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REVIEW ARTICLE

Incorporating Biomarkers Into Cancer and Aging Research

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A B S T R A C T

The challenge in treating the older adult with cancer is accurately accounting for and adapting management to the heterogeneity in health status of the individual patient. Many oncologists recognize that chronological age alone should not be the determinant when deciding on a treatment regimen. Easily measurable markers that provide an assessment of functional age would be ideal to assess frailty, which may predispose the patient to complications from cancer treatment, including increased toxicity, functional decline, decreased quality of life, and poorer survival. Several categories of potential markers, including chronic inflammatory markers, markers of cellular senescence, and imaging to assess muscle mass to detect sarcopenia, may provide insight into the likelihood of treatment-related complications. This article discusses candidate markers and strategies to evaluate these markers in cancer treatment trials, with the aim of developing a method to assess risk of oncologic outcomes and guide management decisions for both the physician and patient.

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INTRODUCTION

There is great heterogeneity in the ability of older adults to tolerate cancer treatment. Older adults are at risk for increased toxicity from cancer therapy, but standard methods to accurately determine this risk are lacking. Clinical factors routinely collected during the cancer assessment such as age, performance status (PS), and comorbidities are not reliable predictors of toxicity.[1-4] Out of concern for poor tolerability, chemotherapy is often withheld from older patients on the basis of age alone, despite evidence that some older adults can derive benefit from treatment similar to that derived by younger patients.[4,5] As a result, older adults with cancer are often undertreated, make up a minority of patients enrolled onto clinical trials,[6] and are not gaining the benefits of cancer therapeutic advances as much as younger patients.[7]

To individualize treatment for the older patient, more data are needed beyond their chronologic age and comorbidities. An accurate sense of their functional age with more objective measures that are easily measured, easily reproduced, and predictive of outcome are needed. Some consider frailty a reflection of functional age because it gives a measure of physiological age not necessarily in proportion to chronological age.[8] Frailty can be defined as the inability of an individual to return to their baseline physical status after an insult to the body, or a measure of resilience. Fried et al[9] described a phenotype of frailty as having three of the following: 10-pound unintentional weight loss, poor grip strength, exhaustion, slow gait, and low physical activity level. The degree of resilience varies among older individuals as commonly seen by the differing degrees to which older patients tolerate treatment in terms of adverse effects.

The ideal marker would reflect the degree of a patient's functional reserve and predict tolerance to cancer treatment. Some measures of this already exist. The comprehensive geriatric assessment can assess multiple aspects of a patient's life, including physical function, physical and mental health, cognition, and socioeconomic circumstances. The application of the geriatric assessment in oncology is discussed elsewhere in this issue. But, likely because of lack of time, resources, and expertise, the comprehensive geriatric assessment is not widely used in clinical practice. In addition, one could imagine that it may be difficult to measure repeatedly in patients who are likely fatigued from the cancer treatment itself. There are several proposed biologic markers of aging with various amounts of data on their ability to correlate with physical function or predict functional decline and/or mortality. Another largely unexplored area is the use of imaging studies for assessment of the ratio of muscle mass or fat to muscle. This assessment could be done on computed tomography scans commonly used for tumor staging evaluations that could potentially give more information on functional reserve and/or predict a decline in physical function.

Table 1. Summary of Proposed Markers of Functional Age

Marker	Source	Test	Association With Frailty and/or Function	Association With Mortality	References
Chronic inflammatory markers	Serum or plasma	ELISA	Yes (CRP, IL-6, TNF-α, D-dimer, IL-1RA)	Yes (CRP, IL-6, D-dimer, sVCAM)	Cesari et al[10] Ferrucci et al[11] Hubbard et al[12] Leng et al[13] Walston et al[14] Cohen et al[15] de Saint-Hubert et al[16] Huffman et al[17] Puts et al[18] Reuben et al[19] Rønning et al[20]
Telomere length	Leukocyte DNA	q-PCR or Southern blot	Yes	Yes	Cawthon et al[21] Epel et al[22] Farzaneh-Far et al[23] Risques et al[24]
$p16^{INK4a}$	T-lymphocyte RNA	qRT-PCR	No	No	Krishnamurthy et al[25] Liu et al[26] Song et al[27]
Sarcopenia	CT scan	Commercially available software for body composition analysis	Yes	Yes	Baumgartner et al[28] Heymsfield et al[29] Janssen et al[30] Metter et al[31]

Abbreviations: CRP, C-reactive protein; CT, computed tomography; ELISA, enzyme-linked immunosorbent assay; IL-6, interleukin-6; IL-1RA, IL-1 receptor antagonist; q-PCR, quantitative polymerase chain reaction; qRT-PCR, quantitative real-time PCR; sVCAM, soluble vascular cell adhesion molecule; TNF-α, tumor necrosis factor-α.

