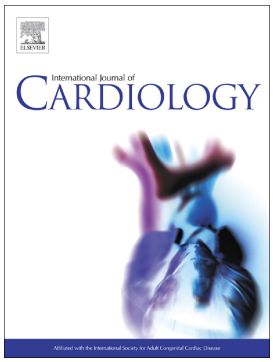
Favorable outcome of cancer patients undergoing transcatheter aortic valve replacement



Fausto Biancari, Sebastian Dahlbacka, Tatu Juvonen, Marko P.O. Virtanen, Pasi Maaranen, Jussi Jaakkola, Teemu Laakso, Matti Niemelä, Tuomas Tauriainen, Antti Vento, Annastiina Husso, Mikko Savontaus, Mika Laine, Timo Mäkikallio, Peter Raivio, Markku Eskola, Stefano Rosato, Vesa Anttila, Juhani Airaksinen, Antti Valtola

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Revised manuscript

Favorable Outcome of Cancer Patients Undergoing Transcatheter Aortic Valve Replacement

Fausto Biancari,[a,b] MD, PhD, Sebastian Dahlbacka,[c] MD, PhD, Tatu Juvonen,[c] MD, PhD, Marko P.O. Virtanen,[d] MD, Pasi Maaranen,[d] MD, Jussi Jaakkola,[a] MD, PhD, Teemu Laakso,[c] MD, Matti Niemelä,[f] MD, PhD, Tuomas Tauriainen,[b] MD, PhD, Antti Vento,[c] MD, PhD, Annastiina Husso,[e] MD, PhD, Mikko Savontaus,[a] MD, PhD, Mika Laine,[e] MD, PhD, Timo Mäkikallio,[d] MD, PhD, Peter Raivio,[c] MD, PhD, Markku Eskola,[d] MD, PhD, Stefano Rosato,[g] MSc, Vesa Anttila,[a] MD, PhD, Juhani Airaksinen,[a] MD, PhD, Antti Valtola,[e] MD.

[a]Heart Center, Turku University Hospital and Department of Surgery, University of Turku, Turku, Finland;
[b]Department of Surgery, Oulu University Hospital and Research Unit of Surgery, Anesthesiology and Critical care, University of Oulu, Oulu, Finland;
[c]Heart and Lung Center, Helsinki University Hospital, Helsinki, Finland;
[d]Heart Hospital, Tampere University Hospital and Faculty of Medicine and Health Technology, [e]Heart Center, Kuopio University Hospital, Kuopio, Finland;
University of Tampere, Tampere, Finland;
[f]Department of Internal Medicine, Oulu University Hospital, Oulu, Finland;
[g]National Centre of Global Health, Istituto Superiore di Sanità, Rome, Italy.

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Address for correspondence:
Prof. Fausto Biancari,
Heart Center,
Turku University Hospital,
PO Box 52, 20521 Turku
E-mail: faustobiancari@yahoo.it

Abstract

Aim: The aim of this study was to assess the outcome of transcatheter aortic valve replacement (TAVR) in patients with cancer.

Methods: This is a retrospective study from the nationwide FinnValve registry on 2130 consecutive patients who underwent TAVR for severe AS from January 2008 to October 2017.

Results: In this cohort, 417 patients (19.6%) had history of cancer and 113 (5.3%) had an active malignancy at the time of TAVR. Patients with any malignancy had similar late mortality than patients without any malignancy (at 7 years, 65.1% vs. 59.3%, adjusted HR 1.105, 95%CI 0.892-1.369). At 7 years, cancer-related mortality was 22.5% among patients with preoperative cancer, and 11.0% in those without preoperative cancer ($p<0.0001$). Among cancer patients, 18 died of the same disease (at 7 years, mortality 12.5%). Active malignancy was not associated with increased risk of all-cause mortality (adjusted HR 1.100, 95%CI 0.757-1.599). However, patients with blood malignancies had a significantly increased risk of mortality (at 4-year, 53.5% vs. 35.4%, adjusted HR 2.029, 95%CI 1.328-3.098).

