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Prevalence of Chronic Pain and High-Impact Chronic Pain in Cancer Survivors in the United States

The population of cancer survivors in the United States is growing rapidly.[1] In 2016, the number of survivors was 15.5 million; with the aging of the population and advances in early detection and treatment methods, this number is expected to reach 26.1 million by 2040.[1] Chronic pain is one of the most common long-term effects of cancer treatment and has been linked with an impaired quality of life, lower adherence to treatment, and higher health care costs.[2] Nevertheless, there is a paucity of information regarding the prevalence of, and risk factors for, the development of chronic pain among cancer survivors. A better understanding of the epidemiology of pain in cancer survivors can help inform future health care educational priorities and policies. Accordingly, the objective of this study was to investigate the prevalence of chronic pain and high-impact chronic pain (HICP, chronic pain with major activity restriction) among cancer survivors in the United States by using data from the National Health Interview Survey (2016-2017).

Methods | We identified 4526 adult cancer survivors from 59 770 participants in the 2016-2017 National Health Interview Survey (https://www.cdc.gov/nchs/nhis/), a national cross-sectional survey of the civilian, noninstitutionalized US population. The survey collects information related to chronic pain (pain on most days or every day in the past 6 months) and HICP (chronic pain limiting life or work activities on most days or every day in the past 6 months), with definitions consistent with those proposed by the National Pain Strategy Population Research Workgroup,[3] and which have been used in a report by the Centers for Disease Control and Prevention on the national estimates of chronic pain.[4] Institutional review board approval and the need for patient informed consent were exempted by the Program for the Protection of Human Subjects at the Icahn School of Medicine at Mount Sinai, given that the data were deidentified and from a publicly available database. Chronic pain prevalence was calculated and stratified by sociodemographic characteristics and cancer type. Respondents with only nonmelanoma skin cancer and those reporting a cancer diagnosis before age 18 years were excluded from the analyses. To account for the complex design of the National Health Interview Survey, all estimates were weighted using SAS statistical software, version 9.4 (SAS Institute Inc) and SAS callable SUDAAN. All statistical significance testing was 2-sided at $P < .05$.

Table. Characteristics and Prevalence of Chronic Pain and High-Impact Chronic Pain Among US Cancer Survivors 18 Years or Older, National Health Interview Survey, 2016-2017

Characteristic	Sample, No. (Weighted %) (n = 4526)	Chronic Pain (n = 1648)[a,b] Adjusted Prevalence (%) 95% CI[d]	*P* Value[e]	High-Impact Chronic Pain (n = 768)[b,c] Adjusted Prevalence (%) 95% CI[d]	*P* Value[e]
Educational level					
<High school	688 (14.8)	39.2 (34.8-43.8)		18.5 (15.3-22.1)	
Graduated high school/GED	1069 (23.2)	32.5 (29.1-36.0)	.04	14.5 (12.2-17.1)	.15
>High school	2769 (62.1)	34.4 (32.1-36.7)		16.1 (14.4-17.9)	
Race					
Hispanic	269 (7.5)	26.6 (21.4-32.5)		12.6 (9.0-17.4)	
Non-Hispanic white	3726 (79.9)	35.8 (33.8-38.0)		16.8 (15.3-18.5)	
Non-Hispanic black	362 (8.2)	33.0 (27.7-38.8)	.02	12.9 (9.7-16.9)	.21
Non-Hispanic Asian	126 (3.7)	28.5 (18.7-40.9)		18.8 (10.4-31.4)	
Non-Hispanic other[f]	43 (0.7)	47.2 (29.1-66.1)		16.7 (9.0-28.9)	
Insurance					
Any private (<65 y)	1184 (31.3)	28.1 (22.6-34.2)		18.1 (12.7-25.0)	
Other coverage (<65 y)	497 (11.8)	43.6 (35.4-52.1)		27.1 (20.0-35.6)	
Uninsured (<65 y)	139 (3.4)	35.3 (30.4-40.4)	<.001	13.3 (10.8-16.3)	.001
Medicare with any private (≥65 y)	1418 (27.9)	37.7 (31.5-44.2)		12.7 (9.8-16.3)	
Public only (≥65 y)	1288 (25.6)	35.3 (30.4-40.4)		13.3 (10.8-16.3)	

