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AGS and NIA Bench-to Bedside Conference Summary: Cancer and Cardiovascular Disease

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Abstract

This report summarizes the presentations, discussions, and recommendations of the most recent American Geriatrics Society and National Institute on Aging research conference, “Cancer and Cardiovascular Disease,” on October 18–19, 2021. The purpose of this virtual meeting was to address the interface between cancer and heart disease, which are the two leading causes of death among older Americans. Age-related physiologic changes are implicated in the pathogenesis of both conditions. Emerging data suggest that cancer-related cardiovascular disease (CVD) involves disrupted cell signaling and cellular senescence. The risk factors for CVD are also risk factors for

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Author Contributions

SM, CB, and HEW worked on study concept and design. SM, CB, PMA, WD, DEF, CF, HMH, JM, KMM, MWR, and HEW worked on analysis and interpretation and prepared the manuscript.

Conflicts of Interest

JM has served on advisory boards for Pfizer, Novartis, Bristol-Myers Squibb, Deciphera, Audentes Pharmaceuticals, Takeda, Myokardia, AstraZeneca, GlaxoSmithKline, Boston Biomedical, ImmunoCore, Janssen, Myovant, Silverback Therapeutics, Amgen, Kurome Therapeutics, Kiniska Pharmaceuticals, Daiichi Sankyo, CRC Oncology, BeiGene, Star Therapeutics, ProteinQure, Pharmacyclics, Mallinckrodt Pharmaceuticals, Boehringer, and Cytokinetics, and is supported by is supported by National Institutes of Health grants (R01HL141466, R01HL155990, R01HL156021). HMH is funded by Healthcare Services Corporation (Blue Cross/Blue Shield), the National Institute on Aging, and the National Center to Advance Translational Sciences. SM, CB, HEW, PMA, WD, DEF, CF, KMM, and MWR have no conflicts to report.

cancer and an increased likelihood of cancer death, and people who have both cancer and CVD do more poorly than those who have only cancer or only CVD. Issues addressed in this bench-to-bedside conference include mechanisms of cancer and CVD co-development in older adults, cardiotoxic effects of cancer therapy, and management of comorbid cancer and CVD. Presenters discussed approaches to ensure equitable access to clinical trials and health care for diverse populations of adults with CVD and cancer, mechanisms of cancer therapy cardiotoxicity, and management of comorbid CVD and cancer, including the role of patient values and preferences in treatment decisions. Workshop participants identified many research gaps and questions that could lead to an enhanced understanding of comorbid CVD and cancer and to better and more equitable management strategies.

Keywords

Cancer; aging; cardiovascular disease; cardiotoxicity

Background

Heart disease and cancer are the two leading causes of death among older Americans, and age-related physiologic changes are implicated in the pathogenesis of both conditions. In addition, cancer and atherosclerosis have many of the same pathological mechanisms and molecular and environmental risk factors.¹ For example, both are driven by age and environmental exposures (e.g., smoking), and their main pathogenic processes include dysregulated cell death, leukocyte infiltration, and extracellular matrix remodeling.

Cardiovascular disease (CVD) is the leading cause of noncancer-related death among cancer survivors, partly because both cancer and heart disease are diseases of older age and therefore often coexist.² A study of Surveillance, Epidemiology, and End Results data on more than 3 million U.S. cancer survivors found that one third as many patients died of CVD as cancer, and for some cancers, CVD mortality rates were higher than cancer mortality rates.³ Older adults with cancer often have subclinical CVD or a greater risk of CVD, and cancer treatments can worsen this CVD vulnerability. CVD and cancer exacerbate risk of one another and management complexity. For example, myocardial infarction after breast cancer diagnosis accelerates cancer progression, people with both cancer and CVD have a higher likelihood of an adverse outcome than those with only cancer or only CVD.^{4,5}

Advances in early detection and combination therapy have contributed to substantial survival gains in people with cancer. But standard-of-care strategies to evaluate and manage the consequences of cancer and its treatment in older adults have remained essentially unchanged for 20 years.⁶ Options to mitigate cancer therapy-related cardiotoxicity are to choose a lower medication or radiation dose or an alternative regimen, or to interrupt, reduce, or modify the dose during treatment.