This review will discuss potential markers of functional age to complement clinical geriatric assessment as well as their potential incorporation into clinical trials to assess their value. Validation will be necessary before any marker can be routinely used in practice to better inform patients and physicians of the potential harms and/or risks associated with treatment and to guide clinical management decisions. A summary of the proposed markers is listed in Table 1.

POTENTIAL BIOMARKERS THAT WARRANT FURTHER STUDY

Markers of Systemic Inflammation

Markers of chronic inflammation are potential biomarkers of frailty and functional reserve that have been studied most in terms of their correlation with clinical measures of frailty, functional decline, and mortality. Prothrombotic factors have also been noted to be increased with chronic inflammatory markers, likely because of a costimulatory effect between the two processes. For instance, inflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) can stimulate production of prothrombotic factors such as plasminogen activator inhibitor-1 (PAI-1) and fibrinogen.[32] The synthesis of cytokines IL-1B, IL-6, and PAI-1 is also induced by D-dimer, a marker of the activated coagulation system [33] Likewise, when vascular cell adhesion molecule (VCAM) is exposed to inflammatory markers TNF-α and IL-1B, it is cleaved to soluble vascular cell adhesion molecule (sVCAM), which has been shown to be increased in patients with age-related diseases such as rheumatoid arthritis.[34] For the purpose of this discussion, markers of the coagulation system such as D-dimer and sVCAM will be included with chronic inflammatory markers. In general, proinflammatory mediators such as IL-6, TNF-α, D-dimer, and PAI-1, increase with age, even among healthy individuals.[36-38] These markers are proposed to accelerate the aging process and exacerbate multiple age-related diseases.[39-41]

Multiple studies have shown that these markers correlate with clinical measures of frailty and are increased to a greater degree in frail patients than in age-matched, nonfrail controls.[10-14,42,43] One study of 110 patients older than age 75 years evaluated a combination of inflammatory markers (TNF-α, IL-6, C-reactive protein [CRP]) and low albumin and their relationship to several different clinical measures of frailty.[12] The degree of clinical frailty independently correlated with increased inflammatory marker levels and lower albumin levels, adjusting for multiple factors, including age, sex, body mass index, smoking status, number of comorbidities, and number of medications. Therefore, these markers might be useful as a quick measure of the patient's degree of frailty or biologic age and might provide insight into an individual's tolerance to cancer treatment.

Decline in physical function and loss of independence is of great concern for older adults undergoing cancer treatment, and several studies in the general geriatric population have shown that increased chronic inflammatory and procoagulant markers predict functional decline.[15-19,45,46] In an analysis of moderately to severely disabled women age 65 years and older on the Women's Health and Aging Study, higher baseline IL-6 levels were associated with significantly higher levels of functional decline, including decreased mobility, activities of daily living deficits, increased walking limitations, and decreased walking speed, compared with women with lower IL-6 levels.[46] Elevated inflammatory cytokines and procoagulant marker levels also correlate with postoperative complications and functional decline after oncologic surgery.[16,20] Whether chronic inflammatory markers can independently predict functional decline associated with cancer treatment warrants further study.

Elevated inflammatory markers are also associated with mortality risk in the elderly.[15,17,19,44] In a study of community dwelling adults (mean age, 78 years), higher levels of sVCAM were independently

associated with poorer baseline functional status and mortality at 4 years (hazard ratio, 1.2; $P = .002$).[17] Higher sVCAM, D-dimer, and IL-6 were independently related to 4-year mortality, adjusting for functional status, demographics, and comorbidities.

