TOTAL HIP REPLACEMENT AND CANCER

A COHORT STUDY

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The incidence of cancer after hip replacement was studied in the 1.6 million inhabitants of Stockholm County, Sweden. A cohort of 10 785 individuals who had had hip replacement between 1974 and 1988 was followed from the date of operation to the first malignant tumour, to death, or to the end of 1989. The follow-up was based on 58 437 person-years at risk as calculated from information obtained by record-linkage with the National Cancer Registry and the National Cause-of-Death Register.

The Standardised Morbidity Ratio (SMR) for all cancer sites, disregarding the length of follow-up, was 0.96 (95% CI 0.90 to 1.03). For lymphoma and leukaemia the corresponding SMR was 0.89 (0.68 to 1.14). Our results do not support previous suggestions of an increased incidence of leukaemia and lymphoma after total hip replacement.

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The use of permanent implants has rapidly increased over the last decade. The incidence of total hip replacements (THR) in Sweden was 131 per 100 000 inhabitants in 1991 and, worldwide, more than 800 000 operations for THR are performed each year (Malchau, Herberts and Ahnfeldt 1993). Three types of metal alloy based on iron, cobalt, or titanium are commonly used and constituents of these, notably chromium, nickel, cobalt and, in particular, some of their compounds may be carcinogenic in man as well as in experimental animal models (Kazantzis and Lilly 1986). The exposure of patients with a THR to metal is significant

(Black 1988) and elevated levels of metals have been demonstrated at the implant site, in blood, in urine and elsewhere in the body (Coleman, Herrington and Scales 1973; Dobbs and Minski 1980; Michel et al 1984; Bartolozzi and Black 1985). Modern designs include features such as porous coatings, and other surface modifications of cement-free devices have enlarged the contact area. Modularity may also facilitate the release of metal (Mathiesen et al 1991; Saikko 1993), which is probably higher with modern implants, especially when mixed metals are used (Collier et al 1991). In addition, patients are now accepted for THR at a younger age, thereby increasing the expected duration of exposure.

Metal particles and ions from the implant, liberated by fretting and corrosion, along with particulate debris from polymethylmethacrylate and polyethylene produce local reactions (Willert and Semlitsch 1977; Harris 1994). Malignant tumours at the implant site are extremely rare bearing in mind the large number of individuals who undergo THR (Apley 1989; Ward et al 1990; Goodfellow 1992; Jacobs et al 1992). The situation regarding tumours distant from the implant is more uncertain. Concern has been expressed at a possible association between THR and malignancies of the lymphatic and haemopoietic systems (Gillespie et al 1988; Visuri and Koskenvuo 1991).

Sweden has had a national population-based Cancer Registry and a Cause-of-Death Register for more than three decades. Since 1969, the Stockholm County Council has had a computerised In-patient Care Register (ICR) to which all hospitals in the county, except one private establishment, are connected. The information available includes data on hospital admissions, demography, diagnostic codes (ICD) and a four-digit code for operative procedures. A unique 11-digit personal identification number composed of seven digits based on century, year, month and day of birth, supplemented by a so-called registration number (three digits) and a check digit, is used in all registers, providing for linkage between them.

We have studied the incidence of cancer in patients after THR and compared it with that of the general population in Stockholm County.

PATIENTS AND METHODS

THR-Cohort. The ICR of Stockholm County was screened

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for patients who had had THR between 1974 and 1988. Codes for primary THR, hemiarthroplasty and revision hip arthroplasty were included, and 12 329 individuals were identified. The numbers of the different types of prosthesis implanted are not known but the original Charnley stainless-steel prosthesis was most commonly used, with a substantial number of chromium-cobalt prostheses such as the Müller, CAD, HD2 and others. Less than 5% were uncemented implants.

