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EDITORIAL

Consensus statement on non-cancer-related risk factors for development of secondary lymphedema

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Abstract

Non-cancer-related risk factors for secondary lymphedema were defined across four categories: co-morbidity, social determinants of health, behavioral factors, and environmental effectors. Based on rapid reviews of the literature and presentations at the ACS/LANA Lymphedema Summit, this working group categorized these risk factors according to the strength of evidence. Consensus agreement on level of evidence was achieved through one face-to-face working session and three follow-up virtual meetings. Findings elucidate strong evidence for co-morbidities, such as cardio/metabolic and vascular factors contributing to the risk for lymphedema. Evidence is low-to-moderate for social and behavioral factors and is lacking for environmental factors. Panel recommendations suggest a tailored approach to prospective surveillance when monitoring for secondary lymphedema that includes social determinants of health considering the growing awareness and evidence of these factors' influence on cancer and cancer-related morbidity.

Keywords Secondary lymphedema · Cancer · Morbidity · Social determinants of health · Risk factors · Prospective surveillance

Introduction

Risk factors contributing to the development of secondary lymphedema have historically been attributed to cancer treatment-related factors [1, 2] (e.g., surgical removal of lymph nodes and irradiation to lymphatic tissue) and non-cancer treatment-related factors [3] (e.g., medical co-morbidities, such as vascular conditions, and behavioral factors, such as limb overuse). Considering the influence that social, behavioral, and environmental factors have on an individual's overall cancer-related health outcomes, it is prudent to consider that these factors may influence the risk for developing cancer-related morbidity, such as secondary lymphedema.

Social determinants of health (SDOH) are defined as non-medical factors that influence health outcomes, commonly characterized based on the … "*circumstances where an individual is born, grows up, lives, works, and ages… and*

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the systems put in place to deal with illness…These circumstances are in turn shaped by a wider set of forces: economics, social policies, and politics" [4]. Social determinants are commonly characterized across five domains: *Healthcare Access and Quality, Education Access and Quality, Neighborhood and Built Environment, Social and Community Context, and Economic Stability* [4]. Heightened awareness has been drawn to the effect of social determinants as factors contributing to cancer onset and outcomes [5], with recent calls to increase awareness of and attention to assessing and addressing these factors in health care settings, specifically as they relate to cancer morbidity [6].

While substantial evidence supports the role of SDOH in influencing cancer incidence and the risk for disease mortality, only recently have these determinants been investigated as potential risk factors for cancer treatment-related morbidity, such as lymphedema. This manuscript provides consensus recommendations to guide clinical practice and research in considering these non-medical factors as risk factors for developing lymphedema.

Rationale for SDOH as lymphedema risk factors

While lymphedema occurs due to a mechanical disruption of the lymphatic system related to cancer treatments, evidence suggests that clustering co-morbidities such as obesity, vascular conditions, and other medical conditions influence risk in the cancer population [3]. Over years of research, characterizing the treatment-related risk factors has largely guided risk stratification models [7]; however, the predictive validity of these models remains moderate. The field of lymphology has been beset for years with the conundrum of risk models suggesting that greater extent of lymph node dissection, presence of radiation therapy, and higher body mass index increase the risk for developing lymphedema; however, many patients fit this risk model and never develop lymphedema. Conversely, many individuals do not fit this risk model and do develop lymphedema. Therefore, it is plausible to consider that additional factors may compound or mitigate this risk. Recent research that explored adaptations to a breast cancer-related lymphedema risk model found improved predictive validity of the model when social factors were included [7].

Social determinants are factors that have recently been studied related to risk for cancer and cancer treatment outcomes [5]. For example, individuals with higher socioeconomic status and higher education levels trend toward lower risk of many types of cancers and lower mortality related to cancer [5]. Factors such as race, ethnicity, income level, and zip code (or other regional indicator) are recognized as factors that influence health and health outcomes. Additionally, access to health care services and the ability to afford those services also influence health outcomes [4]. Therefore, it stands to reason that consideration should be given to the influence of these factors in escalating or mitigating the risk for a disease-related impairment, such as secondary lymphedema.

Foundational to the field of lymphedema over the last decade has been the premise of early identification and early intervention, driven by evidence-based prospective surveillance models. This approach suggests that lymphedema may be avoided or the severity of the condition greatly minimized when prospective screening, identification of limb changes, and early intervention take place [8]. Individuals for whom health care access is limited may not receive these services, suggesting that social determinants such as geographic locality and access to health care services would therefore influence risk. Risk could be further magnified by low socioeconomic status and an inability to afford healthcare insurance or services. Either of these examples identify how social factors may escalate or mitigate the risk of condition onset.

Review of Evidence

A two-day Lymphedema Summit was convened by the American Cancer Society (ACS) and the Lymphology Association of North America (LANA). The aim of the Summit was to disseminate prevailing knowledge and evidence updates in lymphedema management and generate practice recommendation statements to advance the future of lymphedema clinical practice and research. Workshop participants were invited subject matter experts (SME) who participated in evidence reviews to generate recommendations.

