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# Prevalence and cumulative incidence of cancer, and mortality in patients with Takotsubo syndrome with focus on the index event

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## Summary

**Background:** It has been suggested that Takotsubo syndrome (TS) is associated with cancer but previous studies have limitations.
**Aim:** To make a comprehensive analysis of prevalence and cumulative incidence of cancer, and mortality among TS patients with focus on the index event.
**Design:** A register-based case–control study.
**Methods:** The first new cancer occurrences (International Classification of Diseases C00–C75, C81–C96) were compared between 505 patients with TS without obstructive coronary artery disease (CAD) and four age- and gender-matched controls comprising patients with acute coronary syndrome with obstructive CAD (CAD controls), respectively, with chest-pain without obstructive CAD at coronary angiography (controls without CAD).
**Results:** The prevalence of cancer before the index event was non-significantly ($P = 0.052$) higher in TS patients (15.8%) than in CAD controls (11.5%), respectively, higher ($P = 0.028$) than in controls without CAD (11.1%). There were no differences between the groups in cumulative incidence of cancer after the index event but a higher mortality in TS patients who developed cancer when compared with controls without CAD that developed cancer after the index event ($P = 0.018$).
**Conclusions:** There is an increased prevalence of first diagnosed cancer in TS patients before the index event but no increased cumulative incidence of cancer after the index event. The results does not support investigation for the possibility of a malignancy specifically in TS patients but in the event of cancer this patient group might need special care. However, if there is lack of a clear stressor it could be of importance to investigate the possibility of a malignancy.

## Introduction

It has been suggested that Takotsubo syndrome (TS) should be divided into primary and secondary forms where the secondary form is caused by severe underlying disease such as cancer and sepsis or surgical procedures.[1] Several studies have shown an association between TS and cancer, both before and after the index event.[2–6] All studies have been relatively small regarding the number of included TS patients (50–286 patients) and have been performed as

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single-center studies, thus not population-based. Only two studies[2,6] have had age- and sex-matched controls comprising patients with a previous myocardial infarction (MI) that is a group of patients with an increased risk of cancer compared with the population.[7]

The association between TS and cancer has been discussed since the initial observation by Burgdorf *et al.* in 2008[2] who in a single-center study retrospectively investigated 50 TS patients together with 50 age- and sex-matched patients with an MI. In this pivotal study, 18% of the TS patients and 6% of the MI patients had a previous history of cancer. After 3 years of follow-up an additional 14% of the TS patients were diagnosed with cancer compared to none of the MI patients. Recently, Sattler *et al.*[6] presented a single-center study of similar design comprising 138 TS patients with 138 age- and sex-matched MI controls. Twelve percent of the TS patients and 6% of the MI patients had a previous history of cancer. During a follow-up of more than 4 years an additional 9% of the TS patients were diagnosed with cancer compared with only 2% of the MI controls. The results of these studies suggest that TS is a para-malignant phenomenon and that TS patients should be screened for cancer. However, the association between TS and cancer is complex since the mechanisms might be different in cancers detected before and after the index event. For example, in cancer known at the index event TS might be caused by a para-malignant phenomenon, by the treatment for cancer[8] or by the stress of having cancer. After the index event an increased incidence could be observed merely due to investigations instigated by TS or by a true association between TS and cancer where TS could be considered a para-malignant phenomenon.

In 2016, we presented a population-based register study comprising 505 TS patients with age- and sex-matched controls, including not only MI but also healthy controls, with focus on risk markers and prognosis. In this study, in contrast to another register study,[9] we could not observe any overall difference in prevalence of life-time number of cancers or relative risk of death due to cancer between the groups.[10] The aim of the present study, using the same material, was to focus on first time cancer before and in particular after the index event to find support for TS as a para-malignant phenomenon in need for cancer screening. Furthermore, we wished to test the hypothesis that patients with both TS and cancer had a poor prognosis proposed by Sattler *et al.*[6]

## Materials and methods

### Patients and controls

In total, 505 patients with TS without obstructive coronary artery disease (CAD) 2009–2013 were identified from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) together with four age- and sex-matched controls comprising patients with an acute coronary syndrome with obstructive CAD (CAD controls; $n = 1010$), respectively, with chest-pain without obstructive CAD at coronary angiography (controls without CAD; $n = 1007$). Data from SCAAR were merged with the national patient register including International Classification of Diseases-10 (ICD-10) codes from in- and out-patient hospital care. The methodology has been presented in detail.[10] Cancer diagnoses were determined by ICD C00–C75 and C81–C96. Contrary to the original publication[10] where each patients could contribute with more than one cancer diagnosis, each patient contributed only with their first new cancer diagnosis in this study. Follow-up was ascertained, up to a maximum of 5 years, through the national patient register.

