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CANCER INCIDENCE IN PATIENTS TREATED SURGICALLY FOR DUPUYTREN'S CONTRACTURE

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Our aim was to study risk factors for Dupuytren's contracture (DC) by assessing cancer morbidity in a group of Swedish patients treated surgically for Dupuytren's contracture. The risk of cancer was determined in 15,212 patients operated on for Dupuytren's contracture, identified in the nationwide Swedish Inpatient Register during the period 1965 to 1994 by means of record linkage to the Swedish Cancer Register. Standardized incidence ratios (SIRs) were computed using age-, sex- and period-specific incidence rates derived from the entire Swedish population. The overall relative risk of cancer was increased by 24%. There were significantly increased risks for malignancies related to smoking such as buccal, oesophageal, gastric, lung and pancreatic cancers. Significantly increased risks were present for both prostate and rectal cancer in men and an increase risk for breast cancer in women was noted 1 year or more after surgery for Dupuytren's contracture. The present study confirms smoking and alcohol abuse as probable risk factors for DC. There are characteristics in patients with DC that alter the risks for other malignancies compared with the general population.

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INTRODUCTION

The prevalence of Dupuytren's contracture (DC) varies widely in different parts of the world (Early, 1962; Strickland et al., 1990) and there is a strong genetic predisposition. The condition is virtually confined to Caucasians, and is more common in the Scandinavian countries and the British Isles than in other European populations south of the Alps. The incidence increases with age (James and Tubiana, 1952; Millesi, 1965; Skoog, 1948). There is a male predominance of DC, with a male : female ratio of 5 to 9 : 1, which still remains to be explained (Berge and Pohl, 1988; Skoog, 1948; Wilbrand, 1999). The current concept is that the disease is caused by an interplay between some endogenous or exogenous factors and an intrinsic susceptibility (Murrel and Hueston, 1990). Earlier aetiological studies have indicated that there is an association between DC and smoking (An et al., 1988; Bradlow and Mowat, 1985; Burge et al., 1997), alcohol (Attali et al., 1987; Houghton et al., 1983) diabetes mellitus (Arkkila et al., 1997; Eadington et al., 1989; Gamstedt et al., 1993), epilepsy (Critchley et al., 1976; Lund, 1941), phenobarbital (Frosher and Hoffman, 1983), AIDS (Bower et al., 1990), exposure to hard manual labour (Mikkelsen, 1978) and previous hand injuries (MacKenney, 1983; Mikkelsen, 1978; Skoog, 1948). The results of these studies have, however, not always been consistent and have been hampered by low statistical power and questionable control groups.

An alternative approach in the study of risk factors for DC is to assess cancer morbidity over time in a defined group of DC patients in order to analyse to what extent there is an excess risk of malignancies associated with such exposures as smoking and alcohol abuse. Such an approach will also provide a way of assessing whether there are endogenous characteristics in DC patients that are associated with other specific cancer forms. We therefore used Swedish register data to identify all patients treated surgically for DC as inpatients from 1965 to 1994, and followed them up for the development of cancer through the Swedish Cancer Register.

PATIENTS AND METHODS

Study group

In 1965, the Swedish national Board of Health and Welfare began collecting data on individual hospital discharges in the Inpatient Register. The registration expanded steadily to cover 85% of the Swedish population by 1983. In addition to national registration numbers (NRNs – unique personal identifiers assigned to all Swedish residents; Lunde et al., 1980), each record contains medical data, e.g. surgical and anaesthetic procedures, hospital department, and up to eight discharge diagnoses, coded according to the seventh revision of the International Classification of Diseases (ICD-7) during 1968, according to the eight revision during 1969 to 1987 and to the ninth revision thereafter. The codes for the main diagnoses are judged to be correct at the detailed five-digit level in 83 to 86% of the records (Nilsson et al., 1994). Because there is almost no private inpatient treatment in Sweden, patients are obliged to use the public hospitals in the county where they live. The Inpatient Register is essentially population based and referable to the population of the counties covered by the registration. All patients recorded in the Inpatient Register with a discharge diagnosis of Dupuytren's contracture (ICD-7, 744.20; ICD-8, 733.90; ICD-9, 728G and Swedish Classification

of Operations and Major Procedures code 8631) from 1965 to 1994 were initially selected for inclusion in the study. There were 16,175 unique NRNs with one or more records that contained the specified diagnostic codes. NRNs that could not be found in the Register of the Total Population, the Migration register, or the Death Register held by Statistics Sweden were judged to have been incorrectly entered. Records with such NRNs ($n = 735$; 4.4%) were consequently excluded.