(continued)

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Table. Characteristics and Prevalence of Chronic Pain and High-Impact Chronic Pain Among US Cancer Survivors 18 Years or Older, National Health Interview Survey, 2016-2017 (continued)

Characteristic	Sample, No. (Weighted %) (n = 4526)	Chronic Pain (n = 1648)[a,b]		High-Impact Chronic Pain (n = 768)[b,c]	
		Adjusted Prevalence (%) 95% CI[d]	*P* Value[e]	Adjusted Prevalence (%) 95% CI[d]	*P* Value[e]
Paid employment					
Yes	3203 (67.4)	26.7 (23.4-30.3)	<.001	6.8 (5.2-9.0)	<.001
No	1323 (32.6)	38.5 (35.9-41.1)		20.4 (18.5-22.4)	
Poverty status (FPL)					
<100%	450 (8.1)	44.6 (38.1-51.2)	<.001	22.8 (18.3-27.9)	<.001
100%-199%	788 (14.9)	38.9 (34.5-43.4)		20.2 (16.8-24.0)	
200%-399%	1314 (28.5)	36.7 (33.6-39.9)		17.4 (15.0-20.1)	
≥400%	1606 (40.0)	29.6 (26.6-32.8)		11.0 (9.0-13.3)	
Unknown	368 (8.4)	33.6 (27.5-40.2)		15.9 (11.7-21.2)	
Time since diagnosis, y					
0-1	662 (14.8)	36.4 (31.9-41.2)	.80	15.4 (12.5-19.0)	.65
2-5	1035 (24.5)	32.9 (29.4-36.7)		17.1 (14.3-20.2)	
6-10	950 (21.4)	35.3 (31.9-38.9)		17.3 (14.6-20.4)	
11-15	632 (14.0)	34.6 (30.4-39.1)		14.5 (11.6-17.9)	
≥16	1247 (25.3)	34.8 (31.3-38.5)		15.6 (13.3-18.2)	

Abbreviations: FPL, federal poverty level; GED, general equivalency diploma.

[a] Weighted number of survivors, 5 392 634 (95% CI, 4 981 252-5 804 015); weighted prevalence, 34.6% (95% CI, 32.7%-36.5%).

[b] Chronic pain is measured by "pain on most days or every day in the past 6 months"; high-impact chronic pain is measured by "chronic pain limiting life or work activities on most days or every day in the past 6 months."

[c] Weighted number of survivors, 2 512 006 (95% CI, 2 263 616-2 760 395); weighted prevalence, 16.1% (95% CI, 14.8%-17.5%).

[d] The adjusted prevalence values for chronic pain and high-impact chronic pain were estimated with 2 separate multivariable logistic models that included age, sex, educational level, race, insurance, paid employment, poverty status, region, year of survey, time since cancer diagnosis, and cancer type as covariates. Only statistically significant results are presented.

[e] *P* values were obtained from Wald *F* tests in multivariable logistic regression models.

[f] Non-Hispanic other includes non-Hispanic American Indian and Alaska Native only, non-Hispanic Native Hawaiian and Pacific Islander only, and non-Hispanic multiple race.

Results | Overall, of the identified 4526 cancer survivors, 1648 (34.6%, 95% CI, 32.7%-36.5%) reported having chronic pain and 768 (16.1%, 95% CI, 14.8%-17.5%) having HICP, representing approximately 5.39 million and 2.51 million cancer survivors, respectively, in the US population. No significant differences in the prevalence of chronic pain or HICP were found for age, sex, marital status, or region groups. A higher prevalence of chronic pain and HICP was reported among survivors with less than a high school education (adjusted prevalence, 39.2% for chronic pain and 18.5% for HICP), low household income (44.6% and 22.8%, respectively), public insurance (for those aged 18-64 years) (43.6% and 27.1%, respectively), or no paid employment (38.5% and 20.4%, respectively) (**Table**).

