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A cohort study linked increased mortality in patients treated surgically for Dupuytren's contracture

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Abstract

Objective: Dupuytren's contracture (DC) is a fibromatous disease of the palmar fascia of unknown etiology. The objective of this study was to assess whether individuals treated for DC exhibited an altered standardized mortality ratio.

Study Design and Setting: A total of 16,517 patients operated on for DC between 1965 and 1995 were identified by the Swedish Inpatient Register. For the 7,579 patients who had died during that period, cause of death was obtained from the Swedish Death Register.

Results: There was an overall increased mortality (standardized mortality ratio [SMR] = 1.06), inversely related to age and significant for both sexes, in patients under 70 years of age. The risk estimate was highest for endocrine diseases (highest value in patients 40–49 years of age at surgery; SMR = 2.82), gastrointestinal diseases (highest value in those 40–49 years of age at surgery; SMR = 2.69), accidents (highest value in those 30–39 years of age at surgery; SMR = 2.40), and respiratory diseases (highest value in those 50–59 years of age at surgery; SMR = 1.61). There was also an increased SMR for cardiovascular diseases in patients 40–59 years of age more than 10 years after surgery (highest value in those 40–49 years of age at surgery; SMR = 1.65).

Conclusion: The most probable mechanism for the increased mortality is related to smoking and other lifestyle factors.

Keywords: Dupuytren's contracture; Mortality; Vital statistics; Epidemiology; Smoking; Lifestyle

1. Introduction

Dupuytren's contracture (DC) is a fibromatous disease of the palmar fascia of unknown etiology. Its peculiar features have stimulated much thought concerning its etiology and epidemiology. Thus, it has previously been linked to epilepsy [1], diabetes mellitus [2], manual labor [3], alcohol intake [4], and high levels of cholesterol and triglycerides [5]. A certain genetic disposition has also been suggested [6]. There are also indications that autoimmunity or dysregulation of the immune system may play a role in its pathogenesis. Associations with certain HLA-DR subclasses and high levels of anticollagen autoantibodies have been reported [7]. Increased T-cell infiltration and raised levels of IgM and IgA antibodies have been found in diseased palmar fascia [8]. In contrast, it has been reported that DC is uncommon among patients suffering from rheumatoid arthritis [9]. A recent population-based cohort study [10] conducted on a random sample of 2,165 subjects from the Reykjavik population established a correlation with heavy smoking, manual labor, elevated fasting blood glucose but a normal glucose tolerance, low body weight, and low body mass index.

Because several of the proposed associated diseases have an increased mortality compared with that of the normal population, a true association would be discernible as an effect on mortality. An increased overall mortality was also observed in a prospective study on 426 men followed for 26 years [11]. The increased mortality was not influenced by the duration of the disease. It was, however, 70% higher among men who developed the malady before the age of 60 and only 10% higher in those who developed the disease after the age of 60 and seemed confined to patients with a stronger hereditary tendency and stronger diathesis. The data were said to support the theory that from a death risk perspective there are two types of DC, one affecting younger people and one starting later in life. Furthermore, a recent population-based longitudinal study of 1,297 male cases with screening diagnosed signs of Dupuytren's contracture showed an increased total and cancer-related mortality [12].

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This increase in mortality was limited to individuals who exhibited flexion of the fingers or who had required surgery.

Based on these previous investigations, the aim of the present study was to use the Swedish Death Register as data source to further assess the mortality among patients treated surgically for DC and to determine differences compared with the general population in cause of death and age at death. This approach also allows for estimates on the disease group level.