Much more is known about the direct and indirect effects of cancer and its treatment on CVD development than of CVD management on cancer development.⁷ Other research gaps include how to prevent acute and chronic cardiotoxicity from cancer therapies and the mechanisms of CVD's effects on cancer development and progression.

Purpose of this Report

The American Geriatrics Society, National Institute on Aging, and American College of Cardiology held a virtual bench-to-bedside research conference, “Cancer and Cardiovascular Disease,” on October 18–19, 2021. This meeting addressed the interface between cancer and heart disease. This report summarizes the presentations and recommendations from this conference.

This conference was the third and last in the most recent series of American Geriatrics Society Bench to Bedside conferences, which provide updates on cutting-edge research, identify research gaps and opportunities, and facilitate networking among experts and promising new investigators from relevant disciplines in the field of aging.⁸ Each conference in this series examined a different pair of common, age-related conditions.^{9,10}

This conference featured sessions, summarized below, that addressed three major themes.

Theme 1: Mechanisms of Co-Development of Cancer and CVD in an Aging Population

Factors Associated with Increased Morbidity and Mortality Risk

A potentially useful marker of morbidity and mortality risk in older adults with CVD and cancer is cardiorespiratory fitness (CRF), which declines by approximately 13% during about 16 weeks of chemotherapy.¹¹ Such a decline is typical in 10 years of normal aging, and low CRF is associated with a higher symptom burden and increased prevalence of chronic treatment-related CVD risk factors. This decline is also a strong, independent predictor of cancer, cardiovascular, and all-cause mortality.¹²

Cancer therapies might induce accelerated aging phenotypes. For example, cognitive function is significantly poorer in adults treated with chemotherapy for lymphoma than in healthy age-matched individuals. Furthermore, cancer in people with sarcopenia is an independent risk factor for longer hospitalization and mortality in numerous cancer settings.^{13,14} Finally, certain cancer therapies potentiate signs of sarcopenia; for example, androgen deprivation therapy, used to treat prostate cancer, adversely affects cardiometabolic risk profiles and increases adiposity.

Biological Mechanisms Associated with Aging

Biological mechanisms associated with aging can drive age-related diseases and conditions, including CVD, cancer, emphysema, pneumonia, and diabetes. For example, metformin targets the biology of aging directly or indirectly. In clinical studies, metformin has prevented type 2 diabetes, CVD, Alzheimer’s disease and mild cognitive impairment, and cancer mortality.¹⁵ The Targeting Aging with Metformin (TAME) trial is enrolling more than 3,000 individuals aged 65 to 79 to determine whether metformin can delay the development or progression of age-related chronic diseases, including CVD, cancer, and dementia. TAME-like studies can provide insight into aging processes affecting cancer and CVD, as well as repurposing existing drugs to delay aging.

Another example of the potential benefits of targeting the hallmarks of aging pertains to clonal hematopoiesis of indeterminate potential (CHIP), which is characterized by expansions of leukemogenic mutations (typically in *DNMT3A*, *TET2*, *ASXL1*, *JAK2*, and *TP53*) in blood. One in 10 people older than 70 years who have no other symptoms has CHIP, suggesting a potentially long latency period between the acquisition of relevant mutations and the development of overt clinical abnormalities.¹⁶ Many risk factors for CHIP are similar to those for CVD, including age, African American ancestry, and type 2 diabetes, and CHIP is a strong predictor of all-cause mortality.¹⁷ CHIP is associated with an increased risk of blood cancer, coronary artery disease, subclinical atherosclerosis, and early-onset myocardial infarction. Inhibiting the inflammatory process might reduce the risk of atherosclerotic CVD related to CHIP.¹⁸

Role of Health Disparities in Co-development of Cancer and CVD

Research on the co-development of cancer and CVD must address the health disparities involved. Cancer health disparities are differences in incidence, prevalence, mortality, and burden of cancer among certain subgroups that result in health inequities. In addition to members of racial and ethnic minority populations, populations that experience cancer and CVD health disparities include individuals of lower socioeconomic status, people with disabilities, people who live in certain places (e.g., in rural areas), and LGBTQ+ communities. Contributors to health disparities include environmental, behavioral, social, psychological, and biological factors.