Several chronic inflammatory markers, (IL-6, D-dimer, and CRP) also have the ability to predict both decline in function and mortality, even after controlling for age, comorbidities, and physical function,[15,19,42] and may have greater predictive ability among patients without baseline functional impairments, suggesting they may identify prefrail patients that may not otherwise have been identified without extensive geriatric assessment testing. The majority of studies evaluating chronic inflammatory markers in the general geriatric population are mainly epidemiologic observations. The role of these markers in the management of general geriatric patients is being studied in ongoing geriatric research.

The direct link between increased inflammatory markers and functional decline has not been established. It has been postulated that interconnections between inflammatory cytokines and the CNS, endocrine systems, and musculoskeletal system could result in sarcopenia and/or bone loss leading to decreases in function. Several animal model studies suggest a role in the catabolic effects contributing to muscle wasting,[47-49] but whether this is a direct effect of the inflammatory markers or mediated by other circulating factors remains unknown.

The benefits of using chronic inflammatory markers include the ease of measurement. They can be collected during blood draws routinely done for cancer management. They can be measured with enzyme-linked immunosorbent assays, and a panel of inflammatory markers can be included in a multiplex enzyme-linked immunosorbent assay. The problem with assessing chronic inflammatory markers is that they reflect and may be produced by the cancer itself. Experts in the biomarkers of aging development process have recommended that "... an aging marker should both correlate with functional age but also be independent from specific pathologic conditions."[50] Although chronic inflammatory markers may not technically be true aging biomarkers, they are potentially useful in reflecting correlated processes that may predict oncologic outcomes.

An argument for measuring cytokines in the setting of an ongoing malignancy is that they are associated with poorer PS and quality of life (QOL), as well as higher levels of fatigue,[51,52] that may affect a patient's ability to tolerate treatment. There is evidence that cytokine levels may provide prognostic information beyond PS. In a study of 377 patients with acute myeloid leukemia, cytokine expression (IL-6, IL-1, IL-2, TNF-α, and CRP) was evaluated in 58 patients identified at the extremes of survival (median survival, 4.9 months and 46.3 months in patients with poor and good prognosis, respectively).[53] There was no statistically significant difference in survival when evaluated by PS (Eastern Cooperative Oncology Group 0 to 1 v 2). However, when categorized by cytokine expression levels (low, intermediate, high) and PS, there was a large difference in survival between low-, intermediate-, and high-risk groups (56.1 months, 9.85 months, and 8.35 months, respectively; $P = .02$).

Markers of Cellular Senescence

If a cell does not enter the apoptotic pathway in response to DNA damage, the cell can activate a DNA damage response pathway leading to permanent cell cycle arrest termed cellular senescence.[54,55] Cellular senescence, a term for the mitotic arrest of a cell, is induced by DNA damage through several mechanisms, including cell division and subsequent telomere shortening, as well as forms of cellular stress, including activation of oncogenes and oxidative stress.[55] The assumption is that as a person ages, one accumulates more and more senescent cells.

There may be a connection between senescent cells and the increasing levels of chronic inflammatory markers seen in older individuals. Cellular division has ceased in senescent cells, but they actively secrete proinflammatory proteins collectively known as the senescence-associated secretory phenotype (SASP).[56] SASP factors are proposed to increase inflammation in surrounding tissues and in the circulation and contribute to the aging process. Factors within the SASP are similar to the inflammatory and coagulation markers associated with frailty and mortality in the elderly population.[44,57]

Because there are no established circulating markers of cellular senescence, markers associated with senescence, including telomere length and $p16^{INK4a}$, have been explored as potential biologic markers of aging.

Telomere length. Telomeres are proteins at the ends of chromosomes that shorten with each cell division, eventually leading to mitotic arrest termed "replicative senescence," which has been proposed to contribute to the aging process.[58] Because telomere length decreases with increasing age, telomere length has been evaluated as a biomarker of aging. In a study of 143 patients older than 60 years, Cawthon et al[21] demonstrated a correlation between shorter telomere length by age and increased mortality. Since that time, multiple studies have attempted to replicate this finding with varying results, but because of the correlation with aging as well as age-related disease, telomere length continues to be a marker of interest in the search for markers of biologic age.[59]

Interestingly, telomere length may also have a role in predicting cancer prognosis. Shorter telomere length has been associated with poorer prognosis among patients in retrospective studies of colorectal cancer, soft tissue sarcomas, breast cancer, and lung cancer.[60] Other studies on the association between telomere length and cancer-related mortality have yielded conflicting results. Telomere length has also been associated with functional status or mortality in several studies.[21,22-24]

