Review Article

New directions in cancer and aging: State of the science and recommendations to improve the quality of evidence on the intersection of aging with cancer control

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BACKGROUND: The global population of older cancer survivors is growing. However, the intersections of aging-related health risks across the cancer control continuum are poorly understood, limiting the integration of aging into cancer control research and practice. The objective of this study was to review the state of science and provide future directions to improve the quality of evidence in 6 priority research areas in cancer and aging. **METHODS:** The authors identified priority research areas in cancer and aging through an evidence-based *Research Jam* process involving 32 investigators and trainees from multiple disciplines and research centers in aging and cancer; then, they conducted a narrative review of the state of the science and future directions to improve the quality of evidence in these research areas. Priority research areas were defined as those in which gaps in scientific evidence or clinical practice limit the health and well-being of older adults with cancer. **RESULTS:** Six priority research areas were identified: cognitive and physical functional outcomes of older cancer survivors, sampling issues in studies of older cancer survivors, risk and resilience across the lifespan, caregiver support and well-being, quality of care for older patients with cancer, and health disparities. Evidence in these areas could be improved through the incorporation of bias reduction techniques into longitudinal studies of older cancer survivors, novel data linkage, and improved representation of older adults in cancer research. **CONCLUSIONS:** The priority research areas and methodologies identified here may be used to guide interdisciplinary research and improve the quality of evidence on cancer and aging. ***Cancer* 2022;128:1730-1737**.

KEYWORDS: aging, caregiving, cognitive function, health disparities, interdisciplinary research, life course, methodology, physical function, sampling.

INTRODUCTION

The intersection of population aging with peak cancer incidence at ages 65 to 74 years is projected to result in a substantial increase in the number of older adults diagnosed with cancer.[1-3] Population-level data are needed to identify how aging can best be addressed across the cancer control continuum and how aging intersects with cancer across the lifespan. Older adults have heterogenous accumulated lifespan cancer risks, and little is known about the best targeted preventive interventions for this group.[2] The long-term effects of cancer and its treatments for aging are poorly understood, as are the roles of socioeconomic, social, behavioral, and psychological risk and resilience factors that could promote healthy aging for older survivors.[4-8] These critical knowledge gaps limit clinical and public health practice to control cancer as well as improve outcomes for older survivors.

Motivated by the critical gaps described above, the US National Cancer Institute (NCI) issued a call in Spring 2020 for supplemental funding to NCI-funded Comprehensive Cancer Centers to develop sustainable infrastructure to support new interdisciplinary research programs in cancer and aging. Supported by the NCI, we formed an interdisciplinary Cancer and Aging Initiative at the University of Michigan (U-M) Rogel Cancer Center. In February 2021, we held a retreat in collaboration with the Michigan Institute for Clinical and Health Research (MICHR).[9] In this article, we

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describe the *Research Jam* methodology used by MICHR to support our interdisciplinary group in elucidating priority research areas and building collaborations, and we comprehensively review the current state of science and future research directions to improve the quality of evidence in 6 cancer and aging priority research areas.

MICHR RESEARCH JAM METHODOLOGY

Funded by the National Center for Advancing Translational Sciences at the US National Institutes of Health, MICHR is a unique institute that acts as a catalytic partner to support research teams at U-M. MICHR uses various design thinking principles to create *Research Jams*,[10,11] which are facilitated brainstorming sessions that bring together new groups to collaboratively surface novel research ideas, build working groups, and identify next steps. In partnership with MICHR, we held a one-half–day virtual Research Jam for 32 faculty, staff, and community members representing 16 U-M departments/units and 2 community organizations. After opening remarks, attendees participated in 3 rounds of small group networking at which they were asked to discuss the *wicked problems*[12] in research or patient care they would pursue to improve the health and well-being of older adults with cancer. From these interactions, 32 wicked problems were captured during a large group report out. Next, through an activity called *brainwriting*,[13] participants brainstormed research topics (ie, broad, actional strategies) that could address 1 or more of the wicked problems. By using affinity mapping,[14] a method organizing information into related categories, participants grouped the resulting 223 research topics into clusters and assigned overarching themes to each cluster. Each attendee was provided 3 *interest cards* displaying their name, picture, and affiliation, which they were asked to place next to any of the clusters/theme(s) they were most interested in pursuing.[11] These structured activities provided an instant visual representation of the groups' priority research areas and an understanding of where individual interests mapped. Acknowledging there would be expertise outside of the session integral to advancing the proposed work, attendees spent time identifying 20 critical individuals, disciplines, and organizations they would want to engage moving forward. The session ended with action planning, in which attendees identified 18 next steps and took ownership of assignments, including the formation of working groups. We identified 6 research areas to summarize and narratively review here: 1) cognitive and physical functional outcomes of older cancer survivors, 2) sampling issues in studies of older cancer survivors, 3) risk and resilience across the lifespan, 4) caregiver support and well-being, 5) quality and coordination of care for older cancer patients, and 6) health disparities. This review was deemed exempt from regulation by the University of Michigan Health Sciences and Behavioral Sciences Institutional Review Board (HUM00206168).

