

Increased total mortality and cancer mortality in men with Dupuytren's disease: A 15-year follow-up study

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Abstract

The aim of the present study was to evaluate the mortality rate and causes of death of individuals with Dupuytren's disease. In 1981/82, as part of The Reykjavík Study, a general health survey, 1297 males were examined for clinical signs of Dupuytren's disease. Based on the clinical evaluation the participants were classified into three groups: (1) those with no signs of Dupuytren's disease were referred to as the reference cohort; (2) those with palpable nodules in the palmar fascia were classified as having stage 1; and (3) those who had contracted fingers or had been operated on due to contractures were classified as having stage 2 of Dupuytren's disease. In 1997, after a 15-year follow-up period, the mortality rate and causes of death were investigated in relation to the clinical findings from 1981/82. Information about causes of death were obtained from the National Icelandic Death Registry and the Icelandic Cancer Registry. During the follow-up period, 21.5% (225/1048) of the reference cohort were deceased compared to 29.9% (55/184) of those with stage 1 and 47.7% (31/65) of those with stage 2 of Dupuytren's disease. When adjusted for age, smoking habits and other possible confounders, individuals with stage 2 of the disease showed increased total mortality [hazard ratio (HR) = 1.6; 95% CI 1.1–2.4]. Cancer deaths were increased (HR = 1.9; CI 1.0–3.6). In contrast, participants with stage 1 of Dupuytren's disease did not show increased mortality. A moderate but non-significant increase in cancer incidence was observed among individuals with stage 2 of Dupuytren's disease (HR = 1.5; 95% CI 0.9–2.4, $P = 0.15$). The study showed increased total mortality of individuals with Dupuytren's disease stage 2, where 42% of the excess in mortality could be attributed to cancer deaths. © 2002 Elsevier Science Inc. All rights reserved.

Keywords: Dupuytren's disease; Mortality; Cancer mortality

1. Introduction

Dupuytren's disease is common in the northern parts of Europe. Epidemiological surveys have shown high prevalence; up to 40% of men aged 70–75 years being affected by this condition [1–3]. The disease has been related to smoking, alcohol use and several medical conditions [4–7], although this has also been refuted [8–10]. Manual work and social classes have been implicated as risk factors but this may also be debated [11,12]. The disease often has a familial tendency [13].

The histopathology of the Dupuytren's nodules consists of increased number of fibroblasts with excess formation of collagen, occasionally infiltrating the skin and nearby structures [14]. Myofibroblasts seen in the tumors are probably transformed fibroblasts capable of producing actin and my-

osin [15]. Cultures of cells obtained from fibrotic nodules of Dupuytren's patients show severe chromosomal abnormalities including trisomies and unbalanced translocations [16]. Furthermore, expression of a sarcoma-specific antigen in the fibromatous nodules has been reported [17] as well as decreased expression of tumor suppressive genes [18]. Together these findings may suggest defective control of cell proliferation, resembling that observed in malignancies.

The aim of the study was to assess the total mortality and causes of death, especially cancer mortality among Dupuytren's patients, during a 15-year follow-up period.

2. Patients and methods

2.1. General design of The Reykjavík Study

Iceland is a 103,000-km² island in the North Atlantic Ocean with approximately 270,000 inhabitants. The land was settled during the Viking period (874–930) mainly from