We also excluded 27 records (0.2%) in which inconsistencies (e.g. death before entry, or different sex codes for the same NRN) were disclosed during the linkage procedures.

By record linkage to the Cancer Register, which was established in 1958 and is virtually complete (Mattsson, 1977, 1984), we excluded 833 patients (5.2%) who already had cancers or in whom cancer was diagnosed at the index hospitalization, leaving 15,212 patients for follow-up (Table 1).

Follow-up

Record linkage to the Swedish Cancer Register identified all cases of cancer. The Cancer Registry has coded all malignant neoplasms according to the ICD-7 classification during the entire period of study. The Death Register provided information on date and cause of death among those who died. Date of emigration, when applicable, was established in the Migration Register. The time of observation was calculated from the date of discharge after operation for DC until the date of diagnosis of a neoplasm, death, emigration or the end of the observation period (31 December 1994).

Statistical methods

The expected numbers of cancers were calculated by multiplying the observed number of person-years by age- (5-year groups), sex-, and calendar year-specific cancer incidence rates derived from the entire Swedish population. The standardized incidence ratio (SIR), defined as the ratio of observed to expected numbers of cancers, was used as a measure of relative risk. The 95% confidence interval (CI) of the SIR was then calculated on the assumption that the observed numbers followed a Poisson distribution (Bailar and Ederer, 1964).

RESULTS

There were 2,151 patients diagnosed with cancer (1,920 men and 231 women) during follow-up. There was an overall increased risk for all types of cancer of 23% (24% for men and 22% for women) (Table 2) which did not change with increasing follow-up time (Table 3).

There were significantly increased risks of malignancies related to smoking such as buccal, oesophageal, gastric, lung and pancreatic cancers (Table 2). The increased risks for buccal, oesophageal and pancreatic cancers were, however, confined to men. The excess risk for buccal cancer increased with follow-up time, in contrast to oesophageal and pancreatic cancer. The excess risk for lung cancer was constant with follow-up time (Table 3). Although an isolated increase in risk for renal cancer was observed after 5 to 9 years follow-up, there was no increase in risk for bladder and renal cancers, although both malignancies are known to be related to smoking, nor was there any excess risk for cancer of the larynx (Table 2).

There was also a significantly increased risk for primary liver cancer in men and also an increased risk both for prostate and rectal cancer among men, regardless of duration of follow-up. Among women, there was a consistently increased risk for breast cancer 1 year or more after surgery for DC (Table 3).

Five years or more after surgery for DC, there was also an increased incidence of sarcomas of bone and connective tissue (SIR = 2.00, 95% CI 1.10–3.36).

DISCUSSION

There is an increased overall risk for cancer in patients treated surgically for DC which persists 10 years or more after the operation. This excess risk is to a great extent explained by cancers related to smoking, such as lung cancer, but also by the consistently increased risk for prostate cancer among men and breast cancer among women.

As well as smoking, alcohol abuse has been implicated as a risk factor for DC and our findings of increased risks for oesophageal and primary liver cancers in addition to breast cancer in women provide some credence to such an association (Tonnesen et al., 1994). Diabetes has also been suggested as a risk factor for DC, which could be an alternative underlying cause for the increased risk of primary liver cancer among

Table 1—Characteristics of the study group

Characteristics	*Men*	*Women*	*Total*
No. of patients	13098 (86.1%)	2114 (13.9%)	15212 (100%)
Age <49 years	1742 (11.5%)	194 (1.3%)	1936 (12.8%)
Age 50–59 years	3139 (20.6%)	337 (2.2%)	3476 (22.8%)
Age 60–69 years	4743 (31.2%)	764 (5.0%)	5507 (36.2%)
Age >70 years	3474 (22.8%)	819 (5.4%)	4293 (28.2%)

Table 2—Standardized incidence ratios (95% confidence intervals) by sex for major cancer types

