Using Extended Cox Proportional Hazards Models with Time-Varying Covariates to Examine the Effect of Variable Opioid Exposure in Cancer Recurrence in Disease-free Breast Cancer Survivors

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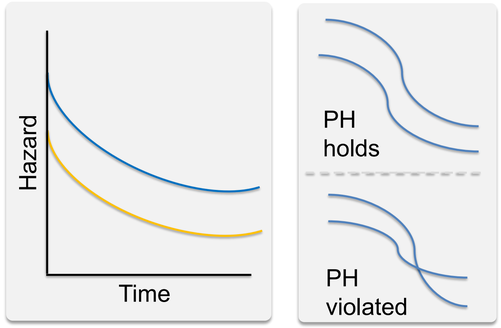
Background

- Chronic pain affects 20–50% of cancer survivors and is commonly managed with opioids during treatment, yet 15–38% of survivors continue opioid therapy into disease-free survivorship.[1-6]
- While survival models are well suited to study time-to-recurrence, the Cox proportional hazards model assumes constant exposure effects over time, an assumption that may not hold for long-term opioid use.[7]

If the effect of treatment changes over time, the PH assumption is violated, and standard Cox models may be misleading.

The hazard ratio between groups is assumed to remain constant over time, even as the baseline hazard changes.



Objectives

- To determine the appropriateness of standard survival analysis to examine association between opioid exposure and cancer recurrence in disease-free breast cancer survivors

Methods

Population	Disease-free breast cancer survivors
Exposure	Opioid Exposure Score in Persistent Opioid Cancer Survivors
Comparator	No persistent opioid use
Outcome	Cancer Recurrence
Time	January 2014 – Dec 2024
Setting	United States
Data Source	IBM MarketScan
Analytical Model	Cox Proportional Hazard Model vs Extend Cox-Proportional Hazards

$$\text{PTEO} = \frac{Days\ Exposed}{Total\ Number\ of\ Days\ of\ Followup}$$

Eq. 1 - Proportion of Time Exposed to Opioids (PTEO)

Opioid exposure scores were defined as a function of average daily MMEs and number of days in the follow-up period with opioids in hand, using the formulas below and categorized in top-bottom percentiles (50:50)

$$\text{ADMMEs} = \frac{\sum MMEs\ during\ period\ of\ exposure}{Days\ Exposed}$$

Eq. 2 - Proportion of Time Exposed to Opioids (PTEO)

$$Opioid\ Exposure\ Score = PTEO \times ADMMEs$$

Eq. 3 – Opioid Exposure Score

Scan the QR code for full methods, patient characteristics, extended results, and references. For questions, please email: vieiradasilvv@vcu.edu

Key References:

Pontinha VM, Aduse-Poku L, Moeller GF, Martins RG, Noreika D, Hong S. Opioid prescription patterns in long-term disease-free cancer survivors: a retrospective analysis at a single NCI-designated comprehensive cancer center. Support Care Cancer. 2025 Nov 3;33(11):1011.

Austin PC, Giardiello D. The Impact of Violation of the Proportional Hazards Assumption on the Calibration of the Cox Proportional Hazards Model. Stat Med. 2025 Jun;44(13-14):e70161

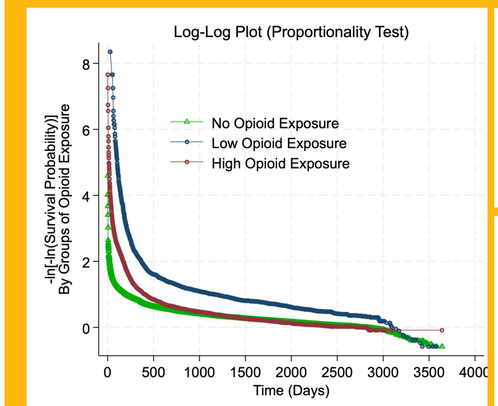
Results

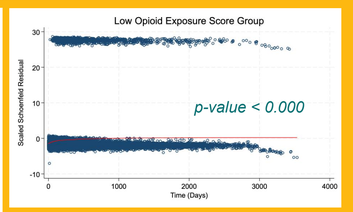
Standard Cox-Proportional Hazards Model

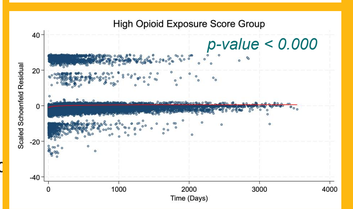
Table 1. Schoenfeld Residual Test

	Rho	P-value
Low Exposure	0.136	0.000
High Exposure	0.070	0.000

Statistical significance (p<0.05) indicates violation of Proportional Hazard Assumptions.





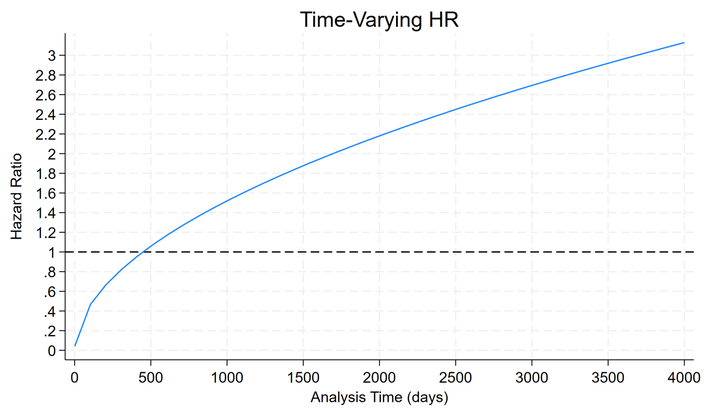


Proportional Assumption in Cox Proportional Hazards Models is **violated**:

The association between opioid exposure and cancer recurrence is time-dependent

Extended Cox-Proportional Hazards Model

Assuming opioid exposure scores as a time-dependent covariate



Opioid exposure during cancer survivorship switches from being protective to a risk factor for cancer recurrence within 1-1.5 years

Table 2. Extended Cox Hazard Model Results

Baseline Effect	Adjusted Recurrence HR (95% CI)	P-value
Low Exposure	0.011 (0.009 – 0.014)	0.000
High Exposure	0.075 (0.063 – 0.088)	0.000
Time-Varying Effect	**Adjusted Recurrence HR (95% CI)**	**P-value**
Low Exposure	1.986 (1.916 – 2.058)	0.000
High Exposure	1.621 (1.571 – 1.672)	0.000

Model was adjusted for age, region, insurance type, comorbidities, and opioid use prior to cancer diagnosis.
CI: Confidence Interval; HR: hazard ratio

Methodological approach **could help explain mixed evidence in opioid use during cancer survivorship** literature