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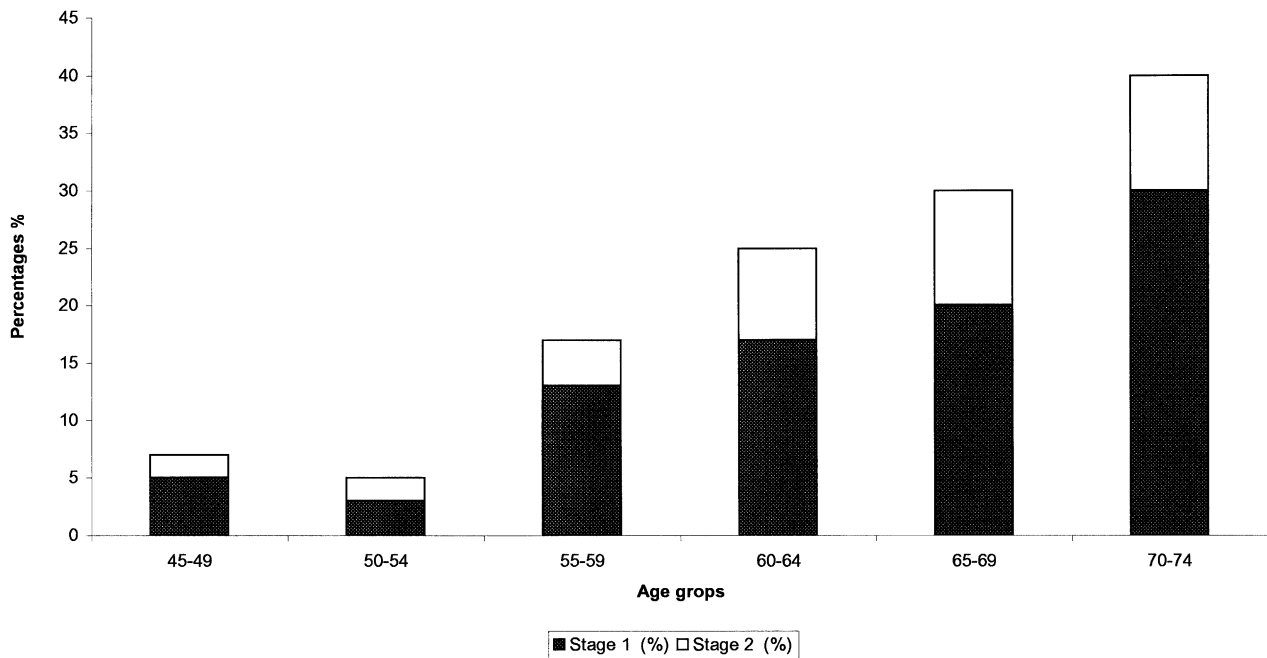


Fig. 1. Prevalence of Dupuytren's disease in the cohort, in percentages stratified by 5-year age groups.

people living in Scandinavia, Ireland and the British Isles. In 1967 a large population-based health survey was started in the Reykjavik area of Iceland (The Reykjavik Study) [19]. The main aim of this study was to investigate the epidemiology and risk factors of cardiovascular diseases. The participants of the study were all males born in the years 1907–1934 and all females born in 1908–1935 with legal residence in the Reykjavik area. The study population was divided into six groups; A, B, C, D, E and F according to certain birth dates and these groups were invited for examination up to six times during the period 1967–1997.

2.2. Participants of the present study

The study on Dupuytren's disease was carried out during the fourth phase of The Reykjavik Study in 1981–1982. Participant in this part were 4609 males belonging subgroups B and D. Those persons selected in subgroup B were born on the 1st, 4th, 7th, etc. of each month in the years 1907, 1910, 1912, 1914, 1916, 1917, 1919, 1920, 1921, 1922, 1924, 1926, 1928, 1931 and 1934. Participants in subgroup D were born on the 1st, 4th, 7th, etc. of each month in the years 1909, 1911, 1913, 1915, 1923, 1925, 1927, 1929, 1930, 1932 and 1933 and living in the same area.

Every participant received a letter of invitation and a detailed questionnaire about past and present health and social situation. Those not responding to the first letter of invitation received another letter and finally non-responders were contacted by telephone. At the visit to the Heart Preventive Clinic, the participants returned their questionnaires and a specially trained secretary reviewed the answers. A physician clinically examined every participant and blood sam-

ples were collected for various biochemical analyses. All the information obtained was registered in a computerized file at the Heart Preventive Clinic. Response rate in The Reykjavik Study was 70.4% [19]. Information on health and causes of death of non-responders in the study has not been published and is not available at this time. The examination was free of charge. The Data Protection and The State Medical Ethical committees approved the study.

2.3. Study of Dupuytren's disease in 1981/82

Although the main aim of The Reykjavik Study was to monitor cardiovascular risk factors, it was also designed to be a general health survey in the Icelandic population in the last 25 years. In collaboration with plastic and hand surgeons, in 1981 and 1982 a total of 1297 randomly selected males belonging to subgroups B and D were examined by one of us (N.S.) for clinical signs of Dupuytren's disease. The aim of this endeavor was to obtain more information about the incidence, prevalence and natural history of the disease through the follow-up period. This was done by inspection and palpation of both palms. Individuals with palpable nodules in the palms were graded as having stage 1, while those with contracted fingers and those who had been operated on for the disease were graded as stage 2 of Dupuytren's disease. In 1997, 15 years after the initial examination, the mortality and causes of death were analyzed in relation to the clinical findings from 1981/82. We have previously published data on the prevalence and incidence of the condition [2] and here we concentrate on the long-term sequelae and causes of deaths in men with Dupuytren's disease.