Conclusions: This analysis showed that, when properly selected by the heart team and oncologists, most cancer patients undergoing TAVR can achieve a good survival and eventually die of other diseases. Blood malignancies seem to carry a poor prognosis in these patients.

Clinical trial registration: ClinicalTrials.gov Identifier: NCT03385915; https://clinicaltrials.gov/ct2/show/NCT03385915

Keywords. Transcatheter aortic valve replacement; TAVR; TAVI; Cancer; Malignancy.

1. Introduction

The development of transcatheter aortic valve replacement (TAVR) has made the treatment of severe aortic stenosis (AS) feasible in high-risk patients [1]. Accordingly, a large proportion of elderly undergoing TAVR have multiple severe comorbidities which may threaten their early and late outcome. Concurrent malignancy may challenge the decision to perform TAVR in AS patients. As in patients undergoing percutaneous coronary intervention [2], history of cancer seems to reduce the survival of patients undergoing TAVR [3]. These findings may challenge the use of this invasive and expensive treatment in AS patients with concomitant malignancies. However, malignant diseases and their clinical stage as well as preoperative selection criteria may significantly differ between studies inasmuch as a few studies showed that active malignancy at the time of TAVR does not significantly affect the prognosis of these patients [4,5]. This controversial issue has been investigated in the present nationwide TAVR registry.

2. Methods

2.1. Study Cohort

The FinnValve registry is a nationwide study (ClinicalTrials.gov Identifier: NCT03385915), which includes retrospectively collected data from consecutive and unselected patients treated with TAVR or surgical aortic valve replacement with a bioprosthesis for AS with or without coronary revascularization between January 2008 and October 2017 at all five Finnish University Hospitals (Helsinki, Kuopio, Oulu, Tampere, Turku).

Patients with a history of any malignancy were identified through electronic patient records. Active cancer was defined according to definition proposed by the National Institute for Health and Care Excellence (NICE), i.e. receiving active antimitotic treatment; or diagnosed within the past 6 months; or recurrent or metastatic; or inoperable [6]. This definition excludes squamous skin cancer and basal cell carcinoma. Baseline variables were defined according to the EuroSCORE II criteria [7]. The decision to perform TAVR in cancer patients was made after a reasonable life expectancy was estimated by oncologists and heart team.

2.2. Outcomes

The outcome measures of this study were all-cause, cancer-related and cardiovascular mortality. Cardiovascular mortality was defined as any death due to heart failure, myocardial infarction, stroke, aortic dissection or rupture, and any major peripheral vascular event. The date and main cause of death were obtained from the National Statistical Institution, Statistics Finland, which collects data from the death certificates issued by physicians. The last date of follow-up of these patients was December 31th, 2017. Follow-up was considered complete in all patients.

2.3. Statistical Analysis

Statistical analysis was performed using Stata v. 15.1 (SAS Institute Inc., Cary, NC, USA) and SPSS v. 25.0 statistical software (IBM Corporation, New York, USA). Continuous variables are reported as means±standard deviation and categorical variables are reported as counts and percentages. Mann-Whitney *U*-test, Fisher's exact test and Chi-square test were used for univariate analysis. Differences in the long-term survival of the study groups were

evaluated by the Kaplan-Meier method with the log-rank test and adjusted for baseline covariates with $p<0.05$ in univariate analysis with Cox proportional hazards method. Risk estimates of mortality are reported as hazard ratio (HR) and 95% confidence interval (95%CI). A $p<0.05$ was set for statistical significance.

3. Results

The FinnValve registry includes data of 2130 consecutive patients who underwent primary TAVR for severe AS. Of these patients, 417 patients (19.6%) had history of cancer before TAVR and their characteristics are summarized in Table 1. Forty-four patients (2.1%) had multiple malignancies. Among them, 113 patients (5.3%) had active malignancy at the time of TAVR. Among patients with active cancer, 33 patients (29.2%) had diagnosis within the last 6 months, 52 patients (46.0%) on-going active antineoplastic treatment (biological, hormonal or chemotherapy), 28 (24.8%) recurrent disease, 29 patients (25.7%) metastatic disease diagnosed any time before TAVR and 19 patients (16.8%) an inoperable malignancy.

