

# Title: Increased Cardiac Risk After a Second Malignant Neoplasm Among Childhood Cancer Survivors, a FCCSS Study.

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**Background:** Advances in cancer treatment have improved childhood cancer survival, leading to an adult population of cancer survivors exceeding 300,000 people in Europe. Many late-effects have been observed at a higher rate than the general population. Cardiac disease (CD) and second malignant neoplasms (SMN) are among the most serious and life-threatening late adverse effects experienced by childhood cancer survivors (CCS). We have studied the effect of a SMN on both the cumulative incidence and the instantaneous risk of CD accounting for the competing risk of death.

**Methods:** Analysis included 7670 CCS diagnosed between 1945 and 2000. To account for the time-dependence of the occurrence of SMN, we employed the landmark approach considering an additive regression model for the cumulative incidence of CD.

Next, the effect of SMN on the instantaneous risk of CD was estimated using a proportional cause specific hazard model considering SMN as a time-dependent exposure.

In both models, we considered death as a competing event while adjusting for treatments.

**Results:** After a median follow-up of 30 years, 369 CDs including 49 experimenting a SMN were identified. An increased cumulative incidence of CD was estimated for patients experimenting a SMN before they reached 35 years old. This excess was of 2.9% [95%CI: 0.1-5.8%] at 30 years old, with a cumulative incidence of 6%. SMN has been estimated to multiply the cause-specific-hazard by a 2.0 fold [95% CI: 1.5-2.8].

**Conclusion:** Our results provide new insight into the CD risk after a SMN that may impact long-term follow-up of CCS.