	Men			*Women*			*Total*		
Cancer type of site (ICD-7 code)	*Observed*	*SIR*	*(95% CI)*	*Observed*	*SIR*	*(95% CI)*	*Observed*	*SIR*	*(95% CI)*
All cancer (140–209)	1920	1.24	(1.19–1.30)	231	1.22	(1.07–1.39)	2151	1.23	(1.19–1.29)
Buccal (140–148)	69	1.77	(1.38–2.25)	3	1.14	(0.24–3.34)	72	1.74	(1.36–2.19)
Oesophageal (150)	36	1.85	(1.30–2.56)	1	0.82	(0.02–4.56)	37	1.79	(1.26–2.47)
Gastric (151)	108	1.21	(1.00–1.46)	11	1.40	(0.70–2.50)	119	1.23	(1.02–1.40)
Small intestine incl duodenum (152)	6	0.96	(0.35–2.08)	3	3.68	(0.76–10.70)	9	1.27	(0.58–2.41)
Colon (153)	133	1.17	(0.98–1.38)	22	1.20	(0.75–1.81)	155	1.17	(0.99–1.37)
Rectum (154)	108	1.34	(1.10–1.62)	9	0.98	(0.45–1.86)	117	1.30	(1.08–1.56)
Primary liver (155)	48	1.47	(1.08–1.95)	9	1.34	(0.61–2.55)	57	1.45	(1.10–1.87)
Nose/Middle ear (160)	3	0.93	(0.19–2.71)	1	3.65	(0.09–20.30)	4	1.14	(0.31–2.91)
Pancreatic (157)	63	1.40	(1.07–1.79)	7	1.05	(0.42–2.16)	70	1.35	(1.05–1.71)
Larynx (161)	23	1.49	(0.95–2.24)	0	0		23	1.47	(0.93–2.20)
Lung (162–163)	245	1.58	(1.39–1.79)	13	1.72	(0.92–2.95)	258	1.59	(1.40–1.80)
Bone and connective tissue (196, 197)	15	1.42	(0.76–2.34)	3	2.22	(0.46–6.50)	18	1.51	(0.90–2.39)
Melanoma (190)	32	0.95	(0.65–1.34)	7	1.62	(0.65–3.33)	39	1.03	(0.73–1.40)
Non-melanoma skin (191)	76	1.07	(0.84–1.34)	5	0.73	(0.24–1.69)	81	1.04	(0.83–1.29)
Breast (170)	3	1.23	(0.25–3.60)	57	1.29	(0.98–1.67)	60	1.29	(0.98–1.65)
Cervix (171)	0	0		8	2.05	(0.89–4.04)	8	2.05	(0.89–4.04)
Endometrial (172)	0	0		10	0.99	(0.48–1.83)	10	0.99	(0.48–1.83)
Testis (178)	2	0.84	(0.10–3.04)	0	0		2	0.84	(0.10–3.04)
Ovarian (175)	0	0		13	1.43	(0.76–2.45)	13	1.43	(0.76–2.45)
Prostate (177)	528	1.20	(1.10–1.30)	0	0		528	1.20	(1.10–1.30)
Bladder (181)	134	1.17	(0.98–1.38)	6	1.10	(0.40–2.39)	140	1.16	(0.98–1.37)
Kidney (180)	59	1.22	(0.93–1.58)	6	1.21	(0.44–2.64)	65	1.22	(0.94–1.56)
Brain (193)	24	0.86	(0.55–1.28)	6	1.45	(0.53–3.16)	30	0.94	(0.63–1.34)
Thyroid (194)	3	0.58	(0.12–1.70)	0	0		3	0.44	(0.09–1.29)
Endocrine (195)	10	0.90	(0.43–1.66)	2	0.48	(0.06–1.73)	12	0.78	(0.41–1.37)
All haematopoietic (200–209)	119	1.05	(0.87–1.26)	14	1.06	(0.58–1.78)	133	1.06	(0.88–1.25)
Lymphoma (200, 201, 202, 205)	45	0.91	(0.66–1.21)	4	0.67	(0.18–1.72)	49	0.88	(0.65–1.16)
Multiple myeloma (203)	22	0.87	(0.54–1.31)	3	0.94	(0.19–2.76)	25	0.87	(0.57–1.29)
All leukaemia (204)	47	1.24	(0.91–1.65)	6	1.48	(0.54–3.20)	53	1.27	(0.95–1.66)
ALL (2043)*	5	4.73	(1.54–11.00)	0	0		5	4.23	(1.37–9.80)
CLL (2040)**	18	0.99	(0.59–1.57)	5	3.00	(0.98–7.01)	23	1.16	(0.74–1.74)
NLL (2041, 2, 6)***	21	1.50	(0.93–2.29)	1	0.57	(0.01–3.21)	22	1.39	(0.87–2.11)
ANLL (2042, 2046)****	16	1.65	(0.94–2.68)	1	0.79	(0.02–4.42)	17	1.55	(0.91–2.49)
CNLL (2041)*****	4	1.08	(0.29–2.77)	0	0		4	0.97	(0.27–2.50)

SIR, standardized incidence ratio.
*ALL, acute lymphocytic leukaemia; **CLL, chronic lymphocytic leukaemia; ***NLL, non-lymphocytic leukaemia; ****ANLL, acute non-lymphocytic leukaemia; *****CNLL, chronic non-lymphocytic leukaemia.

these patients (Adami et al., 1996). However, there have been consistent reports of a decreased risk of prostate cancer in patients with diabetes (Giovannucci et al., 1998), indicating that if such an association exists, the part played by diabetes in DC patients is small.