PRIORITY RESEARCH AREAS IN CANCER AND AGING

Cognitive and Physical Functional Outcomes of Older Cancer Survivors

Cognitive and physical function impairments among older cancer survivors have been reported in clinic-based and population-based observational studies.[15-18] Prevalence estimates among older cancer survivors vary widely because of heterogeneity in study methodologies, and, although functional impairment assessments exist, there are inconsistencies in the definitions of and methods for ascertainment of functional impairment.[5,19-21] The causal roles of carcinogenesis and cancer treatments in altering ongoing physical and cognitive aging trajectories among older adults with cancer thus remain unclear.[22] However, the biologic rationale for accelerated physical and cognitive aging trajectories among older cancer survivors is strong.[23] Radiation therapy and several cytotoxic and genotoxic chemotherapies induce cellular changes that are consistent with several hallmarks of biologic aging, including inflammation,[24] cellular senescence,[25] and DNA damage.[25] Furthermore, social factors, such as psychosocial stress,[26] financial cost,[27] and disruption to social relationships,[28] involved with a serious chronic disease diagnosis like cancer may negatively affect functional aging outcomes.

The prototypical trajectories of functional aging among the general population of older cancer survivors have not been definitively identified.[22] There remain challenges around the definition and measurement of physical and cognitive outcomes and around the definition of a *normal* functional aging phenotype for comparison.[22] Functional aging is highly heterogeneous even in the general cancer-free population,[29] with a range of risk and protective factors that may interact with a cancer diagnosis and treatment. Physical and cognitive function may be measured objectively and subjectively, with both constructs having salience for different research and clinical purposes.[30,31] There are several opportunities to improve causal inference about the role of cancer and cancer treatments in exacerbating functional impairments over and above what is typically seen with aging. Valid causal estimates are necessary for the development

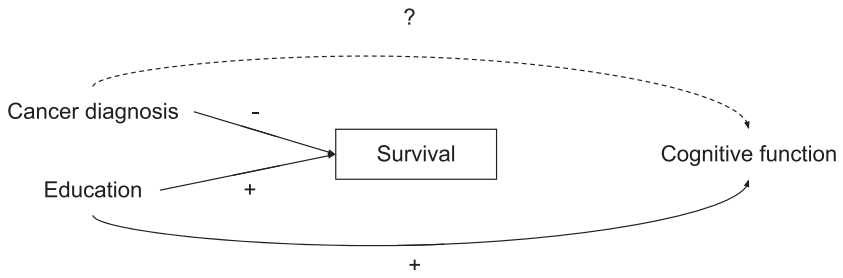

Figure 1. Selective survival bias is illustrated using education as an example of a factor that could bias a hypothesized relation between cancer and subsequent cognitive function (indicated by the dashed arrow with a question mark above it). The box around *survival* indicates that research studies are restricted to individuals who survive to the time of study enrollment, whether they are cancer survivors or cancer-free controls as a comparison group. The minus (–) and plus (+) signs next to the solid black arrows indicate known relations with negative and positive directions, respectively. A spurious observed relation between cancer and subsequent cognitive functioning could be induced through the *back-door path* opened by the 3 causal paths (indicated by the solid black arrows) because the study sample was restricted to survivors.

and implementation of effective interventions to support healthy aging among older cancer survivors.[32]

Four possible approaches to improve the quality of evidence on functional outcomes of older cancer survivors are: 1) to incorporate prediagnostic data on risk factors, covariates, and outcomes; 2) to account for bias due to the selective survival of healthier cancer survivors; 3) to include cancer-free controls, and 4) to improve the population-representativeness of studies.