2. Patients and methods

2.1. Study group

The Swedish Inpatient Register covers all inpatient treatments by county. It included six counties at its start in 1965 and has included the entire Swedish population since 1987. For each hospitalization, the national registration number (NRN)—a unique personal identifier assigned to all Swedish residents [13]—date of admission and discharge, medical data such as surgical and anesthetic procedures, hospital department, and up to eight discharge diagnoses are registered. The codes for the main discharge diagnoses are judged to be correct at the detailed five-digit level in 85% of the records [14]. Because there is almost no private inpatient treatment in Sweden, patients are obliged to use the public hospitals in the county where they live, and the Inpatient Register is therefore population-based. We confined our study to all patients registered in the Inpatient Register, and to minimize the risk for misclassification we identified patients with a combination of a discharge diagnosis of DC (744.20 in ICD-7, 733.90 in ICD-8, and 728G in ICD-9) and a Swedish Classification of Operations and Major Procedures code 8631 (aponeurosectomy in the hand) for the years 1965–1995. There were 16,857 unique NRNs with one or more records that contained the specified combinations of diagnostic codes. We excluded 340 NRNs that could not be found in the Register of the Official Total Population, the Migration Register, or the Death Register kept by Statistics Sweden. Eight records with inconsistencies in dates of death or gender codes in the Inpatient Register and Cancer Register, respectively, were disclosed during the linkage procedure. This left us with 16,517 patients (98 %) for follow-up (Table 1).

Table 1
Patient groups according to age at surgery and gender

Age group (yr)	Men	Women	Total
<20	23 (0.2)	11 (0.5)	34 (0.2)
20–29	105 (0.7)	28 (1.2)	133 (0.8)
30–39	429 (3.0)	46 (2.0)	475 (2.9)
40–49	1.258 (8.9)	116 (4.9)	1.374 (8.3)
50–59	3.275 (23.1)	369 (15.7)	3.644 (22.0)
60–69	5.073 (35.8)	836 (35.5)	5.909 (35.8)
⩾70	4.002 (28.3)	946 (40.2)	4.948 (30.0)
No. of patients	14.165 (100)	2.352 (100)	16.517 (100)
Mean ± SD	63.4 ± 11.3	66.2 ± 11.8	63.8 ± 11.4

[a] Figures in parentheses indicate percentage of entire group within each column.

2.2. Follow-up

The NRNs were used to follow the 16,517 study subjects by record linkage to the Death Register at Statistics Sweden. The Register includes all deceased persons, whether they died abroad or in Sweden, and provides information on date and primary underlying cause of death using the International Classification of Diseases codes, 7th version (ICD-7) before 1969 and ICD-8 codes thereafter. Date of emigration, when applicable, was established through the Migration Register.

The time of observation was calculated from the date of discharge after surgical treatment for DC until date of death or up until the end of the observation period (December 31, 1995).

2.3. Statistical measures and methods

The expected numbers of deaths were calculated with respect to 5-year age group, gender, and calendar year-specific death incidence rates derived from the entire Swedish population. The computation of person-years at risk started at the time for discharge after surgery for DC. Each cohort member was followed to the date of death or to the closing date of follow-up (December 31, 1995). Official statistics from the Swedish Death Register included annual sex- and age-specific incidence rates for different ICD codes for the entire country. Multiplying the number of person-years at risk by 5-year age group, gender, and year-specific mortality rates yielded the number of expected cases. The standardized mortality ratio (SMR), the ratio of observed to expected number of deaths, was used as a measure of risk. The 95% confidence interval (CI) of the SM was calculated on the assumption that the observed number of deaths in each group followed a Poisson distribution [15].

3. Results

A total of 16,517 cases, 14,165 men (85.8%) and 2,352 women (14.2%), were discharged from hospital after surgery for DC during the observation period (Table 1). The largest male age group at the time of surgery was 60–69 years of age, and the largest female group was >70 years of age. There were 7,579 deaths in the cohort during the 30 years of observation (Table 2), of which 6,660 (87.9%) were men and 919 (12.1%) were women, compared with the expected number of 7,132, resulting in a SMR of 1.06 (95% CI 1.04–1.09). The SMR was somewhat higher among men (SMR = 1.07; 95% CI 1.04–1.09) than among women (SMR = 1.03; 95% CI 0.96–1.10).