The mean follow-up was 2.1±1.7 years. Thirty-day mortality was 3.1% in cancer patients and 2.9% in those without cancer ($p=0.779$). Cancer patients with any malignancy at the time of TAVR had similar early and late all-cause mortality to patients without cancer (at 7 years, 65.1% vs. 59.3%, adjusted HR 1.105, 95%CI 0.892-1.369, Tab. 2) (Fig. 1). Patients with cancer had also comparable cardiovascular mortality (at 7 years, 45.1% vs. 42.0%, adjusted HR 0.902, 95%CI 0.676-1.204). At 7 years, cancer-related mortality was 22.5% among patients with cancer, and 11.0% in those without cancer ($p<0.0001$). Among cancer patients, 18 died of the same disease (at 7 years, mortality 12.5%).

Active malignancy was not associated with increased risk of all-cause mortality (adjusted HR 1.100, 95%CI 0.757-1.599). Similarly, patients with multiple malignancies (adjusted HR 1.567, 95%CI 0.899-2.730), breast cancer (only women in sub-analysis: adjusted HR 0.995,

95%CI 0.683-1.451) and prostate cancer (only men in sub-analysis: adjusted HR 0.714, 95%CI 0.435-1.174) were not associated with increased risk of all-cause mortality. Instead, blood malignancies (58 patients) was associated with increased risk of mortality (at 4-year, all-cause mortality 53.5% vs. 35.4%, adjusted HR 2.029, 95%CI 1.328-3.098; cancer-related mortality 19.2% vs. 5.1%, adjusted HR 4.413, 95%CI 2.308-8.439).

4. Discussion

4.1. Lessons Learned

The main findings of this nationwide study are: 1) in Finland, the proportion of patients with cancer undergoing TAVR is rather high (19%); 2) 5% of patients who underwent TAVR had an active malignancy; 3) a diagnosis of cancer, even when requiring active treatment, was associated with favorable survival after TAVR provided a preoperative estimation of good life expectancy; 4) only a minority of cancer patients died of the same malignancy.

4.2. Results Discussion

The risk of cancer increases with age [8] and the high prevalence of malignancies in our TAVR cohort is not surprising. Advanced age is associated also with high cancer-related mortality [8]. The relatively short life expectancy of AS patients aged >75 years may therefore raise concern regarding the clinical benefit and cost-efficacy of TAVR when cancer and other significant comorbidities coexist [9]. Indeed, a few studies argues against TAVR in patients with malignancies [9]. A recent large multicenter study by Landes et al. [3] demonstrated poorer survival in patients with cancer undergoing TAVR. However, their conclusions are based on a patient cohort with advanced disease in more than 40% of cases. Furthermore, it is unclear how a throughout clinical staging could have been performed immediately before TAVR in all their patients. The rather short follow-up is also a major

limitation of their study [3]. Still, patients with stage I-II cancer had similar 3-year survival compared to patients without cancer. The results of series evaluating the outcome of cancer patients undergoing interventional cardiology and cardiovascular surgery may be biased by the heterogeneous nature and aggressiveness of the disease as well as by the preoperative selection of these patients. In this regard, the decision-making process should involve oncologists within the heart team in order to exclude from TAVR treatment those patients with cancer- and other comorbidities related short life expectancy. On the other hand, this study showed that when properly selected and with current cancer therapies, most cancer patients undergoing TAVR may have a good survival (35% at 7 years) and eventually die of other diseases.

There are also reasonable clues to support invasive treatment of cardiovascular diseases in cancer patients with advanced age. Although the risk of cancer increases significantly with age, elderly with some malignancies seems to have a survival similar to that of the general population [10,11]. This means that elderly who develop a malignancy are in excellent general conditions and oncological treatment in these patients may lead to a significant prolongation of life.