Sampling Issues in Studies of Older Cancer Survivors

Incorporation of prediagnostic data

Most cancer survivorship studies recruit participants at the time of or after a cancer diagnosis. Prediagnostic data on aging outcomes are unavailable in these studies unless retrospectively self-reported or collected from medical records. As a result, within-person changes in ongoing aging trajectories from prediagnosis to postdiagnosis cannot easily be identified, and study results may be biased because of recall error from retrospective self-reports. Access to data collected before diagnosis would ensure that results of survivorship studies among older adults are free from recall bias. Furthermore, modelling changes in functional aging trajectories from prediagnosis to postdiagnosis using prospectively collected data would allow empirical testing of hypotheses about accelerated aging and cancer.[33,34]

Selective survival bias

Cancer survivorship studies, by definition, are studies of individuals with cancer from the time of diagnosis through the end of life.[35] Individuals who die before study recruitment can take place, such as those with cancer types or stages that have lower survival or whose health precludes them from taking part in a research study, are excluded, meaning that cancer survivorship studies represent a selective, and likely healthier, fraction of all older adults diagnosed with cancer.[36-38] Figure 1 presents a directed acyclic graph that illustrates a potential mechanism through which selective survival bias could induce a spurious link between cancer and a functional aging outcome. Where possible, cancer survivorship studies should gather data on the potentially eligible individuals who died rapidly after diagnosis or otherwise did not participate to enable an evaluation of the potential magnitude of selective survival bias in their study. Inverse probability weights for study participation, as well as attrition because of death or loss to follow-up, can be created to help deal with selective survival bias in cancer survivorship studies.[38] This issue is particularly relevant in survivorship studies among older adults, who have higher risk of mortality than younger populations.

Appropriate selection of cancer-free controls

Cancer survivorship studies often do not include cancer-free controls.[6] The lack of cancer-free controls limits our understanding of how cancer and its treatments affect outcomes, over and above normal aging alone. Studies that have included cancer-free controls suggest that cancer survivors often report poorer health and more psychological and functional disabilities[16,39-41] compared with their cancer-free counterparts. However, there remains a need to better understand how cancer and its treatments could accelerate the normal aging process through appropriate comparisons with cancer-free controls.

The appropriate selection of cancer-free controls is a methodological challenge because the inappropriate selection of controls can result in biased estimates.[37,42]

Cancer-free controls need to represent the source population from which cancer cases arose, representing the population that the cancer cases would have become had they not developed cancer. In clinical settings, this means that controls should be recruited from the same catchment areas as the cases and that they should be eligible to have developed the cancer in question and to have presented to the health care system in a similar way had they developed the cancer in question. Investigators should also consider matching on key sociodemographic and other factors.

Population-representativeness of studies

Although not all studies need to be population-representative, selection bias can distort results if participation in a study is correlated with both the exposure and the outcome.[43] There has been limited research on cognitive and functional aging outcomes in population-representative samples of older cancer survivors. Clinic-based studies have been instrumental in shaping this research field by illustrating functional aging and its clinical risk factors.[44,45] However, study samples recruited from clinical settings often tend to be of higher socioeconomic status and relatively healthier compared with the general population, except for their cancer diagnosis, creating a potential selection bias. Furthermore, studies that disproportionately represent those with higher education, socioeconomic status, or health status can be limited in their exposure and outcome variable ranges, which can lead to inaccurate conclusions and recommendations for specific population groups only. Under-representation and nonrepresentation of historically under-represented and marginalized population groups limit the potential for investigating cancer and aging outcomes for the whole population and for addressing disparities in these outcomes.

Role of ongoing cohort studies of aging

Ongoing cohort studies of aging adults, such as the US Health and Retirement Study, the Atherosclerosis Risk in Communities study, and the Women's Health Initiative, can provide high-quality prediagnostic data on risk factors, covariates, and outcomes and provide a well defined sampling frame of older adults with cancer, allowing the implementation of methods to help deal with selective survival bias. These cohorts also provide appropriate comparison groups of cancer-free individuals. Although each cohort study has limitations, such as limited cancer treatment and other clinical data, several can be linked to cancer registries or have cancer-specific substudies that can be used by researchers. The use of ongoing cohort studies for cancer and aging research is important for the triangulation of evidence across different study designs and populations and for providing insights that are not possible to gain from smaller, clinic-based studies.