Cardiovascular diseases were the most common cause of death, (3,934 deaths; 52%), although there was no overall increased mortality (SMR = 0.99) (Table 2). Cancer was the second most common cause of death in the study cohort (1,887 deaths; 25%), with a significantly increased overall

Table 2
Observed deaths (Obs) and standardized mortality rates (SMR) with 95% confidence intervals (CI) for different causes of death according to ICD-9 groups

		Men			Women			Total			Total after exclusion of diabetes mellitus		
	ICD-9	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI
Infection	I	35	0.88	0.68–1.23	6	0.93	0.34–2.03	41	0.89	0.64–1.21	34	0.82	0.57–1.15
Cancer	II	1,687	1.21	1.15–1.27	200	1.13	0.98–1.30	1,887	1.20	1.15–1.26	1,728	1.22	1.17–1.28
Endocrine	III	142	1.45	1.22–1.71	27	1.42	0.94–2.07	169	1.45	1.24–1.68	30	0.29	0.19–0.41
Hematopoietic	IV	14	0.97	0.53–1.62	5	2.06	0.67–4.82	19	1.12	0.68–1.76	17	1.11	0.65–1.78
Mental	V	86	0.97	0.77–1.19	20	0.89	0.54–1.37	106	0.95	0.78–1.15	95	0.94	0.76–1.15
Nervous system	VI	47	0.94	0.69–1.24	7	0.97	0.39–2.00	54	0.94	0.71–1.23	51	0.98	0.73–1.30
Cardiovascular	VII	3,431	0.99	0.96–1.02	503	0.99	0.91–1.08	3,934	0.99	0.96–1.02	3,233	0.90	0.87–0.94
Respiratory	VIII	540	1.09	1.00–1.18	65	0.97	0.75–1.23	605	1.07	0.99–1.16	534	1.05	0.96–1.14
Gastrointestinal	IX	236	1.28	1.12–1.45	31	1.10	0.75–1.57	267	1.26	1.11–1.42	226	1.18	1.03–1.35
Urogenital	X	80	0.78	0.62–0.97	9	0.75	0.34–1.43	89	0.77	0.62–0.95	71	0.69	0.54–0.86
Autoimmune	XIII	17	0.93	0.54–1.49	7	1.43	0.58–2.95	24	1.04	0.66–1.54	24	1.16	0.75–1.73
Accidents	XVII	293	1.35	1.20–1.51	34	1.38	0.96–1.93	327	1.35	1.21–1.51	296	1.36	1.21–1.52
All causes		6,660	1.07	1.04–1.09	919	1.03	0.96–1.10	7,579	1.06	1.04–1.09	6,387	1.00	0.97–1.02

SMR of 1.20. There was also an increased SMR for endocrine diseases in both genders and for gastrointestinal (GI) diseases and accidents, although significance was attained only in men (Table 2).

The results of a previous study [11], showing considerable differences in mortality in those developing the disease before and after 60 years of age, motivated a separate analysis of whether age at surgery had any impact on overall mortality. First, a dichotomization into those having surgery before and after 60 years of age showed that the increased SMR was restricted to this group (SMR = 1.40; 95% CI 1.34–1.47 versus SMR = 0.99; 95% CI 0.97–1.02). In detail, a significant increase in mortality was observed for both genders in all age groups except in patients under 20 years of age, where no cases were observed, in women between 30 and 39 years of age, and among patients over 70 years of age at the time of surgery. Among men who were 30–49 years of age at the time of surgery, the increase in risk was as high as 67% (SMR = 1.67; 95% CI 1.17–2.30 for the age group 30–39 years and SMR = 1.67; 95% CI 1.47–1.80 for the age group 40–49 years), and in women the risk was more than doubled if they underwent surgery before 50 years of age (Table 3).

The overall increase in mortality was augmented by the time since surgery (Table 4). The increase was not significant up to 5 years after surgery, but the SMR was 1.08 (95% CI 1.03–1.12) 5–9 years after surgery, 1.13 (95% CI 1.07–1.18) 10–14 years after surgery, and 1.26 (95% CI 1.19–1.32) ⩾15 years after surgery.