### Statistics

Data before and after the index event were studied separately. Data are presented as mean ± standard deviation and percentage (number). Characteristics and cardiovascular risk factor were compared pair-wise between TS patients and CAD controls, respectively, controls without CAD by independent Student's *t*-test for mean or Fishers exact test for percentage. Cancer diagnoses were determined by ICD C00–C75 and C81–C96 divided into solid malignancies (C00–75) excluding breast cancer (C50) and blood malignancies (C81–96). To study the occurrence of a first new cancer and survival between the groups, we used the Kaplan–Meier method with the corresponding log-rank test. We defined time (Figure 1) from index event to first new cancer (event), death, or 31 December 2013, whichever occurred first. Time (Figure 2) from index event in patients with first new cancer before the index event to death (event) or 31 December. Or time (Figure 3) from first new cancer after the index event to death (event), or 31 December. In addition, we used cox regression to adjust for factors that differed between the groups at the index event (Tables 1 and 2) to study the occurrence of first new cancer and mortality after the index event (Figures 1 and 2). Analysis was done with the use of SPSS version 25 (IBM, Armonk, NY, USA). The results were considered significant if $P < 0.05$, two sided.

## Results

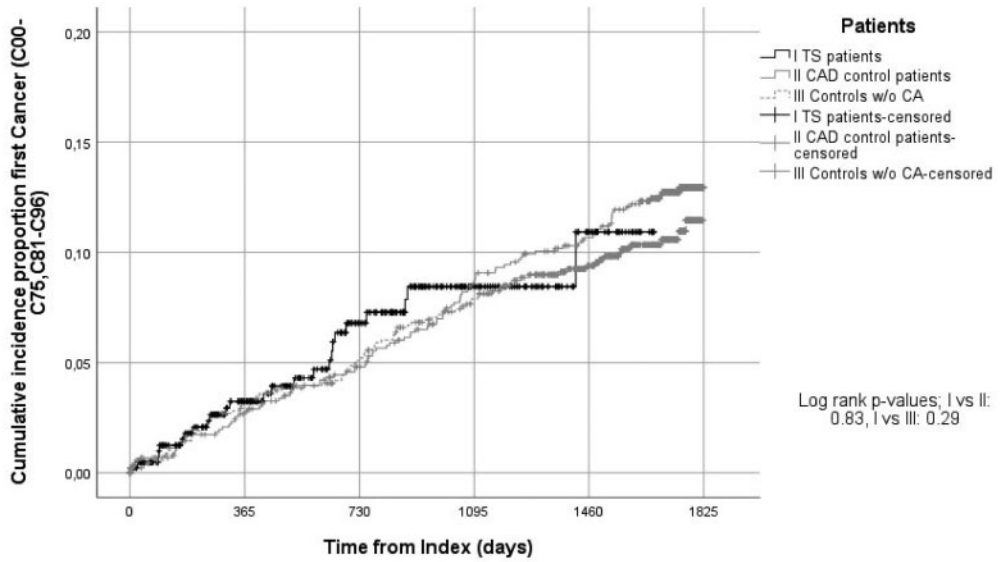
Characteristics and cardiovascular risk factors for TS patients and their respective controls, 'including cancer patients', have been described.[10] In Table 1, characteristics and cardiovascular risk factors for TS patients and their respective controls, 'excluding patients with cancer before the index event', are described. Consistent with the original publication, TS patients and controls were typically women with a mean age of 67 years.[9] As described, TS patients had less frequently treated hypertension and hyperlipidemia whereas smoking habits were intermediate when compared with both control groups. Furthermore, a diagnosis of diabetes mellitus was less common in TS patients than in CAD controls.[8] TS patients had more often a diagnosis of chronic obstructive pulmonary disease (COPD) than the two control groups also consistent with our original study.[8] Further analyses are divided according to if the first new cancer occurred before or after the index event.

