Biomolecules and Biomedicine
ISSN: 2831-0896 (Print) | ISSN: 2831-090X (Online)
Journal Impact Factor® (2025): 2.8
CiteScore® (2025): 4.7
www.biomolbiomed.com | blog.bjbms.org

**SUPPLEMENTAL DATA**

# Competing cardiovascular and tumor-specific mortality in malignant phyllodes tumor

**İsmail Zihni[1], Burcu Zihni[2*], Mehmet Zafer Sabuncuoğlu[1]**

[1]Department of General Surgery, Akdeniz University Medical Faculty, Antalya, Türkiye;

[2]Department of Cardiology, Antalya City Hospital, Antalya, Türkiye.

*Correspondence to **Burcu Zihni**: burcuzihni@yahoo.com

**Full article is available at the following link:** Competing cardiovascular and tumor-specific mortality in malignant phyllodes tumor

## Standardized mortality ratio (SMR) computation

Expected cardiovascular deaths were determined through indirect standardization, utilizing age-specific female circulatory-disease mortality rates (ICD-10 I00–I99) from the United States general population via CDC WONDER. Each woman's follow-up period was partitioned into 5-year attained-age strata (Lexis expansion) based on her single-year age at diagnosis, ensuring that person-time accumulation accurately reflected the occupied age band. Expected deaths were calculated by summing person-years multiplied by the corresponding age-specific reference rate. An additional analysis further stratified person-time by calendar period (2000–2010, 2011–2020) and applied period-specific rates. In contrast, a diagnosis-age analysis assigned all person-time to the diagnosis-age band. The SMR was computed as the ratio of observed to expected deaths, with exact Poisson 95% confidence intervals. Attained-age standardization yielded 89.9 expected deaths, calendar-period matching produced 82.9, and diagnosis-age assignment resulted in 42.5, consequently altering the SMR from 0.92 and 1.00 to 1.95, respectively.

## SEER*Stat case-listing selection statement

Database: Incidence – SEER Research Data, 17 Registries, November 2025 Submission (2000–2023). Session: Case Listing. Selection Criteria: Site recode ICD-O-3/WHO 2008 = 'Breast' AND ICD-O-3 Hist/behav = '9020/3: Phyllodes tumor, malignant' AND Year of diagnosis = 2000–2020 AND Diagnostic Confirmation = 'Positive histology' AND (Sequence number = 'One primary only' OR 'First of 2 or more primaries') AND Sex = 'Female'. This query initially retrieved 2163 records. Hierarchical exclusion was applied to remove 20 records with zero or missing survival time, 13 with unknown cause of death, and 24 individuals under 18 years of age, resulting in a final cohort of 2106 records.

## Alignment of cardiovascular numerator and reference denominator

Cohort cardiovascular deaths (numerator) were defined using the SEER cause-of-death recode. Broad cardiovascular deaths encompassed: diseases of the heart, hypertension without heart disease, cerebrovascular disease, atherosclerosis, aortic aneurysm and dissection, and other diseases of arteries/arterioles/capillaries. Heart-

only deaths were restricted to: diseases of the heart and hypertension without heart disease. Reference rates (denominator) from CDC WONDER employed matching groupings: broad = ICD-10 I00–I99; heart-only = diseases of the heart (I00–I09, I11, I13, I20–I51). Due to the fixed priority assignment of deaths, the cardiovascular count represents a conservative lower bound.

**Missing tumor size: comparison and sensitivity analyses**

Tumor size data were available for 1501 patients and missing for 605. Patients with and without recorded tumor size exhibited similar characteristics regarding age (median 51 vs. 50 years), stage (localized: 77.7% vs. 78.7%; distant: 1.7% vs. 1.5%), phyllodes-specific death (14.4% vs. 12.9%), and cardiovascular death (3.7% vs. 4.6%). However, a notable difference was observed in follow-up duration (median 111 vs. 234 months), suggesting less complete size recording in earlier diagnosis years. Multiple imputation (10 imputations, Rubin's rules) yielded a tumor-size subdistribution effect of 1.028 (95% CI: 1.018–1.039) per 10 mm, consistent with the complete-case estimate (1.03). Excluding tumor size from the phyllodes-specific model, fitted on the full cohort (n=2106, 294 events), demonstrated minimal change in the hazard ratios for age (1.03) and mastectomy (2.10, compared to 2.42 in the complete-case model).

