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Journal of Clinical Epidemiology ■ (2017) ■
Journal of Clinical Epidemiology

LETTER TO THE EDITOR

Cumulative incidence estimates in the presence of competing risks

In the analysis of time-to-event end points, a competing risk (competing cause or competing event) may be defined as ''an event whose occurrence either precludes the occurrence of another event under examination or fundamentally alters the probability of occurrence of this other event'' [1]. Recent articles in the Journal of Clinical Epidemiology have shown that Kaplan–Meier (KM) estimates biased from competing risks are commonly published in leading medical journals [2,3] and overestimated event risk by over 10% in approximately one-third of studies susceptible to competing events [3]. Thus, they recommend the use of the cumulative incidence function instead of KM to estimate risk in the presence of competing events [2,3].

In this context, we compared the cumulative incidence of second primary cancers (SPCs) estimated using different methods: (1) incidence proportion, calculated as ''the proportion of a closed population at risk that becomes diseased within a given period of time'' [4] (5 years for the entire sample and 10 years for a subsample); (2) 1-KM; and (3) cumulative incidence function introduced by Kalbfleisch and Prentice [5], which takes into account competing events. A population-based cohort of gastric first primary cancers (FPCs) from the North Region Cancer Registry of Portugal, diagnosed in 2000–2006, was followed to December 31, 2011, until the diagnosis of an SPC, or death, whichever occurred first [6]. Whenever more than two primary cancers were observed, only the first SPC was considered, regardless of time elapsed since the FPC. Data were defined to be survival time data with the occurrence of an SPC defined as the event of interest and death as the competing event, as its occurrence hinders the incidence of an SPC.

As depicted in Fig. 1, the cumulative incidence of SPCs was similar between the different methods for the first few months; however, over time, the cumulative incidence estimates obtained with 1-KM tended to be higher and less precise than those calculated using the incidence proportion or competing risks method. Compared to estimates obtained with the competing risks method, 1-KM overestimated cumulative incidence ranging from 25% higher at 1 year to 150% higher at 10 years, with respective differences ranging from +0.4 to +7.2. Conversely, the competing risks method provided estimates similar to those calculated using the incidence proportion, ranging from 20% lower at 1 year to only 17% higher at 10 years, with corresponding differences between −0.4 and +0.7.

To further illustrate the extent to which cumulative incidence estimates obtained from 1-KM and competing risks differ considering various proportions of competing events, we performed a stratified analysis by age at FPC diagnosis. The increase of the 1-KM–based risk compared to the competing risks method got larger as the proportion of outcomes that are competing events increased. According to age (<70 and ≥70 years), a higher percentage of deaths was found among older patients (81.7% vs. 63.2%), while the proportion of SPCs was lower in older patients (4.5% vs. 5.0%). These disparities were reflected in nearly twofold and threefold higher estimates of SPCs obtained from 1-KM for younger (10.9% vs. 5.3%) and older patients (13.9% vs. 4.3%), respectively. In general, the bias observed in 1-KM depended on the incidence rates for both the event of interest and the competing event, and may lead to a considerably large overestimation.

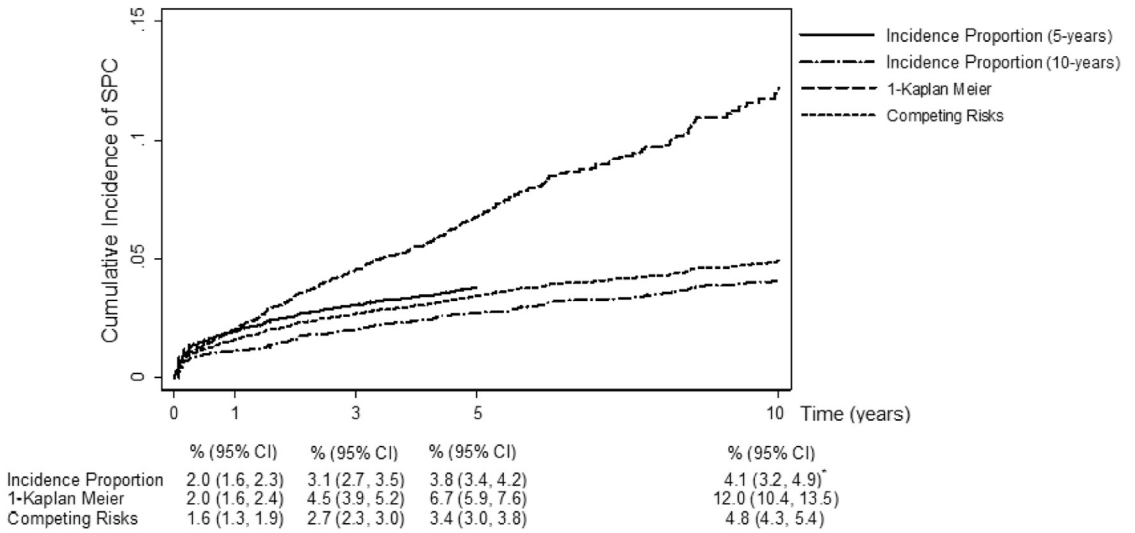
When analyzing competing risks data, it is important to realize the possible contributions of sound statistical methodology for the adequate exploration of the data. The use of the standard 1-KM to estimate cause-specific cumulative probability, which assumes a one-to-one correspondence between rate and risk, can lead to an inflated estimate of the proportion of patients who are at risk of failure at a specific time. This results in an overestimation of the risk [1], though the extent of the bias may not always be immediately perceived.