Theme 1 Discussion

Meeting participants noted that drivers of accelerated aging include poverty (which prevents people from eating a healthy diet, exercising, and obtaining health care), membership in a racial or ethnic minority population, and having an obesity-related disease (such as diabetes or hypertension).

Because promoting healthy aging is an appropriate goal for older adults with CVD and cancer, participants discussed when in the life course to initiate pharmacologic gerotherapies, which aim to slow the aging process and may be deployed at any point in the lifespan, and how to foster other interventions that target the aging process (such as exercise, a healthy diet, or interventions that address the social determinants of health). Discussions between clinicians and patients about initiation of cancer therapies provide opportunities to reevaluate the patient's risk factors and reduce the influence of these treatments on aging.

Too many cancer clinical trials exclude older adults with multimorbidity, frailty, or cognitive impairment, even though cancer risk increases with age. Furthermore, even when older adults do participate in clinical trials, they are often unusually healthy for their age and do not represent most older adults. These trials need to enroll more heterogeneous samples, including adults with advanced physiological age, to produce generalizable findings that can support therapeutic recommendations for such patients.¹⁹ Studies should also determine the characteristics of clinical trial participants to determine who does not participate; the findings could inform strategies to overcome barriers to participation for these populations.

Many researchers are investigating the reasons for the limited participation in clinical trials of members of racial and ethnic minority populations, and older adults in these groups are even less likely to enroll in trials.¹⁹ These studies rarely address the lack of opportunities to enroll for many members of these populations because of structural barriers. For example, eligibility criteria for clinical trials often exclude people with hypertension or diabetes, and individuals from underserved populations might be unable to afford the costs of transportation to participate in a trial. Patient navigators for clinical trials can help these individuals enroll and participate in clinical trials.

Table 1 summarizes knowledge gaps pertaining to the mechanisms of co-development of cancer and CVD in an aging population.

Theme 2: Cardiotoxicity in the Older Cancer Survivor

The most common cause of CVD in cancer survivors is exposure to cardiotoxic cancer therapies. Many oncologists offer less intense cancer therapies to older adults to prevent cardiotoxicity.

Mechanisms and Complications of Cardiotoxicity

Cellular senescence is the process by which damaged cells permanently exit the cell cycle. It has been associated with the development of age-related CVD and, with apoptosis, serves as an important failsafe mechanism against growth signaling by oncogenes. Aging and exposure to cytotoxic cancer treatments (chemotherapy and chest radiation) activate several shared molecular pathways associated with premature cellular senescence, which can lead to CVD. Mechanistic pathways implicated in this process include DNA damage, telomere attrition, effects on nicotinamide adenine dinucleotide levels and sirtuin signaling, oxidative stress, inflammation, impairment of mitochondrial function and biogenesis, and autophagy.

Cancer therapies can result in different types of cardiac complications as a result of mechanisms that lead to cardiotoxicity. For example, anthracyclines, such as doxorubicin, can cause cardiomyopathy and might accelerate vascular aging. Doxorubicin also damages mitochondrial functioning, inhibits mitophagy and autophagy, promotes apoptosis within the nucleus, prevents DNA repair, causes DNA breaks, and promotes fibrosis.

Many cytotoxic and targeted cancer therapies induce mitochondrial dysfunction, which might increase vulnerability to adverse cardiovascular effects from cancer therapies in older adults. Persistent mitochondrial injury leads to the release of mitochondrial DNA that activates inflammatory signaling pathways (serving as a damage-associated molecular patterns [DAMPs]).²⁰ As mitochondrial DAMPs are released into the vasculature, they activate important immune pathways, leading to upregulation of many cytokines, including interleukin 6. In addition, the bone marrow forms more myeloid progenitor cells with age, which can contribute to CHIP, an independent risk factor for cardiovascular events. Progressive mitochondrial dysfunction also challenges the heart's ability to meet its metabolic needs.