When the different ICD-9 disease groups were analyzed separately, a significant increase in mortality for cancer was revealed in all groups more than 1 year after surgery, and this was also the case for endocrine diseases 1–4 years and more than 10 years after surgery, cardiovascular and respiratory diseases more than 10 years after surgery, GI diseases 5–9 years and 15 years or more after surgery, and accidents 5 years or more after surgery (Table 4).

There was a considerably increased mortality for endocrine diseases in those operated on for DC after 40 years of age, with SMRs of 2.82, 2.44, and 1.59 in the age groups 40–49 years, 50–59 years, and 60–69 years, respectively (Table 5).

The considerable difference between overall mortality in those younger than 60 years of age at surgery and those older than 60 years of age at surgery motivated a similar subgroup analysis of cardiovascular diseases. This showed

Table 3
Observed deaths (Obs) and standardized mortality rates (SMR) with 95% confidence intervals (CI) for different age groups at surgery

	Men			Women			Total			Total after exclusion of diabetes mellitus		
Age group (yr)	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI
<20	0	0.00		0	0.00		0	0.00		0	0.0	
20–29	7	2.81	1.13–5.70	3	9.23	1.90–27.00	10	3.55	1.70–6.53	8	3.10	1.34–6.11
30–39	36	1.67	1.17–2.30	3	2.30	0.47–6.70	39	1.70	1.21–2.33	29	1.35	0.90–1.94
40–49	272	1.67	1.47–1.80	20	3.00	1.83–4.60	292	1.72	1.53–1.93	231	1.49	1.31–1.70
50–59	1,246	1.33	1.26–1.40	87	1.42	1.13–1.70	1,333	1.34	1.27–1.41	1,117	1.24	1.16–1.31
60–69	2,602	1.07	1.03–1.10	326	1.12	1.00–1.20	2,928	1.08	1.04–1.12	2,443	1.00	0.96–1.04
⩾70	2,497	0.93	0.89–0.90	480	0.90	0.82–0.90	2,977	0.92	0.89–0.96	2,559	0.89	0.85–0.92
All deaths	6,660	1.07	1.04–1.09	919	1.03	0.96–1.10	7,579	1.06	1.04–1.09	6,387	1.00	0.97–1.02

Table 4
Observed deaths (Obs) and standardized mortality rates (SMR) with 95% confidence intervals (CI) at latency periods up to 15 years after surgery for Dupuytren's contracture

		Within 1 yr			1–4 yr			5–9 yr			10–14 yr			⩾15 yr		
	ICD	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI
Infections	I	3	0.99	0.20–2.88	9	0.73	0.34–1.39	15	1.13	0.63–1.86	8	0.83	0.36–1.65	6	0.75	0.28–1.64
Cancer	II	84	0.75	0.60–0.93	501	1.13	1.03–1.23	585	1.26	1.16–1.37	387	1.24	1.12–1.37	330	1.38	1.24–1.54
Endocrine	III	8	1.09	0.47–2.15	43	1.42	1.03–1.92	44	1.31	0.95–1.76	41	1.66	1.19–2.26	33	1.57	1.08–2.21
Hematopoietic	IV	0	0.00	0.00–4.31	4	1.06	0.29–2.72	4	0.85	0.23–2.19	4	1.03	0.28–2.64	7	1.88	0.76–3.87
Mental	V	1	0.19	0.00–1.07	20	0.84	0.52–1.31	35	1.15	0.80–1.60	21	0.81	0.50–1.24	29	1.09	0.73–1.57
Nervous system	VI	2	0.53	0.06–1.93	12	0.78	0.41–1.37	16	0.97	0.56–1.58	18	1.52	0.90–2.40	6	0.59	0.22–1.29
Cardiovascular	VII	170	0.66	0.57–0.77	933	0.88	0.83–0.94	1,168	1.00	0.94–1.06	885	1.06	1.00–1.14	778	1.17	1.09–1.26
Respiratory	VIII	20	0.67	0.41–1.03	100	0.76	0.62–0.92	163	1.01	0.86–1.17	157	1.23	1.05–1.44	165	1.46	1.25–1.71
Gastrointestinal	IX	14	0.91	0.50–1.53	71	1.19	0.93–1.50	87	1.42	1.14–1.75	44	1.05	0.76–1.41	51	1.50	1.12–1.97
Urogenital	X	2	0.29	0.04–1.06	20	0.70	0.43–1.08	25	0.76	0.49–1.12	15	0.60	0.34–1.00	27	1.24	0.82–1.81
Autoimmune	XIII	2	0.90	0.11–3.24	6	0.75	0.27–1.63	7	0.99	0.40–2.05	8	2.13	0.92–4.20	1	0.47	0.01–2.65
Accidents	XVII	29	1.46	0.98–2.10	90	1.23	0.99–1.51	87	1.24	1.00–1.53	73	1.61	1.27–2.03	48	1.41	1.04–1.87
All causes	All	337	0.72	0.65–0.80	1,823	0.96	0.91–1.00	2,248	1.08	1.03–1.12	1,670	1.13	1.07–1.18	1,501	1.26	1.19–1.32