**Inverse-probability-of-treatment-weighting diagnostics**

The surgical comparison (breast-conserving surgery versus mastectomy) included 1482 women (781 and 701, respectively). Stabilized weights had a mean of 0.98 and ranged from 0.49 to 4.94 after truncation at the 1st and 99th percentiles. The effective sample size was 1033 (69.7%). The positivity assumption was met, with overlapping propensity scores across treatment arms (treated: 0.013–0.994; control: 0.008–0.982). Robust (sandwich) standard errors were employed. This analysis is exploratory and cannot definitively resolve confounding by indication given the limited covariate data available in SEER.

## Crossover analysis and reproducibility code

The crossover time, defined as the first month at which cardiovascular cumulative incidence equals phyllodes-specific incidence, did not achieve a stable estimate. No crossover was observed overall or in tumors smaller than 100 mm. For women aged 65–79 years (matching the age band in Table 1), the point estimate showed no crossover, the bootstrap 95% confidence interval spanned 4–236 months, and 73.3% of resamples indicated no crossover. Estimates in older strata demonstrated discordance between R and Python analyses. These analyses are considered exploratory. The code for the Lexis expansion and standardized mortality ratio computation is provided as a separate file (Supplementary_Code.py).

**Table S1. Justification for omitting stage from the cardiovascular models**

| Stage level (cardiovascular model) | Estimated HR / sHR | Standard error |
|---|---|---|
| Localized | ~3.2 x 10^7 | 3.8 x 10^3 |
| Regional | ~4.5 x 10^7 | 3.8 x 10^3 |
| Unknown/unstaged | ~1.4 x 10^7 | 3.8 x 10^3 |
| Distant | non-estimable | non-estimable |

Including stage in the cardiovascular models resulted in quasi-complete separation. Stage was therefore omitted from the cardiovascular models but retained in the phyllodes-specific models, where its effect was estimable. **Abbreviations:** HR, hazard ratio; sHR, subdistribution hazard ratio.

**Table S2. Cross-validation of key estimates between R and Python**

| Estimate | R | Python | Diff |
|---|---|---|---|
| CIF phyllodes, 180 mo | 14.6% | 14.58% | 0.13% |
| CIF cardiovascular, 180 mo | 4.4% | 4.36% | 0.95% |
| CIF other-cause, 180 mo | 8.1% | 8.06% | 0.44% |
| Cardiovascular cause-specific age HR | 1.1232 | 1.116 | 0.62% |
| SMR (deterministic) | 0.92 | 0.92 | 0% |

A pre-specified discrepancy exceeding 1% prevented table lock. Fine-Gray subdistribution hazards were computed in R and reproduced in Python via an inverse-probability-of-censoring-weighted risk set. **Abbreviations:** CIF, cumulative incidence function; Diff, difference; HR, hazard ratio; mo, months; SMR, standardized mortality ratio.

**Table S3. Sensitivity analysis: Broad versus heart-specific cardiovascular definitions**

| Definition / person-time | Value | Comparison |
|---|---|---|
| Broad cardiovascular deaths | 83 | primary |
| Heart-only cardiovascular deaths | 60 | sensitivity |
| Broad SMR, attained age | 0.92 (0.74-1.14) | primary |
| Broad SMR, attained age x calendar period | 1.00 (0.80-1.24) | sensitivity |
| Heart-only SMR, attained age | 0.90 (0.69-1.16) | sensitivity |
| Broad SMR, age at diagnosis | 1.95 (1.56-2.42) | biased contrast |

The heart-only definition encompassed cardiac diseases and hypertension without cardiac involvement. All analyses stratified by attained age were concordant. **Abbreviation:** SMR, standardized mortality ratio.