Adverse cardiovascular events are common during proteasome inhibitor therapy (e.g., with carfilzomib for relapsed multiple myeloma) and are associated with poorer outcomes. Patients with higher levels of natriuretic peptides are more likely to have an adverse cardiovascular event.²¹ Immunotherapies, sometimes used in combination with other cancer treatments or other immunotherapies, might cause myocarditis that, although rare, is associated with a high rate of death within 30 days of diagnosis.²² Immune checkpoint inhibitor therapy can lead to adverse events of the electrical circuit (e.g., atrial fibrillation, ventricular and supraventricular tachycardia), pericardium (e.g., pericarditis), and arteries (e.g., coronary artery disease, atherosclerosis, hypertension).²³ Finally, other cancer immunotherapies, such as chimeric antigen receptor (CAR) T-cell therapy, can lead to many adverse cardiovascular events, including hypotension and arrhythmias.

Cardiotoxicity Management

Top priorities in cardio-oncology are determining the unique underlying mechanism of cardiovascular toxicities, clarifying the role of cardioprotection, identifying robust predictors of cardiotoxicity, and detecting and treating cardiovascular events resulting from immunotherapy.²⁴ Research and guidelines need to examine the optimal roles of imaging techniques, such as echocardiography or magnetic resonance imaging to assess myocardial strain, in identifying early cardiotoxicity from cancer treatment and guiding the timing for administering cardioprotective therapies. Another research gap is how to incorporate prevention of mitochondrial injury in therapeutic strategies to address cancer therapy-associated toxicity.

Most cytotoxic chemotherapies induce senescence in tumor cells through DNA damage, activation of the DNA damage response, telomerase inhibition, and oxidative stress.²⁵ Therefore, therapies that target cellular senescence, or senolytics, might prevent cardiotoxicity in patients undergoing cancer treatment.²⁶ In addition, many drugs used to treat systolic heart failure (including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, beta blockers, and statins) might prevent cardiotoxicity.²⁷ Finally, preventing mitochondrial oxidative stress using DAMPs, or inhibiting the receptors activated by DAMPs might reduce cancer therapy-related inflammation and thus its cardiotoxic effects.

The National Institutes of Health (NIH) Improving Outcomes in Cancer Treatment-Related Cardiotoxicity initiative funds grants to identify and characterize patients at risk of cardiotoxicity as a result of cancer treatment to mitigate cardiovascular dysfunction and optimize cancer outcomes. Since this funding opportunity's initial release in 2016, NIH has funded 37 grants, and the funding rate, 12.6%, is similar to that for NIH grants in general. Approximately a third of these studies focus on preventing cardiotoxicity, and another third address risk prediction for decision-making. The most recent version of this initiative was released in December 2021 (<https://grants.nih.gov/grants/guide/notice-files/NOT-CA-22-001.html>).

Understanding the pathophysiology of chemotherapy-induced cardiotoxicity could shed light on aging and CVD development and vice versa. Partnerships are needed among

cardiologists, oncologists, and geriatricians to develop strategies for monitoring and treating patients undergoing cardiotoxic cancer therapy.

Theme 2 Discussion

During the discussion, meeting participants identified therapies that can inhibit cellular senescence, including metformin and rapamycin, and noted that small molecules are being developed that target apoptosis. More preclinical data are needed before treatments are used to prevent or treat cardiotoxicity in patients undergoing cancer treatment because lysis appears to kill cancer cells, and interrupting this process could reduce the treatment's antitumor effects. Targeting upstream processes (e.g., senescence) might induce multiple deleterious pathophysiologies. Because the secretory inflammatory phenotype is used to define cellular senescence, whether targeting senescence or its downstream effects is optimal is difficult to determine.

Many cardiovascular toxicities from immunotherapies appear to be related to the strength of the immune response. Senescence of immune cells mitigates the antitumor effect of these treatments, so distinguishing the effect on the cardiovascular system from that on the tumor could be challenging. Some drugs in development, including some used to treat heart failure, target various aspects of mitochondrial function and might prevent or mitigate mitochondrial injury from chemotherapy.

See Table 2 for a list of knowledge gaps pertaining to cardiotoxicity in older cancer survivors.