a significantly increased SMR for cardiovascular diseases in those under 60 years of age (1.24; 95% CI 1.15–1.32) but not in those older than 60 years of age (SMR = 0.95; 95% CI 0.91–0.98). The overall risk was apparent ⩾10 years after surgery (Table 5) and was substantial in individuals operated on between 40 and 49 years of age (SMR = 1.65; 95% CI 1.38–1.97) and less prominent in those operated on between 50 and 59 years of age (SMR = 1.17; 95% CI 1.08–1.27). In men, there was an increased risk of 53% (SMR = 1.53; 95% CI 1.26–1.80) and 15% (SMR = 1.15; 95% CI 1.06–1.20) in the age groups 40–49 and 50–59 years, respectively (data not shown). In women there was a similarly increased risk of 49% (SMR = 1.49; 95% CI 1.05–2.00) in the age group 50–59 years (data not shown).

A more detailed evaluation within the cardiovascular disease group showed a significantly increased SMR for the dominant ICD-9 diagnoses ischemic heart disease (ICD-9 410–414) and cerebrovascular diseases (ICD-9 430–438) in men and women (data not shown). It was especially evident in women and men operated on between 40 and 49 years of age (SMR for ischemic heart disease in women: 11.0 [95% CI 5.27–20.2] and SMR for cerebrovascular disease in men 2.03 [95% CI 1.22–3.16], respectively).

With respect to respiratory diseases, there was a 61% increase (SMR = 1.61; 95% CI 1.29–1.99) and a 22% increase (SMR = 1.22; 95% CI 1.07–1.39) in the risk for death in patients operated on between 50 and 59 years of age and 60 and 69 years of age, respectively, and there was a 169% increase (SMR = 2.69; 95% CI 1.66–4.11) and a 119% increase (SMR = 2.19; 95% CI 1.72–2.75) in the risk for death from GI causes in those operated on between the ages of 40 and 49 and between 50 and 59 years, respectively (Table 5). There was also an increased risk for accidental death in patients operated on between 30 and 69 years of age (Table 5), but this was confined to men (data not shown).

To test whether diabetes mellitus caused the increased mortality, we constructed a new cohort after exclusion of patients with diabetes mellitus as one of the discharge diagnoses. This reduced the cohort from 16,517–14,603 patients and reduced the number of deaths from 7,579–6,387. In this cohort, there was no overall increased mortality in patients operated on for DC (Table 2), although the pattern with respect to an increased disease-specific mortality in patients affected by DC was unchanged (Tables 2 and 3). The main exception was a considerably decreased mortality for endocrine diseases (overall SMR 0.29). The risk estimate

Table 5
Standardized mortality rates (SMR) with 95% confidence intervals (CI) in relation to age at surgery for Dupuytren's contracture (DC) in ICD-9 groups in the entire cohort that exhibit an increased mortality in relation to age at surgery