We excluded five non-Swedes without a complete personal identification number, eight patients, mostly with juvenile arthritis who had had multiple operations and who were 20 years or younger at the time of operation, and nine who had died during the initial hospital admission. We also excluded 620 individuals who had the code number for revision arthroplasty as their first registration in the ICR, implying that they had undergone a primary hip operation elsewhere or earlier than 1974, and 902 who, according to the Swedish Cancer Registry, had been treated for cancer before their first hip operation.

Our study was based therefore on a cohort comprising 10 785 individuals; 68.7% were women and 31.3% were men. Rheumatoid arthritis was the primary diagnosis in 8.3% according to the diagnostic code.

Follow-up and incidence of cancer. Information on patients who had been diagnosed with malignant tumours during the period 1958 to 1989 and on the incidence of cancer for the years 1974 to 1989 in Stockholm County was obtained from the Swedish Cancer Registry and the Stockholm County Council Regional Cancer Registry. Information on deaths was obtained by record-linkage with the Cause-of-Death Register. Person-years at risk were calculated from the date of primary hip surgery to the first diagnosis of cancer, to death, or to the end of 1989, which was the latest calendar year available at the Cancer Registry at the time of the matching. The observed number of tumours in the THR-cohort (O) was compared with the corresponding expected numbers (E), based on the number of person-years at risk in the cohort and on regional incidence rates in Stockholm County. The expected numbers were calculated with stratification for calendar year by five-year periods, gender and age by five-year age groups, and statistical analyses were carried out using SAS (SAS Institute Inc, Cary, North Carolina). A Fortran program was written to calculate person-years at risk, the expected number of malignant tumours and the ratio of the observed and the expected number of cases (O/E or the standardised morbidity ratio (SMR) with 95% confidence intervals). We used the Rothman and Boice approximation when the number of observed cases exceeded 20 (Breslow and Day 1987); otherwise the exact method based on the Poisson distribution was used.

Individuals with high exposure. Two categories of patients were selected for separate analysis since we thought that they might have been subjected to higher levels of metal exposure. We identified 2172 with a history

of bilateral hip replacement, 167 of whom were excluded because they had previously been treated for cancer, and 1347 who had undergone revision arthroplasty during the period of observation, of whom 89 had a previous cancer. Thus, 2005 patients with bilateral implants and 1258 with at least one revision were available for analysis. Patients who had their primary operation outside Stockholm County or before 1974 were included in the latter group. Person-years were calculated from the date of the second operation to the date of the first tumour, to death, or to the end of 1989.

RESULTS

Follow-up. A total follow-up of 58 437 person-years at risk, contributed by 10 785 patients, was available for the main analysis. At the end-point of the study 8 408 individuals (78%) were alive and 2377 (22%) had died. Person-

Table I. Person-years at risk for 10 785 individuals followed from the date of primary hip replacement to the first cancer, to death, or to the end of 1989

Follow-up in years	Person-years at risk
< 1	5412.74
1 < 2	18945.01
2 < 5	18317.74
5 < 10	12930.62
> 10	2831.42
Total	58437.53

years at risk calculated for follow-up for less than 1 year, 1 to 2 years, 2 to 5 years, 5 to 10 years and more than 10 years are presented in Table I.

Tumour incidence. A malignant tumour had developed in 881 patients (8.2%) during the period of observation. The calculated number of expected cancers was 917.7, which gave an SMR of 0.96 (CI 0.90 to 1.03). Observed and expected cancers at follow-up for less than 1 year, 1 to 2 years and the total number of malignancies which occurred during the observation period, including SMR with 95% confidence intervals, are shown in Tables II to IV. The CI of the SMR for all cancer sites, disregarding the length of follow-up included 1.0 with the exception of lung cancers which were fewer than expected (O/E = 56/74, SMR = 0.76, 95% CI 0.57 to 0.98; Table IV). For lymphoma and leukaemia taken together we observed 62 cases corresponding to a SMR of 0.89 (CI 0.68 to 1.14).