It is worth noting that patients with and without cancer had a comparable prevalence of most baseline comorbidities and similar operative risk as stratified by the Society of Thoracic Surgeons score (Tab. 1). In fact, the study cohort differed only in terms of age, gender and diabetes prevalence and this may contribute to the reliability of the present findings.

4.3 Limitations

The retrospective nature is the main limitation of this study. Secondly, we do not any information about the clinical stage of the disease at the time of TAVR. Instead we adopted

the NICE definition criteria for active malignancy. Thirdly, the heterogeneity and somewhat limited number of certain tumours does not allow sensitivity analysis of the outcome of different cancers. In this regard, our analysis found blood malignancies as a significant risk factors for mortality, but this findings should be confirmed in future studies. Finally, these findings may not apply to patients undergoing surgical aortic valve replacement, because of their different age and risk profile as well as the possible immunological implications of the surgical treatment and of using cardiopulmonary bypass.

Despite these limitations, this study deals with one of the largest series of cancer patients who underwent TAVR with a rather long follow-up. Date and causes of death of this series were retrieved from a reliable national registry collecting these information from the authorities and allowed a solid survival analysis. Furthermore, this study is a consecutive series from a nationwide patient cohort and reflects the current clinical practice in Finland.

5. **Conclusions**

This study demonstrated that, in Finland, the proportion of patients with cancer undergoing TAVR is rather high and many of these patients are considered having an active malignancy at the time of procedure. This analysis showed that cancer patients with good life expectancy may undergo TAVR with favorable survival. In this patient cohort, blood malignancies seem to carry a poor prognosis. We recommend that the decision on whether to perform TAVR in all cancer patients should be made by the heart team and oncologists.

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Legend to figure

Figure 1. Kaplan-Meier estimate of all-cause mortality in patients with and without cancer after transcatheter aortic valve replacement. Number at the bottom of graph are patients at risk.

Table 1. Characteristics of patients with and without cancer who underwent transcatheter aortic valve replacement.

Clinical variables	*No malignancy N=1713*	*Malignancy N=417*	*P-value*
Age (years)	81.4±6.6	80.6±6.6	0.015
Female	959 (56.0)	213 (51.1)	0.071
Hemoglobin (g/L)	126±15	124±16	0.116
eGFR (mL/min/1.73 m^2)	59±19	60±19	0.482
Diabetes	510 (29.8)	95 (22.8)	0.005
Stroke	195 (11.4)	52 (12.5)	0.534
Recent myocardial infarction	41 (2.4)	8 (1.9)	0.562
Pulmonary disease	372 (21.7)	84 (20.1)	0.483
Atrial fibrillation	751 (43.8)	181 (43.4)	0.872
Oxygen therapy	10 (0.6)	4 (1.0)	0.495
Extracardiac arteriopathy	345 (20.1)	67 (16.1)	0.062
Severe frailty	247 (14.4)	71 (17.0)	0.180
Recent AHF/critical preop. state	195 (11.4)	58 (13.9)	0.149
NYHA class IV	196 (11.4)	48 (11.5)	0.968
Urgent procedure	124 (7.2)	34 (8.2)	0.523
LVEF≤50%	468 (27.4)	128 (30.8)	0.166
Coronary artery disease	480 (29.8)	123 (29.5)	0.549
STS score (%)	4.6±3.3	4.4±3.2	0.103
Operative data			
Concomitant PCI	94 (5.5)	25 (6.0)	0.686
Third generation prosthesis	1175 (68.7)	259 (62.1)	0.010
Transapical approach	147 (8.6)	48 (11.5)	0.063
Type of malignancy			
Breast cancer	-	128 (30.7)	-
Prostate cancer	-	96 (23.0)	-
Colon cancer	-	36 (8.6)	-
Lymphoma	-	35 (8.4)	-
Rectal cancer	-	23 (5.5)	-
Bladder cancer	-	19 (4.6)	-
Melanoma	-	19 (4.6)	-
Uterine cancer	-	17 (4.1)	-
Skin cancer	-	13 (3.1)	-
Renal cancer	-	12 (2.9)	-
Myeloma	-	11 (2.6)	-
Leukemia	-	10 (2.4)	-
Thyroid cancer	-	8 (1.9)	-
Lung cancer	-	7 (1.7)	-
Oral cancer	-	6 (1.4)	-
Ovarian cancer	-	4 (0.9)	-
Pharyngeal/laryngeal cancer	-	4 (0.9)	-
Liver cancer	-	3 (0.7)	-