Risk and Resilience Across the Life Span

Most cancer survivorship studies recruit participants at the time of or shortly after a cancer diagnosis. Similarly, most mature cancer incidence cohorts have recruited participants in middle or older age and have assessed exposures prospectively from enrollment. However, early life exposures may be important for cancer and aging outcomes.[46,47] The field of life course epidemiology has focused extensively on these lifetime *windows of susceptibility*, with many epidemiologists arguing that exposures, both detrimental and protective, throughout the lifespan likely contribute to chronic disease risk and resilience later in life.[48] For example, there are important windows of susceptibility for breast cancer throughout the lifespan, including prenatal, puberty, pregnancy, and the menopausal transition, all periods when changes are occurring in the breast tissue and microenvironment.[49] This is likely true for cancer at other sites and for functional aging outcomes like cognitive and physical impairments, but the lifetime windows of susceptibility are less easily defined and more difficult to assess than those for breast cancer, in which major life events like puberty and pregnancy are associated with tissue changes and are relatively easy for participants to define and recall.

Accurately collecting exposure data from early life for the investigation of cancer risk as well as aging in cancer survivors is challenging but essential to establishing and implementing effective prevention strategies. Some researchers have used creative solutions to this problem. For example, some US states, such as Michigan, have established biobanks of neonatal blood spots.[50] The Michigan Neonatal Biobank includes dried blood-spot specimens from newborns representing nearly every Michigan birth since October 1987.[51] Linking existing study populations with these banked biospecimens may prove invaluable to future studies of cancer and aging. Some researchers have suggested that *-omics* approaches, such as metabolomics, may provide an integrated measure of lifetime exposure, although these technologies have yet to fully deliver on that promise.[52] Ideally, future cohort studies will recruit younger populations, enabling prospective exposure assessment from younger ages while developing novel strategies to assess early life exposures using novel biomarkers as well as integrating data from stored records, such as electronic health records, and using enhanced questionnaire techniques.

Caregiver Support and Well-Being

Health care systems routinely depend upon support provided by the friends and family of patients (ie, caregivers).[53] Cancer caregivers provide approximately 8 hours of care per day for approximately 15 to 18 months,[54] with the amount and intensity of care increasing with advanced disease.[55] The age of the older adult with cancer,[56] comorbid health conditions,[57] stage of illness, and type and duration of treatment influence the care needs of recipients and the responsibilities placed upon cancer caregivers. Although cancer caregivers have reported positive aspects of serving in this role,[58] health problems like sleep disturbances, fatigue, and psychological distress are common issues that affect caregiver well-being.[59] Because cancer caregivers may be managing their own health conditions,[60] and the health of caregivers and care recipients are interconnected,[61] improving the supports provided to cancer caregivers is critically important.

Cancer caregivers often report feeling inadequately prepared for the level of care needed, the provision of medical and nursing tasks, communication with medical professionals, and the emotional needs of patients and other family members.[59] A lack of routine and standardized education and skills training for cancer caregivers[55] contributes to the onset and persistence of these challenges. Caregiver assessments, such as the Zarit Burden Interview[62] and geriatric assessments, are also useful tools for collaborating with patients and caregivers to identify strengths and supportive care needs. For timely interventions to occur, it will be important to overcome barriers to routine provision of caregiver education and use of caregiver and geriatric assessment tools.

Broader policy efforts to increase resource allocation to support caregiver and family health needs during acute and chronic illness can also contribute to strengthening support for cancer caregivers in clinical and community contexts.[63] The National Family Caregiver Support Program aims to address the unmet needs experienced by informal caregivers by funding programs to assist with counseling, companionship, supervision, and respite care.[64] This program has been successful in decreasing the burden felt by caregivers,[65] but its effect on cancer caregiving for older adults is unclear. Finally, it is important to recognize that, for many families, multiple individuals work together to form a caregiving unit. Therefore, the common tasks of cancer caregivers, such as assistance with mobility, emotional support, care coordination, and nursing and medical duties, may be completed by more than 1 individual and can shift over time based on the resources and needs of the patient and the caregiving unit. Greater attention to caregiving systems in cancer care and their implications for research, policy, and clinical practice is needed.