### Prevalence of cancer before the index event

In total, 308 first new cancers occurred before the index event, divided into 80 (15.8%) in TS patients, 116 (11.5%) in CAD controls and 112 (11.1%) in controls without CAD. The different forms of cancer are shown in Table 2 and Supplementary Table. The prevalence of cancer was borderline increased in TS patients when compared with CAD controls ($P = 0.052$) and significantly increased when compared with controls without CAD ($P = 0.028$). When characteristics and cardiovascular risk factors were compared between patients with cancer before the index event, TS patients had a lower prevalence of treated hypertension and hyperlipidemia than both control groups. Furthermore, the prevalence of present smoking and COPD was increased 5-fold in TS patients when compared with controls without CAD (Table 2).

### Cumulative incidence of cancer after the index event

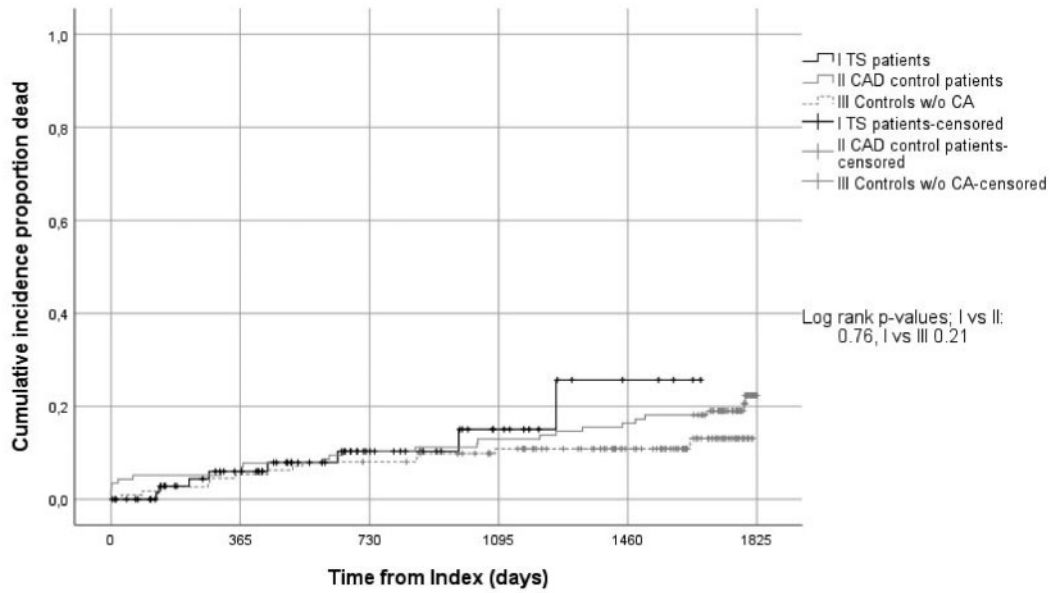
In total, 221 first new cancers occurred after the index event, divided into 25 (5.9%) in TS patients, 106 (11.8%) in CAD




Numbers at risk

| | | Index | 365 | 730 | 1095 | 1460 | 1825 |
|---|---|---|---|---|---|---|---|
| Patients | I TS patients | 425 | 306 | 200 | 96 | 30 | 0 |
| | II CAD control patients | 894 | 829 | 791 | 745 | 710 | 6 |
| | III Controls w/o CAD | 895 | 855 | 824 | 778 | 639 | 0 |