Theme 3: Management of Comorbid Cancer and Heart Disease and Challenges in Medical Decision-Making

Adults with three or more conditions have significant therapeutic complexity and a high risk of institutionalization, complications, and uncertain likelihood of benefit from treatment.²⁸ Siloed approaches to the management of cancer and CVD in older adults can lead to misperceptions of risk and inappropriate delays in care.

Shared Decision-Making

The comprehensive geriatric assessment should be the standard approach to evaluation and follow-up of older adults before and during cancer treatment. This multidisciplinary diagnostic process determines an older patient's medical, psychological, and functional capacity to develop a coordinated treatment and follow-up plan. Validated tools to assess the risk of toxicity from cancer treatment are the Cancer and Aging Research Group Chemotoxicity Risk Score²⁹ and the Chemotherapy Risk Assessment Scale for High-Age Patients Score.³⁰

Clinicians should assess patient values and preferences, including whether they value quality or quantity of life more and which outcomes, other than survival, are important, such as functional status, cognition, or treatment burden and toxicity. Other considerations

are the patient’s capacity to make a decision, patient and clinician biases, and long-term implications.

In shared decision-making, clinicians and patients discuss the best available evidence, and the clinician helps the patient consider available options to made decisions that align with informed patient preferences.³¹ Shared decision-making is used for high-cost, preference-sensitive procedures in cardiology. Requirements for shared-decision-making include the following:

- Patient trust in the clinician and clinician respect for the patient
- Review of treatment options and their attendant risks and benefits using language the patient can understand, including answering any questions from the patient or family in an unbiased manner
- Review of services available to the patient (requires determining whether the patient has access to transportation and can afford each treatment option)
- Determination of whether the evidence base for each option applies to the patient
- Determination of whether the patient is eligible for clinical trials

Shared decision-making tools—which can include pictures, videos, and mobile device apps—increase patient knowledge and satisfaction and reduce anxiety.³² However, these decision aids might not be appropriate for complex decisions, such as for older adults with cancer, CVD, and other comorbidities. In addition, aging-related barriers, such as sensory and cognitive impairments, might make these aids unsuitable for this population.

The bidirectional geriatric and cardiology conference could be extended to cardio-oncology decision-making and can be conducted virtually. In this model, geriatricians, cardiologists, other specialists, and patients discuss the patient’s values and goals in addition to treatment options.

Management of Comorbid Cancer and CVD

Cancer and CVD share several risk factors, including some (e.g., physical activity, diet, and environmental exposures) that are modifiable.³³ These shared risk factors are ripe for collaboration between cardiologists and oncologists and for the use of a public health and preventive medicine approach. Physical activity interventions, for example, could prevent worsening disease and mitigate new onset of disease in both oncology and cardiology.

The Patient Perspective

Older adults with cancer and CVD must make many preference-sensitive decisions, and patient preferences should drive all of these decisions. Probabilities, if available, should be provided to patients because words like “rarely” or “frequently” can be interpreted in different ways that can lead to misunderstanding of risk.

Older adults with cancer have suffered from the cardiotoxicity of certain cancer treatments for a long time, and efforts to minimize risk have been insufficient. This situation has

become dire because of a lack of coordination between cardiology and oncology providers, even though evidence increasingly shows the close connections between cancer and CVD.

Even patients who respond well to cancer treatment and have no evidence of disease face the specter of recurrence, just as patients with CVD fear a stroke or heart attack. This complexity weighs heavily on patients, perhaps especially those who are older, and on providers. The rapid pace of research often provides too many choices and can contribute to conflicting recommendations.

Theme 3 Discussion

Older adults often question whether to use treatments when risks seem to be greater than benefits. Clinicians often overtreat older adults with cancer or CVD, even when patients want to optimize their quality of life. To prevent the use of interventions that might cause treatment burden beyond patients' tolerance threshold, clinicians should talk to patients and family members about the likelihood of problems and management options. Clinicians can ask patients about outcomes and values instead of whether they prefer quality or quantity of life, which is not a meaningful choice to many patients.

Challenges in determining patient values and preferences include cultural factors and language barriers as well as changes in preferences over time. For these reasons, "values" might be a better term than "preferences." Patients need to be at the center of all decisions, even if a family member disagrees with the patient's decisions.