Telomere length can be measured in peripheral blood leukocytes under the presumption that it represents telomere length in other tissues. This marker could be obtained in conjunction with routine blood draws, but it requires laboratory methods that have technical limitations. Telomere length can be measured by estimating the size of cleaved telomere fragments (by using the terminal restriction fragment method[61]), shortest telomere length by fluorescent in situ hybridization, or by quantitative real-time polymerase chain reaction.[59] A potential disadvantage to using telomere length as a biomarker is that it could be affected by many processes other than age, including genetic factors, environmental exposure, and dietary intake.[59] As with chronic inflammatory markers, a correlation of frailty and telomere length may be important for predicting outcomes of interest, regardless of whether it is considered a pure aging biomarker.

Dysfunctional telomeres. Dysfunctional telomeres may also have a role as biomarkers of aging. In a preclinical study, Jiang et al[62] identified markers secreted by bone marrow cells with telomere dysfunction (stathmin, CRAMP, EF1α, and chitinase 3). These markers were found to distinguish old from young adults and healthy older adults versus older adults with age-related diseases. The benefit to

these markers is that they can be detected in the serum, making their measurement much easier than assessments of telomere length.

p16^{INK4a}. The activation of oncogenes or the loss of tumor suppressor function can also induce senescence, primarily controlled by the p53 pathway and its downstream mediators.[63,64] p16^{INK4a} is involved in an alternate pathway involved in permanent cell-cycle arrest that is now recognized as a marker of cellular senescence in animal models.[25] It has been demonstrated that p16^{INK4a} levels increase with age in mammalian models and humans, and its expression has also been correlated with higher levels of IL-6.[25-27]

The role of p16 levels in the geriatric oncology population is currently being evaluated in an ongoing clinical trial (NCT00849758). Interestingly, p16^{INK4a} levels have recently been found to increase in patients receiving chemotherapy for breast cancer, making this a potential marker for studying the effects of chemotherapy on the aging process.[65] Levels of p16^{INK4a} can be obtained from the blood via quantitative real-time polymerase chain reaction on T-lymphocyte RNA, although the assay is complicated and not generally available at this time.[60]

Imaging for Sarcopenia

Another modality of evaluation that may predict underlying frailty and/or functional age is imaging for sarcopenia. Sarcopenia can be defined as muscle mass two standard deviations below that of a healthy adult.[66] Sarcopenia is more prevalent in older adults and is a hallmark of frailty and subsequent disability.[67] In addition, circulating inflammatory mediators likely contribute to the development and progression of sarcopenia.[68,69]

Beyond sarcopenia, there is currently major interest in body composition and how it correlates with sarcopenia; for example, obese patients can have a decrease in muscle mass termed sarcopenic obesity. A study of 250 patients with body mass index more than 30 evaluated muscle mass by using whole-body dual-energy x-ray absorptiometry and computed tomography scans.[70] Patients with sarcopenic obesity had poorer response to chemotherapy, poorer PS, and a 10-month decrement in median survival after adjusting for standard predictors of cancer-related mortality.

The advantages to using radiographic technology to assess for sarcopenia is that this information could be collected at the time of routine imaging studies done for tumor evaluation and/or restaging.[71] Sarcopenia may be present before the onset of disability,[67] and sarcopenia may be disguised by obesity. Therefore, imaging studies for sarcopenia may identify the prefrail or frail patient who otherwise may not have been detected. There is also evidence that body composition may be related to toxicity from cytotoxic chemotherapy.[72] A disadvantage of imaging evaluation for sarcopenia is the cost of the computerized imaging technology and the expertise required to calculate the degree of muscle mass in each patient. It is uncertain whether radiographic evaluation for sarcopenia will add more to geriatric assessment than standard measures such as grip strength and timed up and go. One possibility would be to use the aforementioned measures as a screening tool, which might prompt further evaluation for sarcopenia.

Other Potential Aging Markers

There are other aging biomarker candidates that may prove to be helpful predictors of oncologic outcomes. These include genes associated with longevity, single nucleotide polymorphisms associated with aging, lymphopenia, and oxidative stress markers.[50,60] Data for these potential markers in relation to clinical measures of frailty and mortality prediction is currently scant, but future studies may provide more insight into their use in geriatric oncology.