For the purposes of this consensus statement, categories of risk factors were defined based on the World Health Organization [4] (WHO) definitions:

- *Environmental:* Factors related to the place where individuals live and work and the surroundings they are exposed to, e.g., geographic locality, the related air and water quality, and socioeconomic status of the local area. These factors also influence access to health care services.
- *Behavioral/Personal:* Factors related to an individual's activities and behaviors, specifically lifestyle choices and preferences, such as surrounding culture, interpersonal connections, personal beliefs, and preferences.
- *Co-morbidity*: Medical conditions, aside from cancer and cancer treatment-related side effects, including physiologic interrelationships between body systems that influence lymphatic function.
- *Social:* Factors related to an individual's social support network, including income, socioeconomic status, educa-

tion level, literacy, and support from family and caregivers.

Risk factors were categorized based on their locus of influence on the individual; for example, income level is characterized as a *Social* factor, whereas economic stability of the region in which an individual lives is characterized as an *Environmental* factor. Consensus on categorization of factors was achieved by discussion and agreement.

The level of evidence for each risk factor was characterized as *strong, moderate,* or *insufficient* (See Table 1). Participants agreed that the absence of evidence did not discount plausibility and that a theoretical basis for recommendations could be made in the absence of published evidence specific to lymphedema. Recommendations were developed by group consensus based on the evidence presented at the workshop. Stout et al. [9] article that will be published along with this special issue.

Results and recommendations

Overall, evidence is lacking to support the strength of social determinants of health as risk factors for the development of lymphedema. Most studies that provide insight on SDOH as risk factors do so as descriptive variables in a study population. Few studies have purposively examined SDOH as independent variables of interest in a risk factor analysis or model. Nearly all studies with strong evidence for any social determinants as risk factors were conducted in a breast cancer population. Medical co-morbidities were the most common category of non-cancer

Table 1 Characterization of the evidence for non-medical risk factors for secondary lymphedema

Strong Evidence

- Risk factors were studied as the primary variable of interest in a large cohort study in a population of patients with secondary lymphedema
- Risk factors studied as the primary variables of interest in a population of patients with secondary lymphedema with a comparison control group
- Systematic review or meta-analysis of risk factor studies

Environmental Factors	Behavioral / Personal Factors	Co-morbid Conditions	Social Factors
N/A	• Insufficient levels of physical activity	• > 30 BMI • Cardiovascular/ Vascular • Physical Trauma • Hypertension • Cellulitis • Deep vein thrombosis • Wounds • Diabetes • Medication type • Age	• Race (African American)

Moderate Evidence

Risk factors characterized as descriptive variables in a large cohort of patients with secondary lymphedema

Environmental Factors	Behavioral / Personal Factors	Co-morbid Conditions	Social Factors
• Economic / financial stability • Rurality • Access to healthcare	• Poor nutrition	• Pulmonary disease • Hepatic disease • Thyroid conditions • Genetics • Renal disease • Autoimmune disease • High medication count	• Low socioeconomic status • Education level • Health literacy • Support network • Insurance

Insufficient Evidence

- Risk factors identified from a case–control study or small observational study characterizing the population of study participants
- Expert opinion, clinical practice, literature review, or pilot study

Environmental Factors	Behavioral / Personal Factors	Co-morbid Conditions	Social Factors
• Occupational factors (workplace/ work activities) • Proximity to certified lymphedema therapists • Availability of lymphedema health care services • Lack of lymphedema awareness among healthcare professionals	• Tobacco use • Alcohol use • Sleep hygiene • IV Drug use	• Pain	• Language barriers • Transportation accessibility

N/A not applicable, *BMI* body mass index, *IV* intravenous risk factors identified across the literature review and were studied across all types of cancers.

Moderate evidence was identified for select environmental, social, and behavioral risk factors. While race, specifically African American race, was identified as a risk factor, these findings were exclusive to studies of breast cancer-related lymphedema. The preponderance of these findings was descriptive, with environmental, social, or behavioral risk factors identified as a correlate of lymphedema in a study group versus a control group, rather than studied as an independent variable. Among risk factors for which there is insufficient evidence, some factors were extrapolated from evidence reviews of SDOH in cancer treatment outcomes and were agreed upon by the SMEs as important to consider in assessment of lymphedema risk. Recommendations are provided in Fig. 1.

Conclusion

Social determinants of health influence health and health outcomes. Assessing SDOH to inform cancer care delivery has increased in prominence, and frameworks for assessing the role of social determinants among individuals with cancer have been developed and recommended to reduce disparities in health outcomes [6]. It is our strong recommendation that social determinants of health are assessed for all patients experiencing cancer treatments, specifically those being screened and monitored for the onset of cancer treatment-related lymphedema through a prospective surveillance model.