The incidence of several malignancies, for example lymphoma and leukaemia (ICD7 200-209), was significantly higher than expected during the first year of follow-up. A corresponding reduction, however, was seen during the second year after operation (Tables II and III). Individuals followed for ten years or more had a slightly higher total incidence of cancer than the general population (SMR = 1.10; CI 0.83 to 1.42), but the incidence of lymphoma and leukaemia was lower than expected (SMR = 0.25; CI 0.01 to 1.38). Some other tumours had a

Table II. Observed and expected malignancies at a follow-up of < 1 year in 10 785 individuals followed from the date of primary hip replacement to the first cancer, to death, or to the end of 1989

ICD 7	Cancer	Observed	Expected	SMR	95% CI
140 to 152	Upper gastrointestinal	13	6.3	2.07	1.10 to 3.54
153 to 154	Colorectal	19	9.8	1.94	1.17 to 3.04
155 to 158	Bile/liver/pancr	15	6.6	2.28	1.27 to 3.75
162	Lung	11	6.3	1.75	0.87 to 3.12
160 to 164	Resp syst/lung excl	4	1.1	3.72	1.01 to 9.51
170	Breast	26	10.1	2.51	1.64 to 3.68
171 to 176	Female reprod syst	8	6.1	1.30	0.56 to 2.57
177 to 179	Male reprod syst	20	7.3	2.75	1.68 to 4.25
180 to 181	Kidney/urinary org	4	6.2	0.65	0.18 to 1.65
190 to 191	Mal melanoma/skin	11	3.6	3.03	1.51 to 5.42
192 to 193	Eye/nervous syst	2	2.0	1.01	0.12 to 3.66
194 to 195	Thyroid/endocr gl	1	1.6	0.63	0.02 to 3.50
196 to 197	Bone/connect tissue	1	0.5	2.09	0.05 to 11.64
199	Other/unspecified	2	2.0	0.99	0.12 to 3.59
200 to 209	Lymphoma/leukaemia	15	5.6	2.66	1.49 to 4.39
	All sites	152	75.3	2.02	1.71 to 2.37

Table III. Observed and expected malignancies at a follow-up of 1 to < 2 years in 10 785 individuals followed from the date of primary hip replacement to the first cancer, to death, or to the end of 1989

ICD 7	Cancer	Observed	Expected	SMR	95% CI
140 to 152	Upper gastrointestinal	14	23.7	0.59	0.32 to 0.99
153 to 154	Colorectal	21	37.4	0.56	0.35 to 0.86
155 to 158	Bile/liver/pancr	11	25.0	0.44	0.22 to 0.79
162	Lung	12	23.3	0.52	0.27 to 0.90
160 to 164	Resp syst/lung excl	1	3.9	0.26	0.01 to 1.43
170	Breast	14	38.3	0.37	0.20 to 0.61
171 to 176	Female reprod syst	15	21.9	0.68	0.38 to 1.13
177 to 179	Male reprod syst	9	28.4	0.32	0.14 to 0.60
180 to 181	Kidney/urinary org	7	23.0	0.30	0.12 to 0.63
190 to 191	Mal melanoma/skin	7	14.4	0.49	0.20 to 1.00
192 to 193	Eye/nervous syst	6	7.2	0.83	0.31 to 1.82
194 to 195	Thyroid/endocr gl	2	5.7	0.35	0.04 to 1.26
196 to 197	Bone/connect tissue	0	1.8	0.00	0.00 to 2.03
199	Other/unspecified	1	7.8	0.13	0.00 to 0.71
200 to 209	Lymphoma/leukaemia	9	21.2	0.42	0.19 to 0.80
	All sites	129	283.2	0.46	0.38 to 0.54

Table IV. Total number of malignancies in 10 785 individuals followed from the date of primary hip replacement to the first cancer, to death, or to the end of 1989

