medicine approach (Ballinger *et al.*, 2021).

Only recently HRQoL became an integral part of the healthcare system and component of modern treatment strategies and translational studies design (Cheng *et al.*, 2017). The ability to precisely assess and define HRQoL determines the success of oncological rehabilitation interventions in breast cancer (Rick *et al.*, 2017). During the past few years, our research groups promoted a paradigm shift for the management of HRQoL issues in breast cancer survivors. This approach, both for translational research and clinical practice, is biomarker-based, akin to that for the management of the neoplasm itself (Pagni *et al.*, 2019; Criscitiello *et al.*, 2022; Pal *et al.*, 2021; Fusco *et al.*, 2021). In particular, we identified relevant subclasses of patients that could benefit from targeted rehabilitation strategies among the major HRQoL issues in breast cancer survivors. We focused our attention on breast cancer-related lymphedema (BCRL) (Invernizzi *et al.*, 2018; Invernizzi *et al.*, 2019; Michelotti *et al.*, 2019; Invernizzi *et al.*, 2020b; de Sire *et al.*, 2021), axillary web syndrome (de Sire *et al.*, 2020a), cancer treatment-induced bone loss (Venetis *et al.*, 2021; Invernizzi *et al.*, 2020c), aromatase inhibitor-induced arthralgia (Grizzi *et al.*, 2020; de Sire *et al.*, 2020b), and cancer related fatigue (Invernizzi *et al.*, 2020d). More in detail, BCRL (i.e., localized retention of lymph, interstitial fluids, and proteins in the subcutaneous tissue of the upper limb after axillary dissection and/or radiation treatment) is an extremely disabling and progressive condition that affects ~20% of breast cancer survivors (Gillespie *et al.*, 2018). Recently, single nucleotide polymorphisms in ctDNA have been documented in BCRL patients, suggesting a possible role for individual predisposition in the development of BCRL (Hadizadeh *et al.*, 2018; Smoot *et al.*, 2017). These genes include lymphangiogenic and angiogenic genes (e.g., LCP2, NRP2, NFKB2), pro-inflammatory (e.g., IL1, IL2, IL8, IL17, NFKB2) and anti-inflammatory (e.g., IL4, IL10, IL13) cytokines, connexins, and potassium channel genes (e.g., KCNA1, KCNJ3, KCNJ6, KCNK3). Of note, specific biological characteristics of the primary tumors (e.g., laterality, lymph-vascular invasion, and extracapsular extension of the lymph node metastasis) can be employed as risk indicators (Invernizzi *et al.*, 2018). Another major health issue in breast cancer survivors is persistent pain after the surgical procedure, which involves almost 30% of patients (Chang *et al.*, 2021). In this condition, the inflammatory milieu is responsible for the peripheral sensitization and inflammatory pain hypersensitivity at inflamed sites, particularly nerves. The role of inflammasome and circulating biomarkers have also been explored in cancer related fatigue, one of the most burdensome and long-lasting side-effects of breast cancers (Vannorsdall *et al.*, 2021). Despite circulating C-reactive protein and IL6 seem to be associated with an increased risk of CRF in long-term breast cancer survivors,

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Received: 24 December 2021; Accepted: 14 February 2022

Doi: 10.32604/biocell.2022.021043

these inflammatory markers are not yet ready to enter the clinical practice (Maurer *et al*., 2021).

The results of our studies provide strong evidence that under the umbrella of "quality of life interventions" stand a multitude of different conditions that are extremely heterogeneous in their biology, even in the presence of the same clinical manifestation. For this reason, individualized therapeutic approaches are required for the management of these conditions at a single-patient level. To achieve this goal, however, a multidisciplinary approach is required. We believe that the breast cancer healthcare community is ready for the "quantum leap" of implementing biomarkers for the clinical management of survivorship issues. Indeed, all these conditions are related not only to the active therapeutic oncological treatments but also to the tumor itself, which hinders cancer patients' HRQoL. Thus, the concept of "quality of life interventions" should be expanded to the concept of Cancer Rehabilitation, which comprises a framework of distinct approaches, from different points of view, and by different specialists.

In conclusion, thanks to the increasing effectiveness of screening programs and treatment schemes, the number of women who die of breast cancer has gradually declined. In this scenario, the prolongation of patients' life is no longer sufficient. Indeed, caregivers are now required to preserve and improve the HRQoL of patients. The next-generation model of "breast cancer survivorship" starts with the initial diagnosis and extends through the rest of the patient's life according to patient-specific (and in some cases tumor-specific) biological characteristics (Duijts and Spelten, 2021; Chan *et al*., 2021). This complex and fascinating field requires dedicated translational research studies and clinical trials to be fully integrated into clinical practice.

Author Contribution: Both authors confirm sole responsibility for the following: study conception and design, manuscript preparation.

Funding Statement: The authors received no specific funding for this study.