Biliary tract cancer	-	2 (0.5)	-
Other malignancies	-	15 (3.6)	-
Multiple malignancies	-	44 (10.5)	-
Active malignancy	-	113 (27.1)	-

Continuous variables are reported as mean and standar deviation; categorical variables are reported as counts and percentages; eGFR, estimated glomerular filtration rate according to the CKD-EPI equation; NYHA, New York Heart Association; AHF, acute heart failure within 60 days; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgery.

Table 2. Independent predictors of early and late all-cause mortality after transcatheter aortic valve replacement.

Covariates	*P-value*	*HR, 95%CI*
Age	0.009	1.021, 1.005-1.037
eGFR	<0.0001	0.991, 0.986-0.996
Hemoglobin	<0.0001	0.987, 0.981-0.993
Female	0.007	0.769, 0.635-0.930
Diabetes	0.008	1.297, 1.070-1.573
Pulmonary disease	<0.0001	1.646, 1.347-2.010
Oxygen therapy	0.001	2.908, 1.541-5.489
Atrial fibrillation	<0.0001	1.413, 1.180-1.692
Severe frailty	0.012	1.342, 1.067-1.688
LVEF≤50%	0.026	1.251, 1.027-1.524
Recent AHF/critical preop. state	0.042	1.300, 1.010-1.672
Transapical approach	0.001	1.455, 1.155-1.833
Malignancy	0.361	1.105, 0.892-1.369

eGFR, estimated glomerular filtration rate according to the CKD-EPI equation; AHF, acute heart failure within 60 days; LVEF, left ventricular ejection fraction.

CRediT author statement

Fausto Biancari: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – Original draft, Writing – review and editing, Supervision.

Sebastian Dahlbacka: Conceptualization, Data curation, Writing – review and editing.

Tatu Juvonen: Conceptualization, Methodology, Writing – review and editing, Supervision.

Marko P.O. Virtanen: Conceptualization, Data curation, Writing – review and editing.

Pasi Maaranen: Conceptualization, Data curation, Writing – review and editing.

Jussi Jaakkola: Conceptualization, Data curation, Writing – review and editing.

Teemu Laakso: Conceptualization, Data curation, Writing – review and editing.

Matti Niemelä: Conceptualization, Data curation, Writing – review and editing, Supervision.

Tuomas Tauriainen: Conceptualization, Data curation, Writing – review and editing.

Antti Vento: Conceptualization, Data curation, Writing – review and editing, Supervision.

Annastiina Husso: Conceptualization, Data curation, Writing – review and editing.

Mikko Savontaus: Conceptualization, Data curation, Writing – review and editing.

Mika Laine: Conceptualization, Data curation, Writing – review and editing.

Timo Mäkikallio: Conceptualization, Data curation, Writing – review and editing.

Peter Raivio: Conceptualization, Data curation, Writing – review and editing, Supervision.

Markku Eskola: Conceptualization, Data curation, Writing – review and editing, Supervision.

Stefano Rosato: Formal analysis.

Vesa Anttila: Conceptualization, Data curation, Writing – review and editing, Supervision.

Juhani Airaksinen: Conceptualization, Methodology, Writing – Original draft, Writing – review and editing, Supervision.

Antti Valtola: Conceptualization, Data curation, Writing – Original draft, Writing – review and editing, Supervision.

Highlights

- It is controversial whether cancer patients undergoing TAVR have worse prognosis.
- This nationwide registry showed that 20% of patients scheduled for TAVR had cancer.
- Provided appropriate selection, cancer patients have favorable survival after TAVR.