ICD 7	Cancer	Observed	Expected	SMR	95% CI
140 to 152	Upper gastrointestinal	67	76.4	0.88	0.68 to 1.11
153 to 154	Colorectal	117	123.3	0.95	0.78 to 1.14
155 to 158	Bile/liver/pancr	77	82.0	0.94	0.74 to 1.17
162	Lung	56	74.0	0.76	0.57 to 0.98
160 to 164	Resp syst/lung excl	12	12.3	0.98	0.51 to 1.71
170	Breast	103	121.8	0.85	0.69 to 1.03
171 to 176	Female reprod syst	80	68.1	1.17	0.93 to 1.46
177 to 179	Male reprod syst	112	94.6	1.18	0.97 to 1.42
180 to 181	Kidney/urinary org	63	74.7	0.84	0.65 to 1.08
190 to 191	Mal melanoma/skin	56	48.6	1.15	0.87 to 1.50
192 to 193	Eye/nervous syst	20	22.7	0.88	0.54 to 1.36
194 to 195	Thyroid/endocr gl	23	17.9	1.28	0.81 to 1.92
196 to 197	Bone/connect tissue	5	5.9	0.85	0.28 to 1.98
199	Other/unspecified	28	25.9	1.08	0.72 to 1.56
200 to 209	Lymphoma/leukaemia	62	69.5	0.89	0.68 to 1.14
	All sites	881	917.7	0.96	0.90 to 1.03

higher incidence than predicted but the total numbers were small.

High exposure and cancer. Data concerning the 1258 patients, contributing 5583 person-years, who had undergone a revision arthroplasty and the 2005, contributing

8861 person-years, with bilateral hip replacement are shown in Tables V and VI. The overall occurrence of malignancies was lower than expected among patients with bilateral implants and slightly increased after revision hip surgery. Lymphoma and leukaemia were slightly less fre-

quent compared with the main analysis, but confidence intervals were wide.

Tumours of bone and connective tissue. Five tumours of bone or connective-tissue origin were seen. This was slightly less than expected. One individual, a man aged 58 years at the time of operation, developed a malignant fibrous histiocytoma in the vicinity of an uncemented Co-Cr-Mo (ASTM-75) prosthesis (Lord madreporique) five years after implantation. This case has not been previously reported. The other four tumours were not located in the same limb as the prosthesis.

DISCUSSION

Epidemiological data concerning the relationship between joint replacement and cancer are rare (Galante et al 1991; Friedman et al 1993). Two studies, however, one from New Zealand (Gillespie et al 1988) and the other from Finland (Visuri and Koskenvuo 1991), have attracted considerable attention since they both reported an increased incidence of leukaemia and lymphoma in the first decade after total hip replacement, which apparently increased with time.

Validity of data. Reliable medical information systems, such as the computerised medical registers which were utilised in our study, are necessary for performing epidemiological studies in large populations. The personal identification number, which is used in all official registers in Sweden, is a prerequisite for performing record-linkage between the different registers.

The validity of the results is dependent on the reliability of the sources of information. The Swedish Cancer Registry is well documented and is considered to be of good quality concerning both completeness and the reliability of data regarding cancer diagnoses (Mattson 1984; Barlow et al 1993). The ICR of Stockholm County has also been assessed by several authors. Ahlbom (1978) found incorrect diagnostic codes in 4% of 269 cases of myocardial infarction. Allebeck (1984) reported only negligible errors in disease coding or person identification. Hedlund, Lindgren and Ahlbom (1987) found that 98% of fractures of the proximal femur at Huddinge University Hospital had been reported to the register. The diagnostic codes in a random sample of 218 cases of fracture of the proximal femur were incorrect in 4.6% of the cases regarding classification of

Table V. Observed and expected malignancies in 1258 individuals followed from the date of revision arthroplasty to the first cancer, to death, or to the end of 1989