Conflicts of Interest: M.I. has received honoraria for consulting, advisory role, and/or speaker bureau from SPA, Errekappa Euroterapici S.p.a. and Amgen. N.F. has received honoraria for consulting, advisory role, and/or speaker bureau from Merck Sharp & Dohme (MSD), Boehringer Ingelheim, Novartis, AstraZeneca, and Daiichi Sankyo. These companies had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and/or in the decision to publish the results.

References

Ballinger TJ, Althouse SK, Olsen TP, Miller KD, Sledge JS (2021). A personalized, dynamic physical activity intervention is feasible and improves energetic capacity, energy expenditure, and quality of life in breast cancer survivors. *Frontiers in Oncology* **11**: 626180. DOI 10.3389/fonc.2021.626180.

Chan RJ, Nekhlyudov L, Duijts SFA, Hudson SV, Jones JM et al. (2021). Future research in cancer survivorship. *Journal of Cancer Survivorship* **15**: 659–667. DOI 10.1007/s11764-021-01102-x.

Chang PJ, Asher A, Smith SR (2021). A targeted approach to post-mastectomy pain and persistent pain following breast cancer treatment. *Cancers* **13**: 5191. DOI 10.3390/cancers13205191.

Cheng KKF, Lim YTE, Koh ZM, Tam WWS (2017). Home-based multidimensional survivorship programmes for breast cancer survivors. *Cochrane Database of Systematic Reviews* **8**: Cd011152. DOI 10.1002/14651858.CD011152.pub2.

Criscitiello C, Guerini-Rocco E, Viale G, Fumagalli C, Sajjadi E et al. (2022). Immunotherapy in breast cancer patients: A focus on the use of the currently available biomarkers in oncology. *Anticancer Agents in Medinal Chemistry* **22**: 787–800. DOI 10.2174/1871520621666210706144112.

de Sire A, Fusco N, Sajjadi E, Lippi L, Cisari C, Invernizzi M (2021). Lymphedema rehabilitation using self-adaptive inelastic compression in breast cancer: A proof-of-principle study. *Applied Sciences* **11**: 1901. DOI 10.3390/app11041901.

de Sire A, Losco L, Cisari C, Gennari A, Boldorini R, Fusco N, Cigna E, Invernizzi M (2020a). Axillary web syndrome in women after breast cancer surgery referred to an Oncological Rehabilitation Unit: Which are the main risk factors? A retrospective case-control study. *European Review for Medical and Pharmacological Sciences* **24**: 8028–8035.

de Sire A, Invernizzi M, Lippi L, Cisari C, Özçakar L, Franchignoni F (2020b). Blurred lines between axillary web syndrome and Mondor's disease after breast cancer surgery: A case report. *Annals of Physical and Rehabilitation Medicine* **63**: 365–367.

D'Egidio V, Sestili C, Mancino M, Sciarra I, Cocchiara R et al. (2017). Counseling interventions delivered in women with breast cancer to improve health-related quality of life: A systematic review. *Quality of Life Research* **26**: 2573–2592.

Duijts SFA, Spelten ER (2021). Cancer survivorship issues: Dissemination and translation of evidence-based knowledge. *Cancers (Basel)* **13**: 5794. DOI 10.3390/cancers13225794.

Fusco N, Marchiò C, Ghidini M, Scatena C (2021). Special issue: Molecular biomarkers in solid tumors. *Genes* **12**: 984. DOI 10.3390/genes12070984.

Gillespie TC, Sayegh HE, Brunelle CL, Daniell KM, Taghian AG (2018). Breast cancer-related lymphedema: Risk factors, precautionary measures, and treatments. *Gland Surgery* **7**: 379–403. DOI 10.21037/gs.2017.11.04.

Grizzi G, Ghidini M, Botticelli A, Tomasello G, Ghidini A, Grossi F, Fusco N, Cabiddu M, Savio T, Petrelli F (2020). Strategies for increasing the effectiveness of aromatase inhibitors in locally advanced breast cancer: An evidence-based review on current options. *Cancer Management and Research* **12**: 675–686. DOI 10.2147/CMAR.

Hadizadeh M, Mohaddes Ardebili SM, Salehi M, Young C, Mokarian F et al. (2018). GJA4/Connexin 37 mutations correlate with secondary lymphedema following surgery in breast cancer patients. *Biomedicines* **6**: 23. DOI 10.3390/biomedicines6010023.

Invernizzi M, de Sire A, Venetis K, Cigna E, Carda S, Borg M, Cisari C, Fusco N (2022). Quality of life interventions in breast cancer survivors: State of the art in targeted rehabilitation strategies. *Anticancer Agents in Medicinal Chemistry* **22**: 801–810. DOI 10.2174/1871520621666210609095602.

Invernizzi M, Corti C, Lopez G, Michelotti A, Despini L et al. (2018). Lymphovascular invasion and extranodal tumour extension are risk indicators of breast cancer related lymphoedema: An observational retrospective study with long-term follow-up. *BMC Cancer* **18**: 935. DOI 10.1186/s12885-018-4851-2.