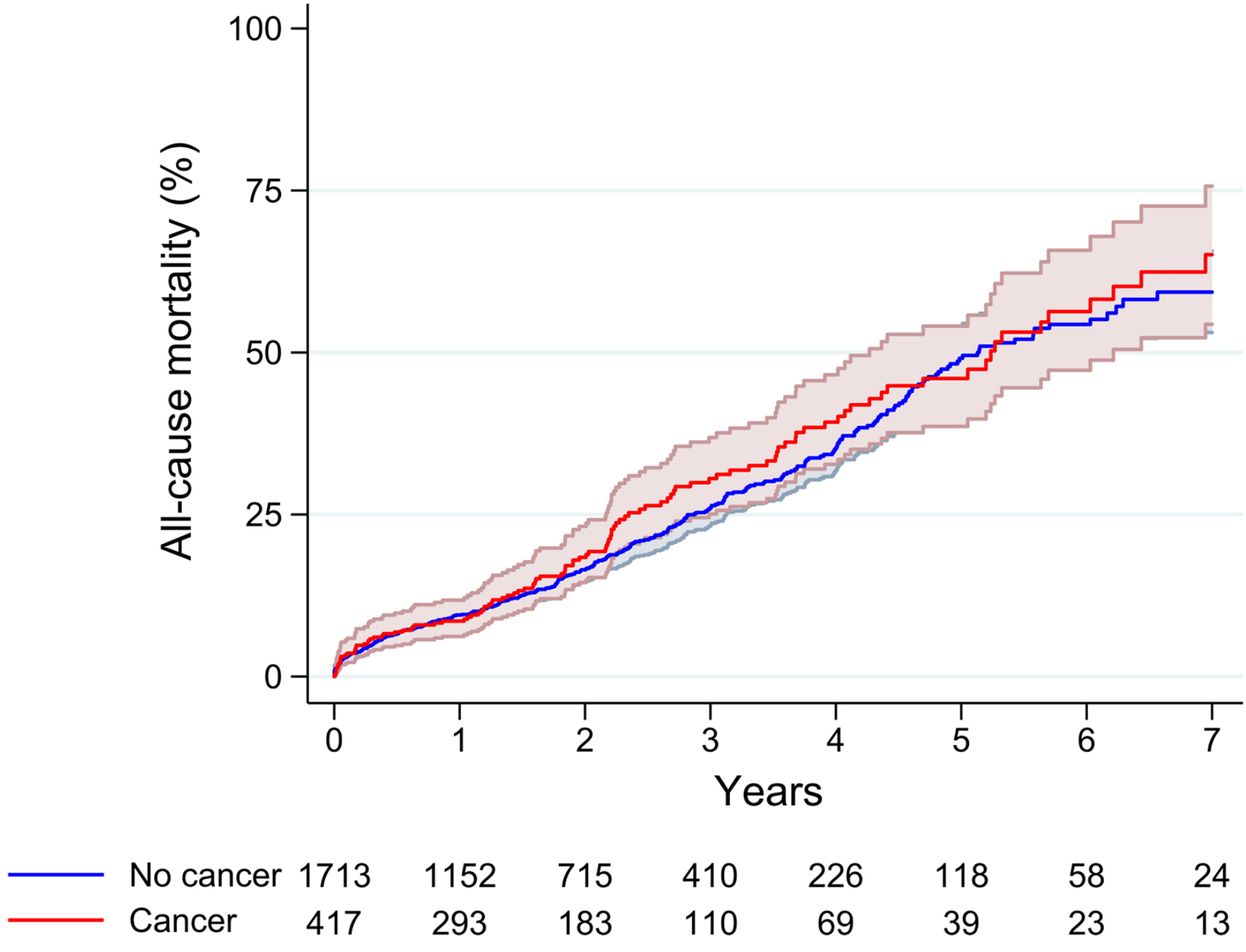
All-cause mortality (%)
100
75
50
25
0
0
1
2
3
4
5
6
7
Years
No cancer 1713 1152 715 410 226 118 58 24
Cancer 417 293 183 110 69 39 23 13

Figure 1