Outdoor work has been shown to be a risk factor for squamous skin cancer and melanoma (Whiteman et al., 1998). The fact that there was no increased risk for these tumours in patients who had operations for DC argues against an association between DC and outdoor work.

Another possible explanation for the pattern of cancers seen in patients with DC could be an interaction between phenotype and dietary factors, especially antioxidants. The antioxidant status is an indicator of the vulnerability of an organ to free radical damage (Hennekens, 1994). Free radicals are a pathogenic factor in carcinogesis and certain cancers, such as gastric and colorectal cancers, which occur more frequently than expected in individuals with low antioxidant intakes (Phull et al., 1998). The fact that these tumours are more frequent than expected in patients with DC supports the hypothesis that free radicals are involved in the pathogenesis of DC (Murrell et al., 1987; Yi et al., 1999). Moreover, some antioxidants appears to have a protective effect against hormone related cancers, e.g. cancers of the breast and prostate (Thompson, 1994). The elevated risk for those malignancies in the group of patients with DC also supports the above-mentioned hypothesis.

The major strengths of our study are the prospective design, the large size and population-based nature of the study group, the quality of the cancer registry data, the nearly complete ascertainment of cancers and deaths and the consistent follow-up over a long period. There are, however, some shortcomings. The study group only contains patients treated as in-patients, so it may have an excess of patients with severe forms of DC or

Table 3—Standardized incidence ratios (95% confidence intervals) of major cancer types in men and women and latency periods