Specific information that should be collected as part of a clinical risk stratification model, including socioeconomic status, education level, and geography, in addition to family and community support, transportation, and insurance coverage. These factors have an emerging evidence to suggest they may play a role in the development of cancer treatment-related morbidity, such as lymphedema. Further, research trials including individuals with or at-risk for lymphedema should collect SDOH variables using a standard assessment

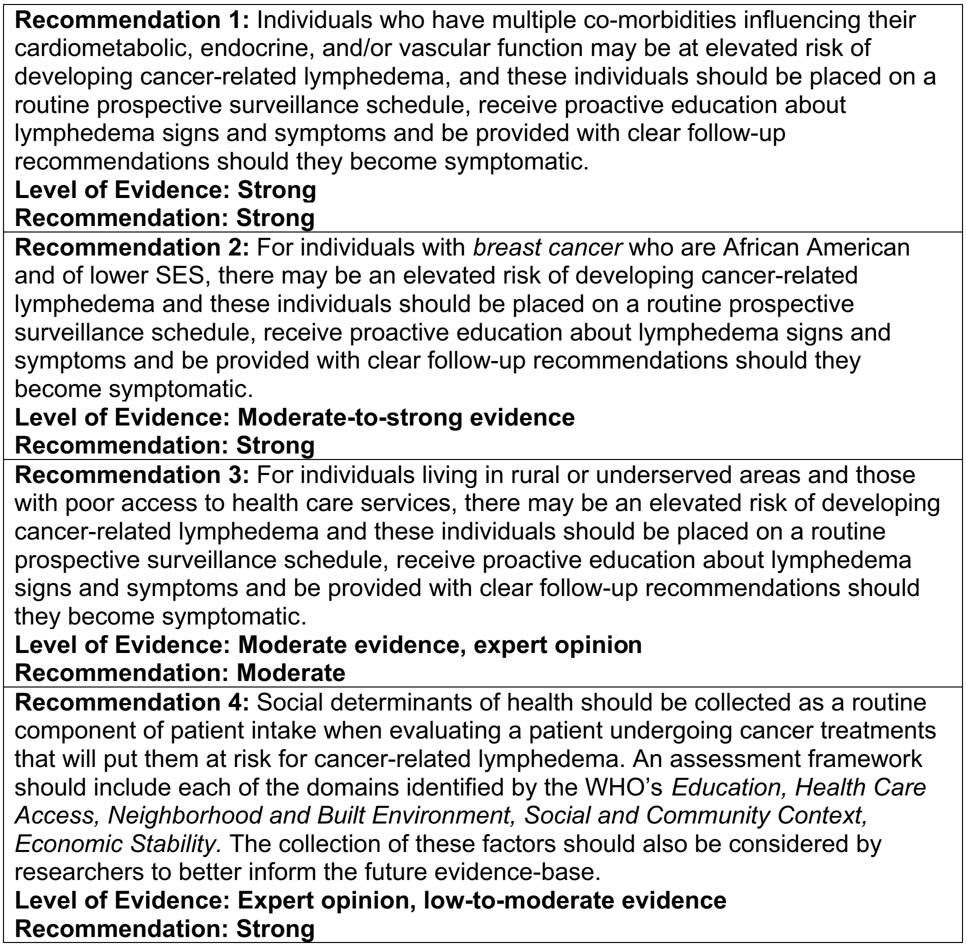

Fig. 1 Recommendations for assessing SDOH and Non-cancer treatment-related conditions as risk factors for lymphedema in individuals undergoing cancer treatments

Recommendation 1: Individuals who have multiple co-morbidities influencing their cardiometabolic, endocrine, and/or vascular function may be at elevated risk of developing cancer-related lymphedema, and these individuals should be placed on a routine prospective surveillance schedule, receive proactive education about lymphedema signs and symptoms and be provided with clear follow-up recommendations should they become symptomatic.
Level of Evidence: Strong
Recommendation: Strong

Recommendation 2: For individuals with *breast cancer* who are African American and of lower SES, there may be an elevated risk of developing cancer-related lymphedema and these individuals should be placed on a routine prospective surveillance schedule, receive proactive education about lymphedema signs and symptoms and be provided with clear follow-up recommendations should they become symptomatic.
Level of Evidence: Moderate-to-strong evidence
Recommendation: Strong

Recommendation 3: For individuals living in rural or underserved areas and those with poor access to health care services, there may be an elevated risk of developing cancer-related lymphedema and these individuals should be placed on a routine prospective surveillance schedule, receive proactive education about lymphedema signs and symptoms and be provided with clear follow-up recommendations should they become symptomatic.
Level of Evidence: Moderate evidence, expert opinion
Recommendation: Moderate

Recommendation 4: Social determinants of health should be collected as a routine component of patient intake when evaluating a patient undergoing cancer treatments that will put them at risk for cancer-related lymphedema. An assessment framework should include each of the domains identified by the WHO's *Education, Health Care Access, Neighborhood and Built Environment, Social and Community Context, Economic Stability.* The collection of these factors should also be considered by researchers to better inform the future evidence-base.
Level of Evidence: Expert opinion, low-to-moderate evidence
Recommendation: Strong

tool. Ideally, better quantification of SDOH provides insight to inform clinical practice and research, improve prospective surveillance monitoring, and improve care for individuals with or at-risk for secondary lymphedema.

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Declarations

Competing interests The authors have not disclosed any competing interests.

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