Table 1
Registered causes of death in the cohort during the 15-year follow-up period 1981/82 to 1997

Causes of death (ICD numbers)	Reference cohort	Dupuytren's disease	
	<i>n</i> = 1048 (%) ^a	Stage 1 <i>n</i> = 184 (%)	Stage 2 <i>n</i> = 65 (%)
Neoplasms	71 (6.8)	18 (9.8)	11 (16.9)
Digestive organs (150–159)	23 (2.2)	10 (5.4)	5 (7.6)
Respiratory organs (160–165)	21 (2.2)	3 (1.6)	3 (4.6)
Bone, connective tissue, breast and skin (170–175)	3 (0.3)	0 (0)	1 (1.5)
Genito-urinary organs (179–189)	16 (0.02)	4 (2.2)	1 (1.5)
Other and unspecified sites (190–199)	4 (0.4)	0 (0)	1 (1.5)
Lymphatic and haemopoietic organs (200–208)	4 (0.4)	1 (0.5)	0 (0)
Ischemic heart diseases	84 (8)	21 (11.4)	7 (10.8)
Myocardial infarction (410)	56 (5.3)	19 (10.3)	6 (9.2)
Chronic ischemic heart disease (414)	28 (2.7)	2 (1.1)	1 (1.5)
Other diseases	70 (6.7)	16 (8.7)	13 (20)
Endocrine, metabolic and immunological (240–279)	0 (0)	1 (0.5)	0 (0)
Nervous system (320–379)	7 (0.7)	1 (0.5)	1 (1.5)
Cerebrovascular and circulatory diseases (415–459)	34 (3.2)	5 (2.7)	4 (6.2)
Respiratory system (460–519)	8 (0.8)	4 (2.2)	3 (4.6)
External causes of injury and poisoning (E-codes)	10 (0.9)	3 (1.6)	2 (3.0)
Various other causes	11 (1)	2 (1.1)	3 (4.6)
Total number of deaths	225 (21.5)	55 (29.9)	31 (47.7)

Percentages of total in each stage in parentheses.

2.4. Registration of mortality and cancer in Iceland

The Death Registry in Iceland is a national register. Medical doctors are obliged to confirm all deaths in Iceland, to set specific death diagnoses and send these for registration at a centralized Death Registry Office in Reykjavik. Similarly, the Cancer Register is a nation-wide register receiving information from several sources about all cancer diagnoses made in Iceland. The main source of information are the histopathology diagnosis from the Department of Pathology at the University of Iceland, but information also comes from other laboratories, from death certificates and directly from physicians and primary health care centers. If physicians report cancer on death certificates without an available histological diagnosis the physicians are always contacted for more detailed information. During the period

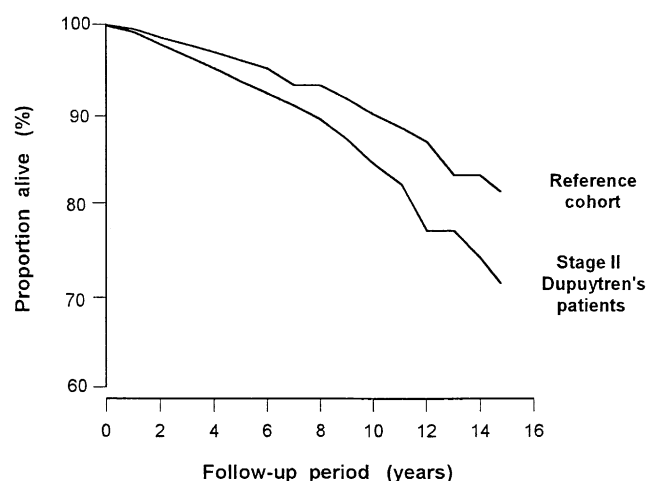


Fig. 2. Survival of patients with stage 2 of Dupuytren's disease compared to the reference cohort during the 15-year follow-up period.