ICD 7	Cancer	Observed	Expected	SMR	95% CI
140 to 152	Upper gastrointest	8	7.2	1.11	0.48 to 2.19
153 to 154	Colorectal	11	11.2	0.98	0.49 to 1.75
155 to 158	Bile/liver/pancr	7	7.3	0.96	0.39 to 1.98
162	Lung	9	7.6	1.18	0.54 to 2.24
160 to 164	Resp syst/lung excl	1	1.2	0.81	0.02 to 4.49
170	Breast	9	9.8	0.92	0.42 to 1.74
171 to 176	Female reprod syst	10	5.5	1.82	0.87 to 3.34
177 to 179	Male reprod syst	11	11.4	0.97	0.48 to 1.73
180 to 181	Kidney/urinary org	7	7.4	0.95	0.38 to 1.96
190 to 191	Mal melanoma/skin	8	4.8	1.66	0.72 to 3.27
192 to 193	Eye/nervous syst	0	2.1	0.00	0.00 to 1.74
194 to 195	Thyroid/endocr gl	1	1.6	0.61	0.02 to 3.43
196 to 197	Bone/connect tissue	0	0.6	0.00	0.00 to 6.63
199	Other/unspecified	3	2.3	1.30	0.27 to 3.80
200 to 209	Lymphoma/leukaemia	5	6.7	0.75	0.24 to 1.75
	All sites	90	86.8	1.04	0.83 to 1.27

Table VI. Observed and expected malignancies in 2005 individuals with bilateral hip replacements followed from the date of the second operation to the first cancer, to death or to the end of 1989

ICD 7	Cancer	Observed	Expected	SMR	95% CI
140 to 152	Upper gastrointest	9	11.4	0.79	0.36 to 1.49
153 to 154	Colorectal	18	18.1	0.99	0.59 to 1.57
155 to 158	Bile/liver/pancr	5	11.8	0.42	0.14 to 0.99
162	Lung	7	11.9	0.59	0.24 to 1.21
160 to 164	Resp syst/lung excl	1	2.0	0.51	0.01 to 2.84
170	Breast	11	17.0	0.65	0.32 to 1.16
171 to 176	Female reprod syst	7	9.6	0.73	0.29 to 1.50
177 to 179	Male reprod syst	18	16.7	1.08	0.64 to 1.70
180 to 181	Kidney/urinary org	14	11.5	1.21	0.66 to 2.04
190 to 191	Mal melanoma/skin	8	7.5	1.07	0.46 to 2.11
192 to 193	Eye/nervous syst	6	3.4	1.78	0.65 to 3.88
194 to 195	Thyroid/endocr gl	4	2.7	1.50	0.41 to 3.85
196 to 197	Bone/connect tissue	0	0.9	0.00	0.00 to 4.23
199	Other/unspecified	4	3.8	1.05	0.29 to 2.68
200 to 209	Lymphoma/leukaemia	5	10.5	0.48	0.16 to 1.12
	All sites	117	138.7	0.84	0.70 to 1.01

Table VII. Observed and expected malignancies in 11 687 individuals including 902 previously treated for cancer followed from the date of primary hip replacement to death or to the end of 1989; all cancers after operation included

ICD 7	Cancer	Observed	Expected	SMR	95% CI
140 to 152	Upper gastrointest	80	85.0	0.94	0.75 to 1.17
153 to 154	Colorectal	136	137.6	0.99	0.83 to 1.17
155 to 158	Bile/liver/pancr	85	91.5	0.93	0.74 to 1.15
162	Lung	70	82.0	0.85	0.67 to 1.08
160 to 164	Resp syst/lung excl	14	13.6	1.03	0.56 to 1.73
170	Breast	129	134.8	0.96	0.80 to 1.14
171 to 176	Female reprod syst	88	75.1	1.17	0.94 to 1.44
177 to 179	Male reprod syst	119	106.2	1.12	0.93 to 1.34
180 to 181	Kidney/urinary org	75	83.1	0.90	0.71 to 1.13
190 to 191	Mal melanoma/skin	72	54.3	1.33	1.04 to 1.67
192 to 193	Eye/nervous syst	26	25.0	1.04	0.68 to 1.52
194 to 195	Thyroid/endocr gl	25	19.8	1.26	0.82 to 1.86
196 to 197	Bone/connect tissue	7	6.5	1.07	0.43 to 2.20
199	Other/unspecified	31	28.8	1.08	0.73 to 1.53
200 to 209	Lymphoma/leukaemia	70	77.4	0.90	0.71 to 1.14
All sites		1027	1020.9	1.01	0.95 to 1.07

cervical versus trochanteric fractures, although all fractures were correctly classified as of the proximal femur.