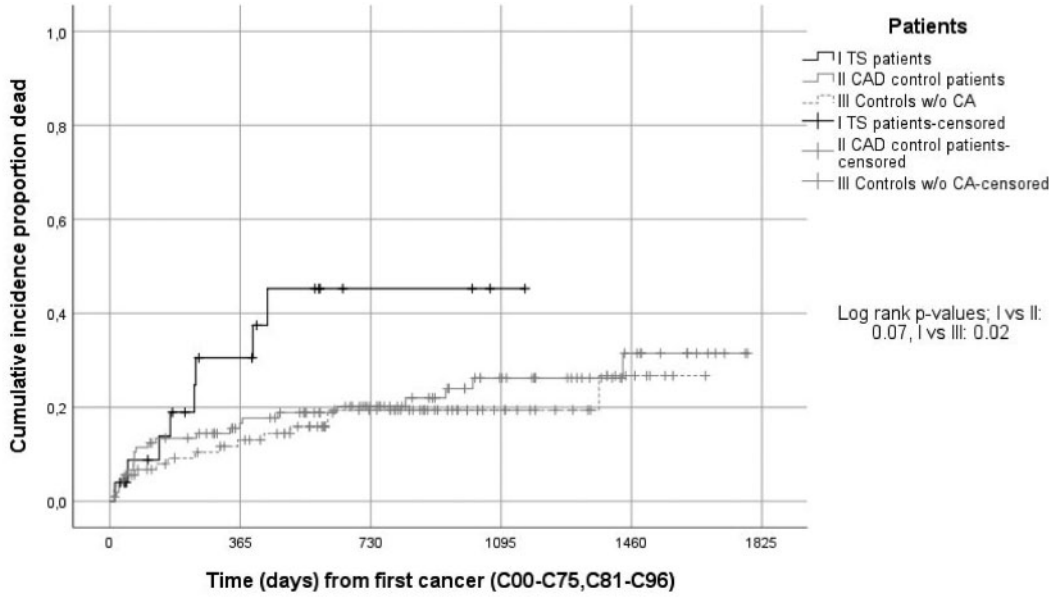
**Figure 1.** Survival curves of a first new cancer 'after the index event' in TS patients and controls with and w/o CAD. CAD: coronary artery disease; w/o: without; TS: Takotsubo syndrome.




Numbers at risk

| | | Index | 365 | 730 | 1095 | 1460 |
|---|---|---|---|---|---|---|
| Patients | I TS patients | 80 | 55 | 28 | 13 | 4 |
| | II CAD control patients | 116 | 109 | 104 | 101 | 97 |
| | III Controls w/o CAD | 112 | 106 | 102 | 90 | 64 |

**Figure 2.** Survival curves of mortality 'after the index event' in TS patients and controls with and w/o CAD and first new cancer 'before the index event'. CAD: coronary artery disease; w/o: without; TS: Takotsubo syndrome.




Numbers at risk

| | | First cancer after index | 365 | 730 | 1095 | 1460 |
|---|---|---|---|---|---|---|
| Patients | I TS patients | 25 | 11 | 3 | 1 | 0 |
| | II CAD control patients | 106 | 75 | 53 | 29 | 12 |
| | III Controls w/o CAD | 90 | 66 | 43 | 20 | 6 |

**Figure 3.** Survival curves of mortality 'after the index event' in TS patients and controls with and w/o CAD and a first new cancer 'after the index event'. CAD: coronary artery disease; w/o: without; TS: Takotsubo syndrome.

**Table 1.** Characteristics and cardiovascular risk factors in percentage (numbers) or mean ± standard deviation in patients without cancer before the index event

| | TS patients I (*N* = 425) | CAD controls II (*N* = 894) | Controls w/o CAD III (*N* = 895) | *P*-value I vs. II | *P*-value I vs. III |
|---|---|---|---|---|---|
| Female gender | 88.0 (374) | 87.7 (784) | 86.9 (778) | 0.93 | 0.66 |
| Age | 67 ± 11 | 67 ± 10 | 67 ± 10 | 0.74 | 0.47 |
| Never smoker | 53.6 (228) | 43.5 (389) | 59.4 (532) | **<0.01** | **<0.01** |
| Former smoker | 25.9 (110) | 23.9 (214) | 28.9 (259) | | |
| Present smoker | 13.6 (58) | 27.3 (244) | 8.4 (75) | | |
| Missing data | 6.8 (29) | 5.3 (47) | 3.2 (29) | | |
| Treated hypertension | 46.1 (196) | 52.9 (473) | 52.6 (67) | **0.04** | **0.03** |
| Missing data | 2.8 (12) | 1.7 (15) | 1.5 (13) | | |
| Treated hyperlipidemia | 26.1 (111) | 40.0 (358) | 43.0 (385) | **<0.01** | **<0.01** |
| Missing data | 3.8 (16) | 3.0 (27) | 1.3 (12) | | |
| Diabetes mellitus type 1 | 1.2 (5) | 6.3 (56) | 2.3 (21) | **<0.01** | 0.20 |
| Diabetes mellitus type 2 | 5.9 (25) | 13.0 (116) | 6.7 (60) | **<0.01** | 0.63 |
| Myocardial infarction | 6.4 (27) | 14.7 (131) | 0.9 (8) | **<0.01** | **<0.01** |
| Heart failure | 3.8 (16) | 5.1 (46) | 5.5 (49) | 0.33 | 0.22 |
| Atrial fibrillation | 5.2 (22) | 6.5 (58) | 11.6 (104) | 0.39 | **<0.01** |
| Stroke/TIA | 5.0 (4) | 7.8 (9) | 7.1 (8) | 0.40 | 0.24 |
| Asthma | 4.9 (21) | 3.8 (34) | 6.3 (56) | 0.38 | 0.38 |
| COPD | 8.7 (37) | 3.6 (32) | 3.8 (34) | **<0.01** | **<0.01** |

CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; TIA: transitory ischemic attack; TS: Takotsubo syndrome. Bold numbers denote significant differences between groups.

**Table 2.** Characteristics, cardiovascular risk factors and type of malignancy in percentage (numbers) or mean ± standard deviation in patients with first new cancer before the index event

| | TS patients I ($N = 80$) | CAD controls II ($N = 116$) | Controls w/o CAD III ($N = 112$) | *P*-value I vs. II | *P*-value I vs. III |
|---|---|---|---|---|---|
| Female gender | 85.0 (68) | 86.2 (100) | 92.0 (103) | 0.84 | 0.16 |
| Age | 68 ± 9 | 71 ± 9 | 72 ± 8 | 0.12 | **<0.01** |
| Never smoker | 38.8 (31) | 45.7 (53) | 68.8 (77) | 0.80 | **<0.01** |
| Former smoker | 35.0 (28) | 31.0 (36) | 25.0 (28) | | |
| Present smoker | 18.8 (15) | 15.5 (18) | 3.6 (4) | | |
| Missing data | 7.5 (6) | 7.8 (9) | 2.7 (3) | | |
| Treated hypertension | 45.3 (33) | 54.2 (74) | 53.4 (67) | **<0.01** | **<0.01** |
| Missing data | 5.0 (4) | 0.9 (1) | 0 (0) | | |
| Treated hyperlipidemia | 26.3 (21) | 46.6 (54) | 48.2 (54) | **0.01** | **<0.01** |
| Missing data | 5.0 (4) | 3.4 (4) | 0.9 (1) | | |
| Diabetes mellitus type 1 | 0 (0) | 4.3 (5) | 3.6 (4) | 0.08 | 0.14 |
| Diabetes mellitus type 2 | 3.8 (3) | 19.8 (23) | 8.9 (10) | **<0.01** | 0.24 |
| Myocardial infarction | 7.5 (6) | 22.4 (26) | 0 (0) | **<0.01** | **<0.01** |
| Heart failure | 5.0 (4) | 11.2 (13) | 6.3 (7) | 0.20 | 0.76 |
| Atrial fibrillation | 10.0 (8) | 6.9 (8) | 13.4 (15) | 0.44 | 0.51 |
| Stroke/TIA | 5.0 (4) | 7.8 (9) | 7.1 (8) | 0.56 | 0.76 |
| Asthma | 12.5 (10) | 6.0 (7) | 8.0 (9) | 0.13 | 0.33 |
| COPD | 17.5 (14) | 12.1 (14) | 3.6 (4) | 0.30 | **<0.01** |
| Solid malignancies | 71.3 (57) | 61.2 (71) | 68.8 (77) | 0.34 | 0.92 |
| Blood malignancies | 3.8 (3) | 6.0 (7) | 3.6 (4) | | |
| Breast cancer | 25.0 (20) | 32.8 (38) | 27.7 (31) | | |

CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; TIA: transitory ischemic attack; TS: Takotsubo syndrome. Bold numbers denote significant differences between groups.