1980–1984, a total of 91.4% of registered cancer deaths of males in Iceland were histologically verified [20,21].

2.5. Statistical analysis of mortality and causes of death

After a 15-year observation period, we studied the cancer diagnoses and analyzed the mortality and causes of death of the 1297 males examined for Dupuytren's disease in 1981/82. The study is based on main cause of death as registered in the Icelandic Death Registry and on cancer diagnoses in the Cancer Register. For statistical evaluation Cox regression analysis was used. The findings are reported as hazard ratios (HR) with 95% confidence intervals (95% CI). Men who did not have signs of Dupuytren's disease in 1981/82 are referred to as the reference cohort in this study. The level of significance was set at $P \leq 0.05$.

Table 2

Risk of death of Dupuytren's patients with stage 1 (palmar nodules) and stage 2 (finger contractures) during the 15-year follow-up period 1981/82 to 1997

Causes of death	Stage 1			Stage 2		
	HR	95% CI	P-value	HR	95% CI	P-value
Cancer deaths	1.0	0.6–1.7	NS	2.0	1.0–3.7	0.04
Coronary heart deaths	0.9	0.6–1.5	NS	0.9	0.4–2.0	NS
Total deaths	0.9	0.7–1.2	NS	1.6	1.1–2.3	0.01

Mean age in 1981; in stage 1: 60.3 years, (± 8.2), for stage 2 62.0 years (± 8.0), and 55.9 years (± 7.5), for the controls. Mean death age was 73.3 years for stage 1 and 72.9 years stage 2 and 69.3 year for the reference control.

Ever smoked: yes or no. In stage 1; 154 men had ever smoked and 30 were non-smokers, while in stage 2; 50 men had ever smoked and 15 were non-smokers. In comparison 812 men had ever smoked in the reference cohort and 236 were non-smokers.

All calculations were done with Cox regression analysis, with adjustment for age and smoking habits.

The results are reported as hazard ratios (HR) with 95% confidence intervals (CI).

Table 3
Cancer mortality in men with stage 2 of Dupuytren's disease after adjusting for age, smoking and occupation

	HR	95% CI	P-value
Dupuytren's disease stage II	2.0	1.0 to 3.8	0.04
Age	1.1	1.0 to 1.1	0.00
Former smoker	1.5	0.7 to 3.0	NS
Smoking pipe/cigars	2.3	1.1 to 4.8	0.02
Smoking 1–14 cigarettes/day	3.5	1.5 to 8.1	0.01
Smoking 15–24 cigarettes/day	3.2	1.4 to 7.0	0.01
Smoking \geq 25 cigarettes/day	1.9	0.5 to 6.8	NS
Manual labor ^a	0.7	0.3 to 1.5	NS
Occupation with higher education ^b	0.9	0.4 to 2.0	NS

^aManual workers were 90/1028 in the reference cohort and 14/63 in stage 2 of Dupuytren's disease.

^bMen in occupation demanding higher education were in 10 categories of men with university degrees and these were 123/1028 in the reference cohort and 4/63 in stage 2 of Dupuytren's disease.

3. Results

Of the 1297 men examined in 1981/82, a total of 249 (19.2%) had clinical signs of Dupuytren's disease; 184 stage 1 and 65 stage 2. The prevalence of Dupuytren's disease was highly age-dependent (Fig. 1). Thus, of those aged 45–49 years, 5.2% had stage 1 and 2.0% stage 2 of the disease compared to 29.4% and 10.0%, respectively, of those aged 70–74 years. The mean age at examination in 1981 was 60.3 years (SD = 8.2 years) and 62.0 years (SD = 8.9 years) among men with stage 1 and 2, respectively. The mean age of the reference cohort was 55.9 years (SD = 7.5 years).

During the follow-up period of 15 years, 21.5% (225/1048) of the reference cohort were deceased compared to 29.9% (55/184) of those with stage 1 and 47.7% (31/65) of those with stage 2 of Dupuytren's disease. The mean age at death was 73.3 years; 72.9 years and 69.3 years for stage 1, stage 2 and the reference cohort, respectively. Table 1 shows in detail the reported death diagnosis according to the International Classification of Diseases (ICD). Patients with stage 2 of Dupuytren's disease had significantly increased total mortality during the 15-year follow-up period (HR = 1.6; 95% CI 1.1–2.3, P = 0.01) (Fig. 2). The increase in cancer deaths was estimated to be responsible for 42% of the total increase in mortality, and cancer deaths were more frequent than expected from the reference cohort (HR = 2.0; 95% CI 1.0–3.7, P = 0.04) (Table 2). In contrast, cardiovascular mortality during the study period was not increased (HR =

Table 4
Relation between mortality in Dupuytren's disease stage 2, corrected for age with and without adjustment for smoking (Cox regressions analysis).