Table 3 summarizes knowledge gaps related to the management of comorbid cancer and CVD as well as challenges in medical decision-making.

Final Conference Discussion

In the final conference discussion, participants focused primarily on practical opportunities. Older adults in general and those with cancer and CVD benefit from exercise interventions, which need to be customized to account for each patient's limitations and safety concerns. Clinicians must support other effective behavior changes as well, including dietary changes and tobacco avoidance.

Disparities related to cancer and CVD are still a substantial problem, and investigators need to be more intentional about enrolling populations that are underrepresented in biomedical research (including groups that do not speak English) in clinical trials. Trials that enroll older adults from racial and ethnic minority groups are challenging because of structural inequities in the clinical trial system. NIH has started requiring investigators to specify how they will recruit study participants and describe the diversity of their sample by race and ethnicity and by age, but investigators must also be held accountable for reaching their accrual goals. Trials that do not meet these goals should receive assistance to overcome recruitment barriers or be shut down.

Most importantly, what matters most to older adults differs by patient. The top priorities for many patients are remaining at home and being able to care for themselves so that they do not burden family members. Clinicians must spend enough time with older patients with

CVD and cancer to engage in meaningful exchanges about the health outcomes that these patients care most about. These discussions should cover patients' top values or priorities (e.g., spending time with grandchildren or great grandchildren, surviving to participate in upcoming events with family members, being able to see well enough to read) and the outcomes (e.g., being unable to read or participate in conversations because of vision and hearing problems) they most want to avoid.

Research Priorities

Issues addressed in this bench-to-bedside conference, "Cancer and Cardiovascular Disease," included mechanisms of cancer and CVD co-development in older adults, cardiotoxic effects of cancer therapy, and management of comorbid cancer and CVD. Presenters discussed approaches to ensure equitable access to clinical trials and health care for diverse populations of adults with CVD and cancer, mechanisms of cancer therapy cardiotoxicity, and management of comorbid CVD and cancer, including the role of patient values and preferences in treatment decisions. Meeting participants noted that exposures—both sociological and physical—across the lifespan influence disease risk and experience and may drive disparities.

Research priorities identified at the meeting included how age-related changes in molecular or cellular pathways drive both conditions and whether treatments that restore or promote favorable biology in these pathways could prevent or treat cancer and CVD in older adults. Figure 1, a modification of a 2019 cardio-oncology framework,²⁴ summarizes cardio-oncology priorities through a geriatrics lens. Filling these and other research gaps identified at the conference could lead to an enhanced understanding of comorbid CVD and cancer and to better and more equitable management strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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- Opening Remarks: Supriya Mohile, MD, MS, University of Rochester; Daniel E. Forman, MD, University of Pittsburgh; Jessica Scott, PhD, Memorial Sloan Kettering Cancer Center
- Mechanisms of Co-Development of Cancer and Cardiovascular Disease in an Aging Population: Michael W. Rich, MD, Washington University in St. Louis; Nir Barzilai, MD, Albert Einstein College of Medicine; Lorna Haughton McNeill, PhD, MPH, MD Anderson Cancer Center; Pradeep Natarajan, MD, MMSc, Massachusetts General Hospital; Anju Nohria, MMSc, MD, MSc, Brigham and Women's Hospital
- Cardiotoxicity in the Older Cancer Survivor: Chunkit Fung, MD, University of Rochester; Aarti H. Asnani, MD, Beth Israel Deaconess Medical Center; Brian Colwell Jensen, MD, University of North Carolina at Chapel Hill; Daniel Lenihan, MD, International Cardio-Oncology Society; Nonniekaye Shelburne, CRNP, MS, National Cancer Institute
- Management of Comorbid Cancer and Heart Disease and Challenges in Medical Decision-Making: William Dale, MD, PhD, City of Hope National Medical Center; Anne Blaes, MD, University of Minnesota; John Dodson, MD, MPH, New York University; Holly M. Holmes, MD, MS, University of Texas Health Science Center at Houston; Beverly Canin, Breast Cancer Options