	Age at surgery for DC				
Follow-up (yr)	30–39 yr SMR (CI 95%)	40–49 yr SMR (CI 95%)	50–59 yr SMR (CI 95%)	60–69 yr SMR (CI 95%)	⩾70 yr SMR (CI 95%)
Endocrine	4.80 (0.99–14.0)	2.82 (1.29–5.35)	2.44 (1.74–3.33)	1.59 (1.24–2.01)	0.88 (0.64–1.17)
Cardiovascular	1.29 (0.59–2.46)	1.65 (1.38–1.97)	1.17 (1.08–1.27)	1.01 (0.96–1.06)	0.89 (0.85–0.93)
Respiratory	1.36 (0.03–7.58)	1.59 (0.79–2.84)	1.61 (1.29–1.99)	1.22 (1.07–1.39)	0.87 (0.77–0.98)
Gastrointestinal	1.50 (0.18–5.41)	2.69 (1.66–4.11)	2.19 (1.72–2.75)	1.15 (0.93–1.42)	0.88 (0.70–1.09)
Accidents	2.40 (1.28–4.11)	2.37 (1.71–3.21)	1.65 (1.31–2.05)	1.30 (1.06–1.56)	0.93 (0.73–1.16)

Shaded figures indicate a significant increase at the 5% level.

was highest for GI diseases (detailed data not shown; highest value in those 40–49 years of age at surgery; SMR = 2.26), accidents (highest value in those 40–49 years of age at surgery; SMR = 2.43), and respiratory diseases (highest value in those 50–59 years at surgery; SMR = 1.55).

4. Discussion

The present investigation shows a modestly increased mortality in patients operated on for DC, with patients who are younger at the time of surgery having the greatest increase in risk for early death. The increase in mortality was observed for subgroups of men and women. The results extend the findings of Mikkelsen et al. [11] in a longitudinal study of 456 men. It could not be shown that the increased mortality was related to the duration of DC. Our results complement information previously reported by Gudmundsson et al. [10], who were not able to reveal any specific epidemiologic factors related to women with DC, possibly due the small number of subjects in their study.

The increased risk for early death in patients operated on for DC as compared with the background population can be explained in several ways. First, there may be common genetic features in diseases causing early death. This is, however, less likely, because the increase in mortality was confined to several disease groups and to accidents.

There may be one or more common pathogenic mechanisms in DC and in conditions leading to death. A possible clue could be that younger individuals tend to be affected by a more aggressive form of DC that requires repeated surgery [16]. Therefore, it is possible that DC affecting younger patients is of a somewhat different pathophysiologic type than that affecting elderly patients and that there is a greater risk for systemic involvement. This is in line with the suggestion by Mikkelsen et al. [11].

Third, there may be an over-representation of one or more behaviors that are related to an increased risk for early death (e.g., smoking or alcohol abuse). There is some evidence for this. We first discuss this in connection with the increased risk for cardiovascular death that was apparent for men and women operated on for DC 10 years or more previously. Risk factors for cardiovascular disease have been sought earlier in these patients. In a large population-based epidemiologic study, patients with clinical signs of DC were found to have a similar glucose tolerance, blood lipid pattern, and blood pressure as the reference population [10], although some earlier conflicting reports suggest otherwise. One of these is the study by Sanderson et al [5], who reported increased levels of blood lipids in patients with DC. Being overweight is one of the most important risk factors for cardiovascular death [17,18], but this is not shared by patients with DC, who have a body mass index that is lower than that of control subjects [10]. There are, however, more smokers among DC patients than among control subjects [4]. This, together with an over-representation of manual work [10], are the most probable explanations for the increased risk for cardiovascular death 10 years or more after surgery for DC.

