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Are the chronological age cutoffs used in clinical oncology guidelines biologically meaningful?

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Abstract

Age is one of the strongest risk factors for cancer, and also affects tumour biology, treatment recommendations and response to therapy. Although clinical oncology guidelines advocate against classifying patients on the basis of chronological age alone, most studies and published guidelines use discrete age cutoffs, often heterogeneously. Herein, we discuss age cutoffs from a historical and biological perspective, focusing on breast cancer.

Cancer is predominantly a disease of ageing: the incidence of many epithelial tumours increases with age. With a peak incidence at around 70 years of age, breast cancer is no exception. Moreover, more than one-third of all breast tumours are diagnosed in patients over this age[1,2]. In older patients with breast cancer, the biology of the disease has a more indolent phenotype that reflects an enrichment of hormone receptor-positive tumours, a phenomenon that has been recognized for decades[2]. A question that remains to be answered, however, is whether this transition occurs at a discrete age or whether breast cancer biology changes gradually with age after menopause.

Despite the marked predominance of breast tumours in older women, the age at which individuals transition from 'younger' to 'older' has been defined in a heterogeneous, unstandardized, arbitrary and disparate manner. The European Society of Breast Cancer Specialists (EUSOMA) and International Society of Geriatric Oncology (SIOG) cite 70 years as the cutoff age for applicability of their joint guidelines for breast cancer in older women[3]. The US National Comprehensive Cancer Network (NCCN) Breast Cancer Guidelines use 65 years as an age cutoff, but defer special considerations for older women with breast cancer to the NCCN Older Adult Guidelines[4]. While the Older Adult Guidelines use the same age cutoff, the studies cited in the Discussion section provided up to seven different definitions for older patients: 55, 60, 65, 66, 67, 70 and 75 years of age[5]. Further complicating the situation, the authors of the guidelines also include their own classification for older adults: young-old (65–75 years), old (76–85 years), and oldest-old (≥85 years). Is there a biological rationale for any of these age cutoffs? Why are they used?

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Competing interests

The authors declare no competing interests.

Most of the original rationale for using these age cutoffs is historical and societal. In the US, Social Security benefits of retirement traditionally begin at 65 years of age; the original Social Security Act of 1935 set this as the minimum age for receiving full retirement benefits. We can continue the chain of questions by asking why this age was chosen. The answer resides in two precedents[6]: (1) various private and state-run pension schemes at the time used age criteria of either 65 or 70 years, and when actuarial studies (that take into account life expectancy and budgets) examined both cutoffs, they concluded that 65 years was optimal both for the individual and the system itself to be self-sustaining; and (2) Germany, one of the first countries to adopt a social assistance programme for its older population, was at that time using 65 years of age to define this population. Therefore, although many of the initial definitions of age cutoffs did not rely on a biological rationale, life expectancy had a prominent role in decision-making.

Thus, the cutoffs initially used in oncology guidelines were borne out of convenience and did not necessarily indicate biological relevance. In reality, the ageing process is dynamic and heterogeneous across the population, occurs at different times in each individual, and can be more dysregulated in those with cancer[7]. The search for a biomarker of ageing, one that indicates impending frailty and/or is associated with physical deterioration, has been elusive[8]. Patient-based metrics, such as comprehensive geriatric assessments and other measurements of frailty or comorbidities, are used in the clinic as proxies for the ageing process, but they have limitations in predicting life expectancy, cancer trajectory or future quality-of-life decrements. Ongoing research is seeking to characterize ageing biomarkers; of note, a study with results published in 2021 identified the chemokine CXCL9 as a potential blood-based biomarker that enables tracking of multimorbidity, immunosenescence and frailty[9]. This research field has its own challenges including, among others, the need for large cohorts of patients to develop and validate such markers, and the need for further insight into whether circulating biomarkers drive or are merely associated with tissue ageing. Nevertheless, the identification of markers of ageing developed on the basis of a biological rationale could aid in the stratification of patients in clinical guidelines. For example, a biomarker-defined age could be identified that is associated with impending onset of multimorbidity and thus, would drive the creation of more tailored guidelines. Such quantitative markers would help to further classify patients in biologically meaningful ways in conjunction with chronological age.

Let’s consider two hypothetical patients as an example. Both have been newly diagnosed with a 1 cm-sized oestrogen receptor-positive (ER+), node-negative tumour. Their ages are 69 and 70 years. Some guidelines would recommend omission of certain interventions, such as axillary staging, in the older patient but not in the younger one purely on the basis of chronological age and not owing to tumour biology or ageing phenotype. However, the use of a biologically developed biomarker might reveal signs of accelerated ageing in the 69 year-old patient, for whom de-escalation of care would be more appropriate, and not in the 70 year-old, who might be quite fit and have a longer life expectancy and limited competing multimorbidity, making her a better candidate for more aggressive care. Thus, heterogeneity in age cutoffs creates challenges when treating older patients.

Inequities in clinical trial enrolment further compound the heterogeneity in age cutoffs in clinical guidelines. The fact that older patients are under-represented in clinical trials is well known, and breast cancer trials are no exception, given that the median age at enrolment is nearly 8 years younger than the median age of disease onset[10]. The increased attention on de-escalating therapy for older women with breast cancer, however, has led to new trials focused specifically on this population. While this interest is welcome, these trials further propagate discrepancies in age cutoffs. For example, three ongoing trials of radiotherapy dosing approaches define older women with ER+ breast cancer using different age cutoffs: 60, 65 and 70 years in DEBRA (NCT04852887), PRIME II (ISRCTN95889329) and EUROPA (NCT04134598), respectively. Standardizing age cutoffs in clinical trials to subsequently facilitate guideline design should be a priority.

Additional research is needed to establish changes that occur with ageing, especially in patients with cancer, in whom the disease and its treatment might alter this biological process. Although research into biomarkers of ageing is progressing, no such biomarkers are currently used in the clinic. In effect, we propose that guidelines, in particular those for older patients, adopt frailty-based instead of chronological age cutoffs. Such efforts are stymied by the fact that, despite being useful, geriatric assessment tools currently available to estimate patient life expectancy are time-consuming and somewhat cumbersome to apply, and therefore not routinely used in clinical practice. A blood-based biomarker or set of biomarkers that enable identification of ageing phenotypes could be easier to adopt in routine clinical practice. Initiatives to reduce ambiguity and standardize the definition of older patient in clinical oncology guidelines are also warranted, and will help to implement homogenous clinical trial enrolment age standards, and guide clinical and translational research. Our ultimate goal as a community should be to integrate biological criteria with clinically and chronologically relevant classifications that will better guide the design of clinical oncology guidelines.

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