MOVING FORWARD: INCORPORATING BIOMARKERS INTO ONCOLOGY CLINICAL TRIALS

The need for more accurate assessment of the functional age of patients with older cancer is clear, and clinical trials are beginning to incorporate some of the aforementioned markers. The European Organisation for Research and Treatment of Cancer is including collection of aging biomarkers such as markers of chronic inflammation, aging genes, and markers of cellular senescence in patients enrolled onto clinical trials. The ideal biomarker of functional age or frailty would provide additional information beyond what is collected during routine oncology evaluation and would be easily measured and easily repeated throughout treatment without causing increased burden to the patient.

When evaluating potential biomarkers in clinical trials, we need end points that will accurately predict treatment tolerance and outcomes. Outcomes should include the development of adverse events, functional decline, QOL, and survival, which would enable patients to make better-informed decisions regarding their treatment. Such markers would also help clinicians identify the most appropriate treatment regimen for the patient (ie, full-dose chemotherapy, modified doses, best supportive care) as well as identify patients in need of additional supportive care during treatment.

When assessing biomarkers in the context of cancer and cancer treatment, it will be important to assess the biomarkers at various time points to evaluate the impact of aging markers at different time points in the cancer evaluation and treatment trajectory. The measurement of biomarkers over time could be used to address four important questions.

First, how much does tumor burden and treatment (recent surgery, radiation therapy, and chemotherapy) affect the physical function (degree of frailty) for the individual patient? Starting with adjuvant therapy trials will likely remove the confounding factor of the underlying malignant process contributing to the biomarker levels and potentially clinical measures of frailty and QOL. Consider measuring markers before tumor removal, and at various time points after surgery because surgery itself would be expected to temporarily elevate these markers and contribute to a temporary decline in physical function, depending on the impact of the surgery on the individual patient. The most appropriate time point after surgery to measure biomarkers is not known, but circulating acute phase reactants from the surgery itself should be resolved by 6 to 8 weeks after surgery.[73,74]

Second, do the increased circulating markers correlate with clinical measures of frailty? And if so, even if the increased biomarkers were the result of the underlying tumor burden, will they still have an impact on treatment tolerance? Will they decrease with treatment or increase? If they decrease, would this improve treatment tolerance to the point that the dose of chemotherapeutic drugs in the regimen could potentially be increased?

Third, will chemotherapy and/or radiation therapy contribute to an increase in senescent cell burden? There are suggestions that chemotherapy contributes to the development of cellular senescence. Would this result in an increase in circulating SASP factors and contribute to a decline in physical function or health-related QOL greater

than that for a patient who had not received chemotherapy? Could a resulting increase in SASP factors contribute to accelerated aging? In studies done on survivors of childhood cancers, investigators have found an increase in age-related pathologies such as atherosclerotic disease.[75,76] Is this a result of the development of senescent cells in response to treatment resulting in premature aging?

Fourth, if senescent cells contribute to local tissue inflammation (destruction?) resulting in changes such as epithelial to mesenchymal transition, would this result in decreased disease-free survival, progression-free survival, or overall survival?

Future Directions

In the development of biomarkers, it is anticipated that there will be a combination or panel of markers that will have the best predictive power of end points such as toxicity, functional decline, QOL, and survival. As with the geriatric assessment, patients would potentially be placed into frailty and/or aging categories (ie, low-, intermediate-, or high-risk groups) to predict risk for the specific end point. This panel of markers should then be validated in older patients enrolled onto clinical trials. If validated, the panel could then be evaluated as a decision tool in a prospective trial, which could be used to stratify patients and assign them into different management categories such as modified treatment regimens.

Ultimately, research on biomarkers of aging may provide us with more accurate assessments of risk and may also identify biologic targets for interventions to ease the burden of cancer treatment for older patients. Future studies using a biomarker of aging panel could be incorporated into interventional studies to assess whether interventions in patients identified as at risk for poorer outcomes (toxicity or decreased survival or decline in physical function) can be modified or prevented by focused interventions. Potential interventions could include pharmacologic agents targeting cachexia/sarcopenia, chronic inflammation, and/or the burden of senescent cells. Other interventions may include physical rehabilitation, nutritional supplementation, or psychosocial methods.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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