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Solicited Editorial

Long-Term Cancer Survival: New Insights From Health Professional Cohorts

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As clinicians are well aware, the first question someone receiving a new cancer diagnosis poses is, "How long will I live?" The response hinges on the stage of the disease, the aggressiveness of the malignancy, treatment options, and the underlying health of the patient. Longevity then depends on the success of treatment; the holistic impact of the diagnosis on the patient's health and well-being; and, broadly, on the social determinants of health as they intersect with the patient. Additionally, factors that increase risk of incident cancers (eg, cigarette smoking) are causally linked to diseases that shorten life span and to increased risk of a second malignancy (1). Treatments for the primary cancer, both radiation and chemotherapy, may also increase risk of a second cancer (1).

Longevity is typically explained with figures about survival, perhaps 1-year, 3-year, and 5-year survival rates, depending on type and stage of cancer, treatment chosen, and the patient's circumstances. In the United States, these figures are generally based on cohort analyses of registry data, including those from the National Cancer Institute's Surveillance, Epidemiology, and End Results program and the North American Association of Central Cancer Registries (2). Using these data, substantial gains in survival over time have been documented for many sites (3).

In this issue of the Journal, Cheng and colleagues (4) describe long-term survival and causes of death after diagnosis of common cancers in 3 well-known cohorts: the Nurses' Health Study, the Nurses' Health Study II, and the Health Professionals Follow-up Study. The investigators estimated long-term overall and cause-specific cumulative mortality to more than 30 years from diagnosis. In considering long-term mortality from cancer, competing risks cloud the picture, particularly as participants in these studies were middle-aged and older across the years of follow-up. Consequently, Cheng and colleagues used a statistical methodology to estimate cumulative mortality under a counterfactual that all other causes of death were removed. The main results are presented as cumulative mortality (ie, the proportion deceased).

As anticipated, 2 distinct patterns of mortality emerged over time: 1) an immediate rise in cancer mortality after diagnosis, with little additional cancer-specific mortality after approximately 10 years (eg, lung cancer), and 2) a slow rise in mortality after diagnosis, reaching a plateau after 10 years (eg, breast cancer and prostate cancer) (4). One key analysis assesses whether there are inflection points in the slopes of mortality, indicative of landmarks in prognosis, other than the generally selected 5- and 10-year survival points. Statistically significant changes in slope were identified for cancers of the lung and urinary bladder as well as melanoma in men and for cancers of the lung, colon and rectum, and uterus in women. The inflection points were at time points beyond 10 years, and the declines in slope after inflection were substantial.

The findings that Cheng et al. (4) reported based on cohort studies of health-care workers do not provide insights concerning the many factors that determine the quality of survival. Cohort participants in the Nurses' Health Study and Health Professionals Follow-up Study presumably had access to a high quality of care, as afforded by their professions, along with high levels of health literacy. Most likely, they had health insurance that shielded them from the severe economic consequences of their diagnosis and ensured follow-up care. For the past several decades, however, advances in cancer treatment have come at greater costs, making cancer one of the most expensive conditions to treat (5). High-deductible health insurance plans that shift financial responsibility for health care to the patient are now more common, with nearly 40% of the US population covered by such plans in 2016 (6). Evidence suggests that as patients increasingly pay higher co-pays and deductibles for health care (7,8), some will forgo preventive services (6), including cancer surveillance. We may have an increasing proportion of people presenting with more advanced cancers as a result.

Although this study shows that long-term cancer survival can be achieved, many economic and social conditions alter long-term quality of life during the survivorship period. Medical financial hardship is common among adult cancer survivors (9). Like other toxicities associated with cancer treatment, financial toxicity lowers quality of life (10), and there is suggestive evidence that it increases mortality (11). Not unsurprisingly, financial hardship is more common among populations that have less education and lower income and that lack health insurance or are underinsured

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(12,13). They are also more likely to report higher levels of pain, fatigue, and depression (14)—all of which potentially affect their physical and social functioning into survivorship.

For many survivors, an important aspect of physical and social functioning is the ability to remain employed. As cancers are detected and treated at earlier stages, working-aged people are more likely to experience treatment consequences that also negatively affect work ability. A conundrum is posed, however, for many patients who face the financial demands of treatment while experiencing a diminished capacity to work: Ceasing work and losing employer-based health insurance may lead to reduced access to care and serious health consequences. Therefore, some insured workers diagnosed with cancer keep weekly hours above a threshold that allows them to maintain employer-based health insurance (15), which may further compromise their health.

As the authors note, the generalizability of findings from the 3 cohorts of health-care professionals to the population at-large is inherently limited. A comparison of lifestyle factors in cohort members shows more favorable risk-factor profiles, and lung cancer incidence and mortality were substantially lower in the health professionals cohort, likely reflecting the higher rate of smoking cessation among health professionals compared with the general population. Relative survival curves also indicate that the cohort members survive longer than expected based on the general population. The authors do provide analyses of long-term survival from the Surveillance, Epidemiology, and End Results data, showing similar patterns of cumulative mortality over time. The generalizability issue could be further addressed with an analysis of population-based cancer registry data that assesses inflection points in cumulative mortality over time.

An additional concern regarding the relevance of the results to the present is the time span that the follow-up intervals of the 3 cohorts covers (4). These were years of progress in the early detection and treatment of some cancers, with substantial improvements in survival for some types of cancer (3). Consequently, long-term survivors had treatment toward the start of follow-up, while those contributing to the estimation of cumulative mortality for shorter intervals are a mix of those treated across follow-up. In the presence of a temporal trend of improving survival, a period-based analysis provides a more useful indicator for prognosticating about the course of current patients (16). Further insight could be gained by stratifying the analyses by calendar period.

Approximately 1.8 million people were diagnosed with cancer in the United States in 2020, and nearly 18 million cancer survivors resided in the United States in 2021 (17,18). As we celebrate advances in cancer detection and treatment alongside behavioral and social changes that reduce cancer risks, we must also be mindful of cancer survivors' needs in the extended survivorship period. Cancer treatment may have adverse consequences that shorten survival, and the impact of a cancer diagnosis may stress the social and economic circumstances of survivors. Strategies that reduce the negative impacts of cancer survivorship include administering treatments that allow survivors to work in a similar capacity as before their diagnosis; offering health insurance plans that do not inflict financial hardship and discourage preventive care; and, importantly, controlling the cost of cancer care. Increased population-based health surveillance also becomes more relevant as cancer survivorship extends. More information is needed about treatment outcomes so that wiser treatment choices are made at the outset and better care is provided during and following treatment, leading to a much deeper understanding of cancer survivorship (19).

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