**Table 3.** Characteristics, cardiovascular risk factors and type of malignancy in percentage (numbers) or mean ± standard deviation in patients with first new cancer after the index event

| | TS patients I ($N = 25$) | CAD controls II ($N = 106$) | Controls w/o CAD III ($N = 90$) | *P*-value I vs. II | *P*-value I vs. III |
|---|---|---|---|---|---|
| Female gender | 85.0 (68) | 86.2 (100) | 92.0 (103) | 0.99 | 0.99 |
| Age | 71 ± 8 | 71 ± 8 | 70 ± 9 | 0.69 | 0.59 |
| Never smoker | 52 (13) | 52.8 (56) | 62.2 (56) | 0.48 | 0.63 |
| Former smoker | 28.0 (7) | 19.8 (21) | 25.6 (23) | | |
| Present smoker | 12.0 (3) | 22.6 (24) | 6.7 (6) | | |
| Missing data | 8.0 (2) | 4.7 (5) | 5.6 (5) | | |
| Treated hypertension | 60.0 (15) | 57.5 (61) | 45.6 (41) | 0.85 | 0.39 |
| Missing data | 4.0 (1) | 2.8 (3) | 4.4 (4) | | |
| Treated hyperlipidemia | 26.1 (7) | 40.8 (43) | 43.6 (29) | 0.51 | 0.28 |
| Missing data | 4.0 (1) | 3.8 (4) | 0 (0) | | |
| Diabetes mellitus type 1 | 0 (0) | 6.6 (7) | 2.2 (2) | 0.34 | 0.99 |
| Diabetes mellitus type 2 | 8.0 (2) | 12.3 (13) | 3.3 (3) | 0.73 | 0.30 |
| Myocardial infarction | 4.0 (1) | 14.2 (15) | 0 (0) | 0.30 | 0.22 |
| Heart failure | 4.0 (1) | 2.8 (3) | 2.2 (2) | 0.58 | 0.52 |
| Atrial fibrillation | 8.0 (2) | 3.8 (4) | 13.3 (12) | 0.33 | 0.73 |
| Stroke/TIA | 12.0 (3) | 6.6 (7) | 6.7 (6) | 0.40 | 0.41 |
| Asthma | 4.0 (1) | 3.8 (4) | 6.7 (6) | 0.99 | 0.99 |
| COPD | 12.0 (3) | 3.8 (4) | 3.3 (3) | 0.13 | 0.12 |
| Solid malignancies | 88.0 (22) | 81.1 (86) | 85.6 (77) | 0.80 | 0.41 |
| Blood malignancies | 0.0 (0) | 3.8 (4) | 6.7 (6) | | |
| Breast cancer | 12.0 (3) | 15.1 (16) | 7.8 (7) | | |

CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; TIA: transitory ischemic attack; TS: Takotsubo syndrome.

controls and 90 (10.0%) in controls without CAD. The different forms of cancer are shown in Table 3 and Supplementary Table. There were neither differences in cumulative incidence of cancer between the groups when the difference in exposure time was taken into account (Figure 1), nor when the results were adjusted for factors that differed between the groups at the index event (Table 1). There were no major differences between the groups in characteristics and cardiovascular risk factors in patients with cancer after the index event (Table 3).

### Mortality after the index event

There were no differences in cumulative incidence of mortality after the index event between the three groups with a first new cancer 'before the index event' (Figure 2), neither in unadjusted nor in analyses adjusted for differences between the groups at the index event (Table 2). The mortality was borderline increased in TS patients when compared with CAD controls ($P = 0.072$) and significantly increased when compared with controls without CAD ($P = 0.018$) in patients that developed a first new cancer 'after the index event' (Figure 3).

## Discussion

The results of this population-based register study comprising 505 TS patients with two age- and sex-matched controls showed that a first new cancer diagnosis was more common 'before the index event' in TS patients than in controls without CAD but there were no differences if the first new cancer occurred 'after the index event'. Intriguingly, the mortality was increased in TS patients with a first new cancer that occurred 'after the index event' but not before when compared with the two control groups.

The results of the present population-based study of TS patients without obstructive CAD confirmed the results of the single-center studies by Burgdorf *et al.*[2] and Sattler *et al.*[6] regarding an increased prevalence of cancer 'before the index event' when compared with age- and sex-matched patients with MI. Of note is that the differences were statistically non-significant, including altogether 26 cancer cases in the TS groups compared with 11 in the MI control groups in these studies. Our results are reinforced by the register study by El-Sayed *et al.*[9] where they in comparison with MI and orthopedic controls showed an increased prevalence of cancer in TS patients. However, controls in their study were only matched for age, thus not taking into account differences in malignancies between men and women. The reason for the association between TS and cancer is not clear but could be due to the malignancy itself, the stress of having cancer or drugs known to cause TS. The results thus support the statement that TS should be divided into primary and secondary forms where the secondary form is caused by an underlying severe disease.[1]