- Moderated Discussion: Karen Mustian, PhD, MS, MPH, University of Rochester Medical Center

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Key Points:

- Heart disease and cancer are the two leading causes of death among older Americans, and age-related physiologic changes might be implicated in the pathogenesis of both conditions.
- Much more is known about the direct and indirect effects of cancer and its treatment on CVD development than on those of CVD management on cancer development.
- Other research gaps include how to prevent acute and chronic cardiotoxicity from cancer therapies (the most common cause of CVD in cancer survivors), the age-related mechanisms that may underlie both conditions, and best models to deliver patient-centered, high-quality care for older adults with these comorbidities.

Why Does This Matter?

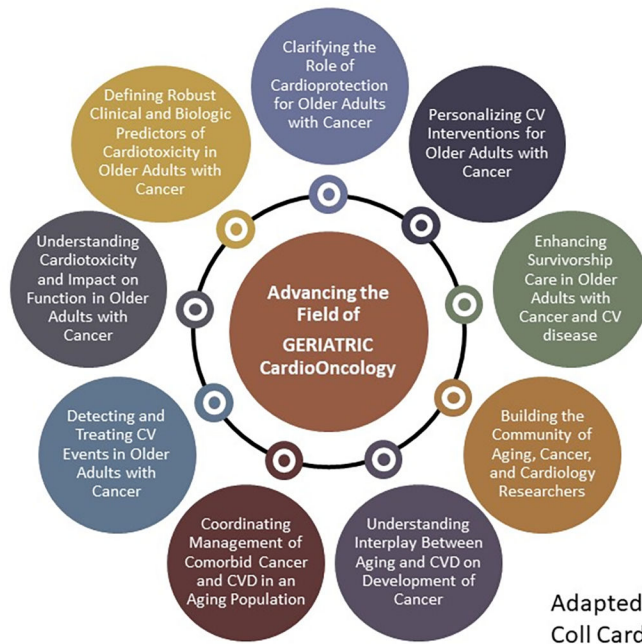
The research gaps and questions identified at this conference enhance our understanding of comorbid CVD and cancer and could lead to better and more equitable management strategies.

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Adapted from: Lenihan DJ et al, J Am Coll Cardiol CardioOnc. 2019;1(2):256-272

Figure 1. Cardio-Oncology Priorities from a Geriatrics Perspective

Adapted from Lenihan DJ, Fradley MG, Dent S, et al. Proceedings from the Global Cardio-Oncology Summit: The top 10 priorities to actualize for CardioOncology. JACC CardioOncol Dec 2019;1(2):256–272. doi:[10.1016/j.jacc.2019.11.007](https://doi.org/10.1016/j.jacc.2019.11.007)

Abbreviations: CV, cardiovascular; CVD, cardiovascular disease.

Table 1.

Co-Development of Cancer and CVD in an Aging Population: Key Knowledge Gaps

| | |
|--|--|
| Mechanisms and risks | What are the direct and indirect effects of CVD and its treatment on cancer development? |
| | What are the mechanisms of CVD's effects on cancer development and progression? |
| | What is the association between the aging process related to CVD and cancer co-development and different sociodemographic characteristics? |
| | Do primary malignancies influence the development or expansion of CHIP mutations? |
| | What are the risk factors for CHIP in older adults? |
| | Which tissues and cell types are involved in cardiotoxicity? |
| | How can existing datasets (e.g., Childhood Cancer Survivor Study, National Cancer Institute's Cancer Research Data Commons) be leveraged for systems epidemiology studies? |
| | Which animal models can represent functional capacity and frailty in humans and thus be of value for examining mechanisms of CVD and cancer co-development? |
| Can dynamic phenotyping stratify older adults with cancer and CVD by risk? | |
| Interventions | How can behavioral interventions (e.g., exercise, healthy diet) be fostered across the life course to prevent cancer and CVD in older age? |
| | How can the baseline cardiovascular assessment in older patients undergoing chemotherapy best be tailored to individual clinical circumstances and patient preferences? |
| | Why do various older patients with a history of cancer and CVD respond differently to exercise therapy? |
| | How can the barriers to participation in cancer and CVD clinical trials of underrepresented populations be overcome? |
| | How can cancer and CVD clinical trials use physiological measures rather than chronological age to determine eligibility? |
| | What should be the components of the baseline cardiovascular assessment for older adults treated with chemotherapy? |
| | When in the life course should pharmacologic gerotherapies be initiated to prevent cancer and CVD co-development? |
| | What are the effects of senolytic therapies on the cardiovascular system and tumors within the same animal model? |
| | Can drugs with U.S. Food and Drug Administration approval (e.g., SGLT-2 inhibitors, rapamycin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers) delay aging and thus prevent cancer and CVD? |
| Can targeted biopsy specimens (e.g., myocardial), novel imaging modalities, or both obtained in patients starting cancer treatment help identify the mechanisms of cardiotoxicity and predict late cardiotoxicity? | |