Quality and Coordination of Care for Older Patients With Cancer

Older adults with cancer face multifactorial and complex challenges. Chronologic age is not a reliable indicator of the functional age of older adults with cancer, and this results in many older patients receiving low-quality cancer care because of overtreatment or undertreatment.[66] In addition, serious medical conditions or dependence on multiple medications often necessitate modifying standard treatment protocols. Although guidelines for cancer treatment in older individuals are available, a lack of evidence has created large knowledge gaps for informing these guidelines.[67] Physiologic changes because of aging, comorbidities, and polypharmacy also affect cancer drug performance and toxicity.[68,69] Additional observational research is warranted to improve understanding how comorbidities and polypharmacy influence the receipt of guideline-concordant treatment among older adults.

Cancer survivorship care is often complex and difficult to coordinate among older adults.[70] With an overburdened oncology workforce and the rapid growth of the aging population with complex care needs, there is a critical need to develop risk-stratified survivorship care that is aligned to the needs of individual patients and, in the case of older adults, that should consider life expectancy, functional status, comorbidities, and polypharmacy.[71] Geriatric assessments provide a comprehensive understanding of physical function, cognition, nutrition, comorbid conditions, psychological status, and social support.[5] Guidelines recommend geriatric assessments for all patients aged 65 years and older diagnosed with cancer who are starting chemotherapy.[68,72] However, only one-third of community oncology practices report having access to a geriatrician for consult, and only 5% have access within the oncology clinic.[73] Future research needs to comprehensively assess the functioning of older adults with cancer, identify their supportive care and social support needs, assess their capability for managing and accessing care, and characterize the involvement and needs of caregivers to facilitate the delivery of high-quality survivorship care to older adults with cancer.[71]

Health Disparities

Given the increasing diversity of the aging population, it is critical to understand health disparities across the cancer continuum[74] to improve equitable healthy aging of older survivors. Sociodemographic subgroups can experience

cancer differently, with many people of color and those with lower socioeconomic status having higher prevalence, incidence, and mortality and lower rates of cancer screening, survivorship, and quality of life.[75] Despite the importance of equitable healthy aging, disparities in the effects of cancer and its treatments on functional aging outcomes are poorly understood. Previous research has identified disparities in aging outcomes of older cancer survivors across the cancer care continuum according to race/ethnicity, income, geographic location, and age, among others.[76-78] Less research has considered the intersectionality of these social determinants. Recognizing within-group heterogeneity is important because individuals have multiple social statuses.

In addition, underserved older adults are less often recruited into cancer research, limiting our understanding of disparities faced by this population group. Underserved older adults may have specific barriers to quality care. More research is needed to better elucidate health disparities across all of the priority research areas identified in this article and to identify modifiable factors that can be used as intervention targets to improve health equity among older cancer survivors. Furthermore, cancer clinical trials are not representative of most older patients. Not only are trials focused on older cancer patient populations with broader eligibility criteria a necessary next step to improve representation and equity, these trials also must evaluate end points relevant to older adults, including functional decline and quality of life. The success of these trials will require addressing common challenges for older adults' participation in trials, including accessibility, the burden of trial procedures, caregiver involvement, and financial challenges.[79,80]

Three approaches to improve the quality of evidence on health disparities among older adults with cancer are: 1) to further develop studies that include multilevel life course data on risk factors and covariates, 2) to improve the representation of people of color and other underserved older adults into cancer research, and 3) to incorporate an intersectional approach to cancer and aging research to account for how the intersection of sociodemographic categories may influence outcomes across the cancer continuum from prevention to the end of life.

CONCLUSION

New, interdisciplinary research teams, programs, and agendas are needed to address the changing landscape of cancer control as influenced by population aging. There are urgent research and clinical questions that require development in the 6 priority research areas described here to improve the health and well-being of older adults with cancer. The key future research directions to improve the quality of evidence on cancer and aging provided in this article may be used to guide interdisciplinary research and improve the quality of evidence on cancer and aging.

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CONFLICT OF INTEREST DISCLOSURES

Katrina R. Ellis reports honoraria from the University of Michigan School of Social Work (the Winkleman Lecture) and service on the Professional Advisory Board of the Cancer Support Community of Ann Arbor (nonpaid) outside the submitted work. Lauren P. Wallner reports an American Cancer Society Research Scholar Grant (ACS RSG-19-015) and service on the Data Safety and Monitoring Board as Chair for the EPICS Study (National Cancer Institute R01CA249419) outside the submitted work. The remaining authors made no disclosures.

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