Invernizzi M, de Sire A, Carda S, Venetis K, Renò F, Cisari C, Fusco N (2020a). Bone-muscle crosstalk in spinal cord injuries: Pathophysiology and implications for patients' quality of life. *Current Osteoporosis Reports* **18**: 422–431. DOI 10.1007/s11914-020-00601-7.

Invernizzi M, de Sire A, Lippi L, Venetis K, Sajjadi E et al. (2020b). Impact of rehabilitation on breast cancer related fatigue: A pilot study. *Frontiers in Oncology* **10**: 556718. DOI 10.3389/fonc.2020.556718.

Invernizzi M, Kim J, Fusco N (2020c). Editorial: Quality of life in breast cancer patients and survivors. *Frontiers in Oncology* **10**: 620574. DOI 10.3389/fonc.2020.620574.

Invernizzi M, Michelotti A, Noale M, Lopez G, Runza L et al. (2019). Breast cancer systemic treatments and upper limb lymphedema: A risk-assessment platform encompassing tumor-specific pathological features reveals the potential role of trastuzumab. *Journal of Clinical Medicine* **8**: 138. DOI 10.3390/jcm8020138.

Invernizzi M, Runza L, De Sire A, Lippi L, Blundo C, Gambini D, Boldorini R, Ferrero S, Fusco N (2020d). Integrating augmented reality tools in breast cancer related lymphedema prognostication and diagnosis. *Journal of Visualized Experiments* **156**: e60093. DOI 10.3791/60093.

Maurer T, Jaskulski S, Behrens S, Jung AY, Obi N, Johnson T, Becher H, Chang-Claude J (2021). Tired of feeling tired–The role of circulating inflammatory biomarkers and long-term cancer related fatigue in breast cancer survivors. *Breast* **56**: 103–109. DOI 10.1016/j.breast.2021.02.008.

Michelotti A, Invernizzi M, Lopez G, Lorenzini D, Nesa F, de Sire A, Fusco N (2019). Tackling the diversity of breast cancer related lymphedema: Perspectives on diagnosis, risk assessment, and clinical management. *Breast* **44**: 15–23. DOI 10.1016/j.breast.2018.12.009.

Nardin S, Mora E, Varughese FM, D'Avanzo F, Vachanaram AR, Rossi V, Saggia C, Rubinelli S, Gennari A (2020). Breast cancer survivorship, quality of life, and late toxicities. *Frontiers in Oncology* **10**: 864. DOI 10.3389/fonc.2020.00864.

Pagni F, Guerini-Rocco G, Schultheis AM, Grazia G, Rijavec E et al. (2019). Targeting immune-related biological processes in solid tumors: We do need biomarkers. *International Journal of Molecular Sciences* **20**: 5452. DOI 10.3390/ijms20215452.

Pal M, Muinao T, Boruah HPD, Mahindroo N (2021). Current advances in prognostic and diagnostic biomarkers for solid cancers: Detection techniques and future challenges. *Biomedical Pharmacotherapy* **146**: 112488. DOI 10.1016/j.biopha.2021.112488.

Rick O, Dauelsberg T, Kalusche-Bontemps EM (2017). Oncological Rehabilitation. *Oncology Research and Treatment* **40**: 772–777. DOI 10.1159/000481709.

Smoot B, Kober KM, Paul SM, Levine JD, Abrams G, Mastick J, Topp K, Conley YP, Miaskowski CA (2017). Potassium channel candidate genes predict the development of secondary lymphedema following breast cancer surgery. *Nursing Research* **66**: 85–94. DOI 10.1097/NNR.0000000000000203.

Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians* **71**: 209–224. DOI 10.3322/caac.21660.

Sunilkumar M, Finni CG, Lijimol AS, Rajagopal MR (2021). Health-related suffering and palliative care in breast cancer. *Current Breast Cancer Reports,* 1–6. DOI 10.1007/s12609-021-00431-1.

Vannorsdall T, Ermiece Straub D, Saba C, Blackwood M, Zhang J, Stearns K, Smith KL (2021). Interventions for multidimensional aspects of breast cancer-related fatigue: A meta-analytic review. *Supportive Care in Cancer* **29**: 1753–1764. DOI 10.1007/s00520-020-05752-y.

Venetis K, Piciotti R, Sajjadi E, Invernizzi M, Morganti S, Criscitiello C, Fusco N (2021). Breast cancer with bone metastasis: Molecular insights and clinical management. *Cells* **10**: 1377. DOI 10.3390/cells10061377.

Zhong L, Guo L, Ye Z, Zhang S, Huang R (2020). Exogenous dendritic cells aggravate atherosclerosis via P-selectin/PSGL-1 pathway. *Biocell* **44**: 225–236. DOI 10.32604/biocell.2020.08714.