	0–1 year			*1–4 years*			*5–9 years*			*> 10 years*		
Cancer type of site (ICD-7 code)	*Observed*	*SIR*	*(95% CI)*	*Observed*	*SIR*	*(95% CI)*	*Observed*	*SIR*	*(95% CI)*	*Observed*	*SIR*	*(95% CI)*
All cancer (140–209)	184	1.26	(1.08–1.45)	674	1.25	(1.15–1.34)	678	1.29	(1.19–1.39)	615	1.17	(1.08–1.27)
Buccal (140–148)	3	0.78	(0.16–2.28)	20	1.45	(0.89–2.24)	22	1.75	(1.09–2.64)	27	2.39	(1.58–3.49)
Oesophageal (150)	1	0.55	(0.01–3.06)	14	2.12	(1.16–3.55)	13	2.07	(1.10–3.54)	9	1.51	(0.69–2.87)
Gastric (151)	14	1.58	(0.86–2.65)	43	1.35	(0.97–1.81)	26	0.88	(0.58–1.30)	36	1.35	(0.94–1.87)
Small intestine incl duodenum (152)	1	1.61	(0.04–8.94)	3	1.32	(0.27–3.87)	3	1.39	(0.29–4.06)	2	0.98	(0.12–3.53)
Colon (153)	16	1.46	(0.84–2.38)	42	1.03	(0.74–1.39)	55	1.36	(1.03–1.78)	42	1.04	(0.75–1.40)
Rectum (154)	11	1.45	(0.72–2.59)	23	0.82	(0.52–1.23)	51	1.87	(1.39–2.45)	32	1.19	(0.82–1.68)
Primary liver (155)	7	2.06	(0.83–4.24)	18	1.44	(0.85–2.27)	18	1.49	(0.89–2.37)	14	1.22	(0.67–2.05)
Nose/Middle ear (160)	0	0		1	0.88	(0.02–4.89)	1	0.96	(0.02–5.33)	2	1.99	(0.24–7.20)
Pancreatic (157)	3	0.63	(0.13–1.85)	33	1.94	(1.33–2.72)	21	1.33	(0.83–2.04)	13	0.91	(0.48–1.56)
Larynx (161)	3	1.98	(0.41–5.79)	6	1.12	(0.41–2.45)	9	1.90	(0.87–3.61)	5	1.23	(0.40–2.86)
Lung (162–163)	25	1.67	(1.08–2.47)	90	1.68	(1.35–2.06)	72	1.46	(1.14–1.84)	71	1.59	(1.25–2.01)
Bone and connective tissue (196, 197)	1	0.93	(0.01–5.16)	3	0.78	(0.16–2.27)	7	1.95	(0.78–4.02)	7	2.06	(0.84–4.25)
Melanoma (190)	5	1.53	(0.50–3.56)	16	1.34	(0.77–2.18)	8	0.70	(0.30–1.38)	10	0.88	(0.42–1.62)
Non-melanoma skin (191)	4	0.75	(0.20–1.92)	22	1.03	(0.65–1.56)	26	1.11	(0.73–1.63)	29	1.04	(0.70–1.49)
Breast (170)	4	0.89	(0.24–2.28)	19	1.20	(0.72–1.87)	20	1.39	(0.85–2.15)	17	1.42	(0.82–2.27)
Cervix (171)	1	2.25	(0.06–12.50)	1	0.70	(0.02–3.89)	4	3.44	(0.94–8.81)	2	2.33	(0.28–8.41)
Endometrial (172)	1	0.96	(0.02–5.34)	2	0.57	(0.07–2.04)	2	0.65	(0.08–2.36)	5	2.07	(0.67–4.83)
Testis (178)	0	0		0	0		2	2.89	(0.35–10.40)	0	0	
Ovarian (175)	3	3.80	(0.64–9.00)	4	1.22	(0.33–3.12)	5	1.81	(0.59–4.22)	1	0.48	(0.01–2.70)
Prostate (177)	39	1.19	(0.84–1.62)	167	1.31	(1.12–1.52)	156	1.17	(0.99–1.37)	166	1.13	(0.96–1.31)
Bladder (181)	11	1.11	(0.56–1.99)	47	1.27	(0.94–1.69)	39	1.07	(0.76–1.46)	43	1.16	(0.84–1.56)
Kidney (180)	5	0.99	(0.32–2.30)	14	0.78	(0.43–1.30)	28	1.74	(1.16–2.52)	18	1.26	(0.75–2.00)
Brain (193)	0	0		10	0.91	(0.44–1.67)	15	1.57	(0.88–2.59)	5	0.61	(0.20–1.43)
Thyroid (194)	0	0		1	0.42	(0.01–2.36)	0	0		2	1.18	(0.14–4.28)
Endocrine (195)	2	1.35	(0.16–4.89)	5	0.97	(0.32–2.20)	1	0.22	(0.01–1.21)	4	0.99	(0.27–2.54)
All haematopoietic (200–209)	18	1.66	(0.99–2.63)	39	0.98	(0.70–1.34)	46	1.20	(0.88–1.61)	30	0.80	(0.54–1.15)
Lymphoma (200, 201, 202, 205)	5	1.05	(0.34–2.46)	17	0.98	(0.57–1.57)	18	1.07	(0.64–1.70)	9	0.54	(0.25–1.02)
Multiple myeloma (203)	3	1.24	(0.26–3.63)	6	0.67	(0.25–1.46)	11	1.27	(0.63–2.27)	5	0.59	(0.19–1.37)
All leukaemia (204)	10	2.73	(1.31–5.01)	14	1.04	(0.57–1.75)	13	1.02	(0.54–1.74)	16	1.34	(0.76–2.17)
ALL (2043)*	3	28.85	(5.95–84.30)	1	2.65	(0.07–14.80)	1	2.79	(0.07–15.50)	0	0	
CLL (2040)**	5	2.91	(0.94–6.79)	7	1.11	(0.44–2.28)	5	0.82	(0.27–1.92)	6	1.05	(0.39–2.29)
NLL (2041, 2, 6)***	2	1.44	(0.17–5.19)	6	1.19	(0.44–2.58)	5	1.04	(0.34–2.43)	9	1.99	(0.91–3.77)
ANLL (2042)****	2	2.18	(0.26–7.87)	4	1.17	(0.32–3.01)	3	0.90	(0.19–2.63)	8	2.43	(1.05–4.80)
CNLL (2041)*****	0	0		2	1.39	(0.17–5.03)	1	0.80	(0.02–4.50)	1	0.99	(0.02–5.50)

SIR, standardized incidence ratio.
*ALL, acute lymphocytic leukaemia; **CLL, chronic lymphocytic leukaemia; ***NLL, non-lymphocytic leukaemia; ****ANLL, acute non-lymphocytic leukaemia; *****CNLL, chronic non-lymphocytic leukaemia.

elderly patients with more associated illness. However, most patients with DC were operated on as in-patients in the 1960s, 1970s and the beginning of the 1980s. Surveillance bias is another concern in studies of this type, i.e. a regular contact with a health care system might lead to detection of malignant tumours earlier or more often in the study group than in the general population. Although earlier detection could affect the SIRs somewhat in the first year after operation, it is unlikely that surveillance or selection bias could have affected the elevated risk estimates 10 years or more after operation.

In conclusion, the present study confirms smoking and alcohol abuse as risk factors for DC. Patients with DC also have other characteristics, which alter the risk of other malignancies when compared with the general population.

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