	Adjusted for age			Adjusted for age and smoking		
	HR	95% CI	P-value	HR	95% CI	P-value
Total deaths	1.6	1.1–2.2	0.02	1.6	1.1–2.3	0.01
Cancer deaths	1.9	1.0–3.6	0.05	1.9	1.1–3.7	0.04
Other causes	2.0	1.1–3.6	0.02	2.0	1.1–3.7	0.02

0.9; 95% CI 0.4–2.0, NS). No single type of cancer was found to be more prevalent than others in this study.

Smoking was prevalent in the study groups. Of subjects with stage 1 disease, 16.3% and 23.1% of men with stage 2 had never smoked compared to 22.5% of the reference cohort. Multivariate Cox regression analysis taking into account risk factors, such as age, smoking habits and occupation, also showed significantly increased cancer mortality (HR = 2.0; 95% CI 1.0–3.8, P = 0.04) among participants with stage 2 of Dupuytren's disease (Table 3). To test the effects of confounding factors, the analysis was repeated with adjustment for age only and for age and smoking combined (Table 4), and secondly with adjustment for age smoking, body mass index (BMI), fasting serum glucose, and manual work or learned trade (Table 5). This did not affect the results considerably, where the total deaths (HR = 1.6; 95% CI 1.1–2.4, P = 0.01), cancer deaths (HR = 1.9; 95% CI 1.0–3.6, P = 0.05) and risk of death by other causes as (HR = 2.0; 95% CI 1.1–3.7, P = 0.02) were all significantly higher than expected in the cohort group.

Patients with stage 1 of Dupuytren's disease showed neither increased total mortality nor increased mortality due to any other specific disorder.

The sample size did not allow detailed age-stratified mortality calculations. However, when the mortality rate was calculated for men older than 65 years and men younger than 65 years of age, both groups with stage 2 disease had increased mortality (HR = 1.8; 95% CI 0.9–3.5, P = 0.1 and HR = 2.3; 95% CI 1.0–5.4, P = 0.05, respectively).

During the study period, the cancer incidence among men with stage 2 disease was moderately elevated (HR = 1.5; 95% CI 0.9–2.4, P = 0.15). Only 17 new cancer cases were diagnosed over the 15-year follow-up period. These few cases did not allow a precise estimate of the incidence, but the types of cancer included four cases of gastrointestinal cancers, two kidney tumors and the rest were single cases from various organs. When adjusted for age and smoking habits there was still a moderate, but non-significant, increase in the cancer incidence (HR = 1.5; 95% CI 0.9–2.4, P = 0.15) during the 15-year follow-up period.

4. Discussion

In northwestern Europe, around 20% of middle-aged men are affected by Dupuytren's disease and around 5% have severe disability with contractures often requiring surgical corrections [1–3,10,22]. Our finding of increased mortality confirms recent results from a Norwegian study indicating increased total mortality (relative risk = 1.7) in men younger than 60 years of age [23]. We, on the other hand, show now that 42% of the excess mortality can be attributed to cancer deaths and that the increase holds also for men in older age groups. Furthermore, together the findings can explain results from another cross-sectional population study in Norway showing a decline in the prevalence of Dupuytren's disease after 75 years of age [3]. Our results also

Table 5
Mortality risk of patients with stage 2 Dupuytren's disease^a

	Total deaths			Cancer deaths			Other causes		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Stage 2 disease	1.6	1.1–2.4	0.01	1.9	1.0–3.6	0.05	2.0	1.1–3.7	0.02
Age	1.1	1.1–1.1	0.00	1.1	1.1–1.1	0.00	1.1	1.1–1.1	0.00
Smoking ^b	1.6	1.2–2.2	0.01	2.4	1.3–4.3	0.01	1.3	0.8–2.2	0.25
Body mass index	0.9	0.9–1.1	0.40	0.9	0.9–1.0	0.07	0.1	1.1–1.1	0.25
Fasting blood glucose	1.0	1.0–1.1	0.00	1.0	1.0–1.0	0.01	1.0	1.0–1.0	0.01
Manual labor ^c	0.7	0.5–1.1	0.12	0.8	0.4–1.6	0.55	0.8	0.4–1.4	0.38
Learned trade ^d	0.6	0.4–0.9	0.04	0.7	0.4–1.5	0.43	0.2	0.1–0.7	0.01