We could not confirm an increased cumulative incidence of cancer 'after the index event' seen in the studies by Burgdorf *et al.*[2] and Sattler *et al.*[6] when compared with age- and sex-matched patients with MI. Although the differences were statistically significant, the numbers were small including altogether 20 cancer cases in the TS groups compared with 3 in the MI control groups. The reason for this spurious discrepancy is not clear but could be due to a statistical type 1 error in the studies by Burgdorf *et al.*[2] and Sattler *et al.*[6] since we included 221 cancer patients in total (25 in TS patients). A further strength to the present study is that we included two control groups. The choice of control groups is also relevant since there has been a report about an association between cancer and a recent MI from a Norwegian population-based study.[7] The incidence of cancer was 22.6 cases per 1000 patient-years in MI patients compared to 7.3 cases per 1000 patient-years in controls without MI. Extrapolating from these figures, the expected total number of cancer in the MI controls in the studies by Burgdorf *et al.*[2] and Sattler *et al.*[6] would have been ~20 that is the number of TS patients who had cancer in these patients thus indicating that the differences seen were caused by a decreased incidence in MI controls rather than an increased incidence in TS patients. Taking study design and size of the study into account there is weak support for TS being a para-malignant phenomenon with an increased incidence of cancer after a TS event. Thus, no recommendation can be made regarding cancer screening in TS patients. However, in our study we had no information about the amount of patients that not could be classified as primary or secondary forms of TS and it can therefore be suggested that if there is lack of a clear stressor it could be of importance to investigate the possibility of a malignancy.

Without surprise, several studies have suggested that cancer increase mortality in TS patients. Girardey *et al.*[5] and Kim *et al.*[11] showed that cancer was a negative prognostic factor in patients hospitalized for TS whereas Möller *et al.*[3] and Sattler *et al.*[4] came to a similar conclusion but included TS patients both 'before and after the index event'. The finding that TS patients with a previous history of cancer or with active cancer have a worse prognosis than TS patients without cancer was reinforced by a recent meta-analysis by Brunetti *et al.*[12] who showed more clinical events both in-hospital and during follow-up in TS patients. These studies emphasize the need for special care, including intensive care from both cardiologists and oncologists, for patients with TS and cancer. Recently, Sattler *et al.*[6] proposed that TS patients with cancer have a worse prognosis compared to MI patients with cancer. Unfortunately, they included cancer patients both 'before and after the index event' making data difficult to interpret. However, in the present study we could confirm that TS patients who developed cancer 'after the index event' had a worse prognosis than controls that developed cancer with and without CAD. This information should be interpreted cautiously since the reason is unclear and the number of patients few. Therefore, more and larger studies are needed to confirm a worse prognosis in TS patients with cancer compared with other groups of patients with cancer.

### Strength and limitations

The major strength of the present investigation is that it is population-based compared to previous single-center studies and that it included both CAD and healthy controls. Furthermore, the number of cancer cases was comparably high compared to previous controlled studies.[2,6] A weakness is the retrospective design with TS cases identified by the individual angiographer in SCAAR. Also, the case–control design with patient characteristics and cardiovascular risk factor data at the time of the index event, rather than at the time of first new cancer diagnosis, made it not relevant to perform multivariable analysis to adjust for factors that differed between the groups when the first new cancer occurred or of the prevalence of cancer at the index event. Furthermore, as controls, patients with an acute coronary syndrome with obstructive coronary arteries but without a confirmed MI were included, thus comprising both MI and unstable angina pectoris. Finally, there is no information regarding cancer treatments that might have influenced in particular mortality after the index event.

## Conclusion

There is an increased prevalence of first diagnosed cancer in TS patients before the index event but no increased cumulative incidence of cancer after the index event. Intriguingly, the mortality was increased in TS patients who developed cancer after the index event. The results does not support investigation for the possibility of a malignancy specifically in TS patients but in the event of cancer this patient group might need special

care. However, if there is lack of a clear stressor it could be of importance to investigate the possibility of a malignancy.

## Supplementary material

Supplementary material is available at *QJMED* online.

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*Conflict of interest*: None declared.

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