In a recent study, Gudmundsson et al. [12] did not observe an increased risk for death from coronary heart disease in patients with DC in spite of indications of increased smoking. In accordance with those findings, we did not find any increased overall mortality for cardiovascular diseases in the present study. Based on the evidence from Mikkelsen [11] showing considerable differences in the risk of death between those developing the disease before 60 years of age and those not doing so, we hypothesized that those with early DC would constitute an especially vulnerable group. This was first validated after dichotomizing the present material at 60 years of age. This showed that the excess mortality was restricted to the younger age group (SMR 1.40 versus 0.99; detailed data not shown), in contrast to the data of Mikkelsen [11] that the excess mortality was restricted to the younger age group (SMR 1.40 versus 0.99; detailed data not shown). Because this subgroup constitutes only about one fourth of those operated on for DC in the present cohort, the increased SMR in those operated for DC before 60 years of age will only affect the total mortality figure to a small extent.

Other lifestyle features linked to smoking [4,19]—manual labor and possibly education [10]—may play contributory roles. It is possible that such features could be related to dietary factors. Thus, it has been suggested that the intake of antioxidants is of importance because free radicals are believed to be a pathogenic factor in the development of cardiovascular disease [20] and in DC [21].

We have previously described an increased risk for malignancy in patients operated on for DC [22]. Here, and analogous to recently published longitudinal data [12], we find that this is also linked to an increased risk for death due to cancer.

After cardiovascular disease and cancer, the third largest cause of death was respiratory diseases. A clear increase in mortality was noted more than 10 years after surgery, and in the age group 50–59 years the increase was greater than 50%. Pneumonia and chronic obstructive lung disease (i.e., asthma, chronic bronchitis, and emphysema, all of which are strongly associated with smoking) are the predominant causes of death in this ICD-9 group.

In the Swedish Death Register, deaths due to endocrine diseases are caused by diabetes mellitus in more than 75% of cases. There is an established relationship between diabetes mellitus and DC, and the incidence of DC among diabetics is reported to vary between 1.6% and 32% [21]. Furthermore, there is a synergistic effect of smoking on the risk for type 2 diabetes mellitus [23,24], diabetic complications [25], and early death due to diabetes mellitus [26,27]. In a population-based study on the prevalence of DC, those afflicted exhibited higher fasting blood glucose than those not afflicted [10], although there were no differences in their glucose tolerance. On the other hand, individuals with diabetes tend to have a mild form of DC, and few require treatment

[28]. Whether there is an increased prevalence of diabetes in those who are treated surgically for DC is not established.

The risk for a GI cause of death is significantly increased in the age group 40–59 years. A possible explanation for this observation is that about half of the deaths in this group are due to causes related to smoking (e.g., ulcer disease, GI bleeding, intestinal arteriosclerotic lesions, or alcohol abuse leading to GI bleeding, pancreatitis, or liver disease). A previous study was not able to link DC to alcoholic liver disease [29].

The strikingly increased risk for an accidental cause of death among men in the study group has no obvious explanation. Reasonable mechanisms are linked to lifestyle, taking into consideration the link between smoking, alcohol consumption, and risk-taking [30].

The major strengths of the present study are its large size, the population-based nature of the study group, the complete ascertainment of deaths, and the consistent follow-up over a long period. A weakness is that the study group contains only patients treated as inpatients, which is why there may be a selection of elderly patients or patients with severe forms of DC. The fact that the estimates of mortality risk were higher in younger than in older patients makes it less likely that the results are influenced by an overrepresentation of patients with general conditions such as cardiovascular diseases. Another weakness is that the underlying causes of death in the Swedish Death Register are based on autopsies in only a minority of cases. Thus, the results of the study are subject to the risk of misclassification, although such misclassifications do not differ from those in the general population from which the expected rates are calculated. Therefore, any association found using a study design of this kind will be an underestimation of the "true" strength of the association, and false associations will not be created.

In conclusion, people operated on for DC at a young age and observed for a long period thereafter have a significant increase in overall mortality. In such individuals there is a greatly increased risk for mortality due to endocrine, cardiovascular, GI, and accidental causes. The explanation is most likely related to lifestyle (e.g., smoking and alcohol abuse).

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