The adjusted prevalence of chronic pain was the highest among survivors of bone (54.0%), kidney (52.3%), throat-pharynx (47.9%), and uterine (44.5%) cancers. The time since diagnosis was not significantly associated with the prevalence of either chronic pain or HICP (Table).

Discussion | We found the prevalence of chronic pain and HICP among cancer survivors to be almost double that in the general US population.[4] Chronic pain and HICP were more prevalent in survivors who were unemployed and who had low socioeconomic status, inadequate insurance, and had some specific types of cancer. Because socioeconomic status and employment are associated with insurance coverage and access to care in the United States,[5] the patterns of chronic pain that we observed in cancer survivors may be explained by barriers to cancer care and pain management as well as by the type and extent of cancer treatment received. In contrast to the general perception of higher prevalence of pain in women than in men,[6] we did not find a statistically significant difference by sex among cancer survivors. This could be owing to insufficient statistical power from the limited sample size, or that the cancer-induced pain in both sex groups may have diluted the relative difference.

Limitations of this study include the potential recall error of self-reported data, limited statistical power for survivors of less common cancers, and no information on cancer treatment, pain management, or the etiology of pain.

In conclusion, the prevalence of chronic pain and HICP is high among cancer survivors compared with that in the general US population, thereby suggesting the presence of important unmet needs in the large and growing cancer survivorship community.

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Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Jiang, Han.
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COMMENT & RESPONSE

Survivorship Bias in Analyses of Immune Checkpoint Inhibitor Trials

To the Editor In a retrospective analysis of 137 patients with advanced non-small cell lung cancer treated with nivolumab or pembrolizumab monotherapy, Toi et al[1] observed larger progression-free survival and overall survival probabilities among 66 patients who developed immune-related adverse events (irAEs) compared with 71 who did not. It is possible that the comparison is biased. The 2 groups are compared with regard to survival from the start of treatment, but the occurrence of irAEs is obviously not determined at baseline but later during follow-up. Patients with irAEs must have survived from treatment initiation to the time of the irAE, but there is no such requirement for patients without irAEs. Toi et al[1] reported a median onset of irAEs of 4.7 weeks. By design, the survival curves will be more favorable to patients with irAEs and less favorable to those without irAEs. This survivorship bias is identical to the time-to-response bias in oncology studies comparing responders and nonresponders.[2-4]

Other statistical methods are needed to conduct an unbiased comparison. For example, the landmark method involves a priori selection of a time point, or landmark time, for the classifying criteria and outcomes.[2-4] In the present case, one could ignore all irAEs after the specified time point and all progressions of disease or death before the specified time point. Kaplan-Meier curves can still be used to display survival conditional on the occurrence of an irAE. Alternative approaches are the Cox proportional hazards model with a time-varying covariate or a marginal structural Cox model.[5] These methods would address the time-varying group membership of patients with and without irAEs. A limitation of the landmark method is the exclusion of patients, although the Cox models would retain all patients.

We would like to know if differences in survival are still apparent when addressing this bias.

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In Reply We thank Conner and Trinquart for their interest in our study[1] on the association between preexisting antibodies and anti-PD-1 (programmed cell death 1) therapy. We agree that it is important to use landmark analysis in the assessment of an association between early immune-related adverse events (irAEs) and survival.

However, the primary aim of the study was to assess the safety and efficacy of anti-PD-1 treatment in patients with subclinical disease with advanced non-small cell lung cancer and with or without preexisting autoimmune markers, including rheumatoid factor, antinuclear antibody, antithyroglobulin, and antithyroid peroxidase.[1] We also sought to assess potential clinical biomarkers that may be meaningfully and conveniently as-

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