^aA multivariate Cox regressions analyses, adjusted for, age, smoking, body mass index, fasting blood glucose and manual labour and learned trade.

^bAdjusted for the parameter “ever smoked.”

^cManual workers are laborers, seamen and farmers.

^dLearned trade are masons, blacksmiths and carpenters.

support findings from a Swedish study that show increased cancer incidence among operated Dupuytren's patients [24].

The main strength of this study is the uniformity of diagnosis (examination done by only one physician) and reliable source of information (nation-wide cancer registry). Their main drawback is the relatively few new cancer cases diagnosed during the follow-up period. This may reduce its power to estimate accurately the incidence of cancer in this group of patients. The incidence of cancer was moderately, but not statistically significantly, higher than expected from the reference cohort. Increased cancer mortality but not increased cancer incidence could indicate that the cancers involved are more aggressive in patients with Dupuytren's disease or that they are diagnosed at a later stage than in the reference cohort.

The method for diagnosing Dupuytren's disease in this study is similar to that used in previous studies [1,3]. Contracted fingers are almost pathognomonic for the disease and the diagnostic specificity is reported to be high [1]. Hand deformity caused by inflammatory arthritis with stenosing tendovaginites or trauma are the most common differential diagnoses, but in general it should not be difficult to distinguish these conditions from advanced Dupuytren's disease with contractures. Early signs of the disease are fibrous nodules in the palms, and the diagnosis at that stage can be a more subjective finding, still the sensitivity and specificity at that stage has been reported to be 76% [1]. Taking this into account our results from the more severely affected group (stage 2) must be regarded as a more representative and reliable indicator for the disease behavior.

When possible explanations for the increased mortality are considered, it is important to evaluate the significance of various risk factors. We have therefore taken into consideration age, smoking, fasting blood glucose, BMI and social classes, but these are factors that may influence total and cancer mortality and may also affect the prevalence of Dupuytren's disease. When corrected for these variables, the observed increase in total and cancer mortality was unaltered.

Dupuytren's disease often has a strong family tendency [13]. In other familial diseases characterized by benign tu-

mors such as neurofibromatosis, tuberous sclerosis and familial adenomatous polyposis coli, high risk of malignancies and increased cancer deaths have been reported [25]. We propose that there could be similarities between these diseases and the pathogenesis or molecular biology of Dupuytren's disease. This hypothesis receives support from reports indicating pathology at the DNA level such as chromosomal instability [16], expression of a sarcoma-specific antigen [17] and decreased expression of tumor suppressive genes [18] in Dupuytren's disease. All this suggests that aberrations in the cell regulation and proliferation mechanism as well as tissue integrity may be important. Underlying genetic predisposition could then be influenced by environmental factors causing both aggressive cancer and Dupuytren's disease. The hands are in contact with numerous chemicals and physical factors, possibly acting directly through the skin causing early expression of tumors in the palms.

However, other explanations have to be considered, and the most obvious one would be that unidentified confounding factors not adjusted for could cause the overall increase in mortality and cancer mortality. Co-morbidity of various disease might, for example, explain the association between Dupuytren's disease and increase in mortality. These questions need to be addressed in a future study. Dupuytren's contracture could also be a paramalignant phenomenon, induced or aggravated by cancers, possibly mediated via humoral factors. It is relevant in this context that immunological deviations have been described in patients with Dupuytren's disease [9,26–28], and immunological defects could possibly influence the survival of affected individuals.

The results presented here, supported by findings from other studies showing increased mortality in Dupuytren's disease [23] and increased cancer incidence [24], indicate that there is an association between Dupuytren's disease, development of cancer and increased mortality rate. Possible implications of these observations is that men with finger contracture because of Dupuytren's disease could benefit from regular medical care or prevention aimed at risk factors for diminished life expectancy.

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