Abbreviations: CVD, cardiovascular disease; CHIP, clonal hematopoiesis of indeterminate potential.

Table 2.

Cardiotoxicity in the Older Cancer Survivor: Key Knowledge Gaps

| | |
|--|---|
| Drivers of cardiotoxicity | Which molecular markers are specific to cellular senescence? |
| | How do cardiotoxic cancer therapies affect genetic alterations associated with aging? |
| | How does cellular senescence predispose older adults with cancer to develop immune-mediated myocarditis or CVD? |
| | Do senolytic cells or the downstream effects of inflammation, mitochondrial dysfunction, and other processes drive cardiotoxicity? |
| | How does stress (including that resulting from social determinants of health and health disparities) affect the severity of and physiologic and psychologic response to cardiotoxicity? |
| | Which cardiovascular cell type(s) are most affected by cancer therapy-induced senescence? |
| | How do we identify risk factors and biomarkers for cardiotoxicity in older adults? |
| Risk prediction | Which factors can reliably predict cardiotoxicity in older adults undergoing cancer treatment? |
| | Which biomarkers can be used to detect cardiotoxicity in older patients with cancer? |
| | What are genetic risk factors for cardiotoxicity in older patients with cancer? |
| | How do we identify risk factors for and biomarkers of cardiotoxicity in older individuals? |
| | How can older patients be stratified by cardiotoxicity risk to determine who needs a referral to a specialist? |
| Prevention and treatment of cardiotoxicity | How can acute and chronic cardiotoxicity from cancer treatments be prevented? |
| | Does inhibition of DAMPs, preventing mitochondrial oxidative stress, or inhibiting receptors activated by DAMPs reduce the cardiotoxic effects of cancer therapy? |
| | How can myocarditis associated with immunotherapy be prevented or treated? |
| | Would targeting senolytic cells with therapy prevent cardiotoxicity? |
| | Can cancer treatment-related cardiotoxicity be prevented with statins, beta blockers, other pharmacologic agents, and lifestyle interventions? |
| | What is the best way to coordinate care for cardiotoxicity in older patients with cancer? |

Abbreviations: CVD, cardiovascular disease; DAMPs, damage-associated molecular patterns.

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Table 3.

Management of Comorbid Cancer and CVD in an Aging Population: Key Knowledge Gaps

| | |
|------------------------|---|
| Management | What is the role of geriatric assessment in prioritizing the care of patients with coexisting cancer and CVD? |
| | How can screening and surveillance strategies for cancer and CVD be adapted to be more informative? |
| | What are ideal models of care for older patients with cancer and CVD? |
| | How can care be best coordinated among primary care, geriatrics, oncology, and cardiology? |
| | How can overtreatment of cancer or CVD in older adults be measured? |
| | What are the appropriate forms, doses, and schedules of exercise interventions in older adults with cancer and CVD? |
| | How can patient and clinician uptake of promising assessment tools for patients with cancer and CVD be increased? |
| Shared decision-making | Which tools can support shared decision-making processes for older adults with cancer and CVD? |
| | Which frameworks can be used for real-time multidisciplinary decision-making? |
| | How can patient priorities drive treatment in the context of cancer and CVD? |
| | Which outcomes other than survival should be measured in adults with cancer and CVD? |

Abbreviations: CVD, cardiovascular disease.

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