Currently, quantifying the risk of SPCs is of particular importance because the number of cancer survivors continues to grow, due to more frequent early detection as well as advances in therapy [7] reaching an estimated 32.5 million 5-year survivors worldwide in 2012 [8].

Funding: This study was funded by FEDER through the Operational Program Competitiveness and Internationalization and national funding from the Foundation for Science and Technology—FCT (Portuguese Ministry of Science, Technology and Higher Education) under the Unidade de Investigação em Epidemiologia—Instituto de Saúde Pública da Universidade do Porto (EPIUnit) (POCI-01-0145-FEDER-006862; Ref. UID/DTP/04750/2013). An individual PhD grant attributed to S.M. (SFRH/BD/102585/2014) was funded by FCT and the ''Programa Operacional Capital Humano'' (POCH/FSE). The funding sources had no involvement in the conduct of the research and/or preparation of the commentary.

Conflict of interest: None.

Ethical approval: The study was approved by the Ethics Committee of the Portuguese Institute of Oncology of Porto (Ref. CES IPO: 173/2015).



	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Incidence Proportion	2.0 (1.6, 2.3)	3.1 (2.7, 3.5)	3.8 (3.4, 4.2)	4.1 (3.2, 4.9)*
1-Kaplan Meier	2.0 (1.6, 2.4)	4.5 (3.9, 5.2)	6.7 (5.9, 7.6)	12.0 (10.4, 13.5)
Competing Risks	1.6 (1.3, 1.9)	2.7 (2.3, 3.0)	3.4 (3.0, 3.8)	4.8 (4.3, 5.4)

Fig. 1. Cumulative incidence estimates of second primary cancers to December 31, 2011, using the incidence proportion (5 and 10 years*), 1-Kaplan–Meier, and competing risks methods. *Only including those diagnosed in 2000–2001, which have 10 years of follow-up (81 second primary cancers in 1995 gastric first primary cancer patients). 95% CI, 95% confidence interval; SPC, second primary cancer).

The present worked example shows that, with the occurrence of competing events, e.g., death, there is an evident overestimation of cumulative incidence by 1-KM, precluding its use to estimate the long-term probability of SPCs.

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References

[1] Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med 1999;18:695–706.
[2] van Walraven C, Hawken S. Competing risk bias in Kaplan-Meier risk estimates can be corrected. J Clin Epidemiol 2016;70:101–5.
[3] van Walraven C, McAlister FA. Competing risk bias was common in Kaplan-Meier risk estimates published in prominent medical journals. J Clin Epidemiol 2016;69:170–173.e8.
[4] Greenland S, Rothman KJ. Chapter 3-Measures of occurrence. In: Rothman KJ, Greenland S, Lash TL, editors. Modern Epidemiology. 3rd ed. Philadelphia: Lippincott-Raven; 2008.
[5] Kalbfleisch J, Prentice R. The analysis of failure time data. 2nd ed. New York: John Wiley & Sons; 2002.
[6] Morais S, Antunes L, Bento MJ, Lunet N. Risk of second primary cancers among patients with a first primary gastric cancer: a population-based study in North Portugal. Cancer Epidemiol 2017; 50(Pt A):85–91.
[7] Mariotto AB, Rowland JH, Ries LA, Scoppa S, Feuer EJ. Multiple cancer prevalence: a growing challenge in long-term survivorship. Cancer Epidemiol Biomarkers Prev 2007;16(3):566–71.
[8] Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet] 2013. Available at: http://globocan.iarc.fr. Accessed December 17, 2016.

https://doi.org/10.1016/j.jclinepi.2017.09.011