To minimise the risk of misclassification in our series, we included all code numbers for prosthetic hip surgery. No controls have been performed, but the inaccuracy is probably no worse than that with proximal femoral fractures (Hedlund et al 1987).

Risk factors for cancer. Individuals with a previous history of cancer were excluded because treatment for such disease is a risk factor for the development of a second tumour. Alkylating agents and radiation therapy may cause leukaemia and other types of tumour. The incidence of leukaemia among patients treated for Hodgkin's disease has been observed to be substantially higher than expected from general population rates (Kaldor 1990). To facilitate a comparison with the results of Gillespie et al (1988) we reviewed the material including the 902 individuals who had previously been treated for cancer, counting all tumours which had occurred during the observation period. This had little effect on the results, although we noticed a slight increase in the general incidence of cancer (Table VII). The occurrence of leukaemia and lymphoma for each follow-up interval is summarised in Table VIII.

Organ transplantation is also followed by an increased risk of cancer (Birkeland, Eklund and Jakobsen 1994). We did not exclude these patients from our series and they are

probably over-represented due to the associated occurrence of femoral head necrosis, but the total number is small and can hardly influence the results.

Incidence of cancer. Like Gillespie et al (1988) we found a significantly increased incidence of leukaemia and lymphoma during the first year after operation. When we included the second year, however, we found no excess of these malignancies. Analysing the cases of the first year in detail 7 out of the 15 had been reported within 30 days after discharge from the hospital, implying that they were accidental findings in routine testing before operation and were obviously not related to the implant, although their detection may have been.

We have failed to find a plausible explanation for the low incidence of lung cancer in patients with THR. It may be a chance finding due to the large number of calculations, but some candidates for hip arthroplasty may have been excluded because of disease related to smoking.

The general incidence of cancer was also somewhat lower than expected. This could reflect bias of selection, that is due to a healthy patient effect. Two Scandinavian studies have shown that patients undergoing total hip replacement are generally healthier and have a longer life expectancy than that of the general population (Holmberg 1992; Visuri et al 1994).

Gillespie et al (1988) reported a significantly decreased incidence of breast and colorectal cancers in their series. Aspirin and other non-steroidal anti-inflammatory drugs commonly used by arthritic patients may be a protective factor for the development of colorectal cancer (Peleg et al 1994). In our study the reduction of breast cancer was not significant, and the number of colorectal cancers was only marginally fewer than expected.

We also noticed a general tendency towards a higher incidence of cancer in patients followed for more than ten years although the occurrence of leukaemia and lymphoma remained low.

We were not able to establish any association between hip arthroplasty and an increased incidence of cancer dur-

Table VIII. Occurrence of lymphoma and leukaemia in 11 687 individuals (64153 person-years) followed from the date of primary hip replacement to death or to the end of 1989

Follow-up in years	Observed cases	Expected cases	SMR	95% confidence intervals
< 1	17	6.2	2.75	1.60 to 4.41
1 to < 2	9	23.5	0.38	0.18 to 0.73
2 to < 5	27	24.5	1.10	0.73 to 1.61
5 to < 10	15	18.6	0.80	0.45 to 1.33
> 10	2	4.6	0.43	0.05 to 1.55
total	70	77.4	0.90	0.71 to 1.14

ing the first decade after replacement arthroplasty of the hip. We saw no increase in the risk of cancer in individuals with bilateral or revised hip prostheses. Considering the long period of latency for other metal-associated cancers, such as those due to workplace exposure, the length of our follow-up is short and the long-term effects of the materials used in orthopaedic implants are yet to be ascertained.

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