Nationwide Study of Cancer Risk Among Hip Replacement Patients in Sweden

Lisa B. Signorello, Weimin Ye, Jon P. Fryzek, Loren Lipworth, Joseph F. Fraumeni, Jr., William J. Blot, Joseph K. McLaughlin, Olof Nyrén

Background: **Orthopedic implants and their fixatives contain materials with carcinogenic potential. Whether these implants are linked to subsequent cancer development remains unknown, mainly because large-scale, long-term follow-up data are scarce.** ***Methods:*** **We conducted a nationwide cohort study in Sweden to examine cancer incidence among 116 727 patients who underwent hip replacement surgery during the period from 1965 through 1994. Through record linkage to the Swedish Cancer Register, we identified all incident cancers through 1995 in this population (693 954 person-years of observation). For each cancer type, the observed number of cases was divided by that expected in the general Swedish population to produce standardized incidence ratios (SIRs).** ***Results:*** **Relative to the general population, the cohort had no overall cancer excess (SIR = 1.01; 95% confidence interval [CI] = 0.99 to 1.03). However, we observed elevated SIRs for prostate cancer (SIR = 1.16; 95% CI = 1.11 to 1.22) and melanoma (SIR = 1.15; 95% CI = 1.01 to 1.30) and a reduction in stomach cancer risk (SIR = 0.83; 95% CI = 0.75 to 0.92). Long-term follow-up (⩾15 years) revealed an excess of multiple myeloma (SIR = 1.86; 95% CI = 1.01 to 3.11) and a statistically nonsignificant increase in bladder cancer (SIR = 1.42; 95% CI = 0.98 to 1.99). There was no material increase in risk for bone or connective tissue cancer for either men or women in any follow-up period.** ***Conclusions:*** **In this, the largest study to date, hip implant patients had similar rates of most types of cancer to those in the general population. Although the excesses of melanoma, multiple myeloma, and prostate and bladder cancers may be due to chance, confounding, or detection bias and should be interpreted cautiously, they warrant further investigation because of the ever-increasing use of hip implants at younger ages.** **[J Natl Cancer Inst 2001;93:1405–10]**

The carcinogenic potential of hip implants is of growing public health interest as they become more common, are implanted in younger patients, and remain in the body for increasingly longer periods of time *(1)*. Various metallic and nonmetallic substances contained within the implants or as components of their fixatives are known or are suspected to cause cancer in humans or animals; in particular, these substances include chromium, cobalt, nickel, beryllium, cadmium, zinc, iron, lead, titanium, and polymethylmethacrylate *(1–5)*. Case reports of bone and soft-tissue sarcomas adjacent to orthopedic implants have suggested that exposure of local tissues to the implanted material may induce cancer at that site *(6–8)*. Systemic exposure to metallic ions and other particulate debris released through corrosion of the implant is another concern, since distant tissues could also be affected. The International Agency for Research on Cancer determined the evidence regarding human carcinogenicity of orthopedic implants to be inadequate, in part because previous cohort studies had limited data beyond 10–15 years' latency to address possible long-term effects.

We reported previously on a nationwide cohort of patients who underwent hip implant surgery during the period from 1965 through 1983 in Sweden and were followed until the end of 1989 *(9)*. This cohort has now been expanded to include new patients who received hip implants through 1994, and the follow-up was updated through 1995. Hence, the total person-years of observation of our original report has more than doubled, and the present study of hip implants and cancer risk is, to our knowledge, the larg-

Affiliations of authors: L. B. Signorello, J. P. Fryzek, L. Lipworth, W. J. Blot, J. K. McLaughlin, International Epidemiology Institute, Rockville, MD, and Department of Medicine, Vanderbilt University Medical Center, and Vanderbilt-Ingram Cancer Center, Nashville, TN; W. Ye, O. Nyrén, Department of Medical Epidemiology, Karolinska Institute, Stockholm, Sweden; J. F. Fraumeni, Jr., Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD.

Correspondence to: Joseph K. McLaughlin, Ph.D, International Epidemiology Institute, 1455 Research Blvd., Suite 550, Rockville, MD 20850 (e-mail: jkm@iei.ws).

See "Notes" following "References."

est to date with the longest follow-up to evaluate potential long-term effects.

METHODS

This study was approved by the regional Ethics Committee of the medical faculty, Uppsala University, Sweden, and by the Data Inspection Board of the National Board of Health and Welfare of Sweden, Stockholm.

Identifying the Cohort

The Inpatient Register was established by the National Board of Health and Welfare in Sweden in 1964 to document individual hospital discharges. Each Inpatient Register record contains (*a*) the patient's national registration number (NRN—a unique identifier assigned to all Swedish residents), (*b*) the date of hospital admission and discharge, (*c*) up to six discharge diagnoses coded according to the International Classification of Diseases (ICD)-7 until 1968, ICD-8 from 1968 through 1986, and ICD-9 thereafter, and (*d*) up to six operation codes from the Swedish Classification of Operations and Major Procedures. The NRN permits unambiguous linkage across all national registers in Sweden.

All records in the Inpatient Register indicating hip replacement surgery (operation codes 8410, 8411, 8412, and 8419 and also codes 8413, 8414, and 8415 since 1984) from January 1, 1965, through December 31, 1994, were initially selected. To remove records with erroneous NRNs (correct NRNs are a prerequisite for record linkages and follow-up), we excluded NRNs that could not be found in either the Register of Total Population, Migration, or Death (n = 799, 0.6% of the identified records).

A total of 128 170 persons were identified as having had hip replacement surgery during the study period. We selected the first recorded discharge to be used as the index surgery in this analysis.

Follow-up/Record Linkage

The nationwide Death Register provided data on all cohort member deaths (date and cause), while dates of emigration for cohort members who left Sweden were identified through the Migration Register. The national Cancer Register, founded in 1958 and estimated to be 98% complete *(10)*, was used to ascertain (via linkage on patients' NRNs) all incident cancers diagnosed in the cohort from the start of follow-up until December 31, 1995. The Cancer Register has coded malignant neoplasms according to the ICD-7 classification scheme during the entire period of the study. To exclude hip replacement surgeries performed as a result of malignant disease and to restrict our outcome to first primary tumors, we excluded from the cohort all persons with a cancer diagnosis preceding their hip implant (n = 10 308). We excluded an additional 1135 subjects because of observed inconsistencies among data from the national registers. Thus, a total of 116 727 patients were entered into the study.

Statistical Analysis

Individual person-time was calculated from the first hip implant surgery until the first cancer diagnosis, death, emigration, or December 31, 1995, whichever came first. Person-time accrued and cancer events observed during the first year of follow-up were not counted in the analysis, since cancer cases diagnosed during this period are assumed to be coincidental, prone to selection and surveillance bias, and unlikely to be causally related to the implant. Cancers found incidentally at autopsy were excluded from the analyses to avoid possible ascertainment bias related to differential autopsy rates between hip implant patients and the general population. The number of expected events was calculated by multiplying age-, sex- and calendar year-specific incidence rates (expected rates) from the general population by the person-time accrued in the cohort. In the calculation of the expected rates, person-time at risk in the general population did not include that contributed by individuals who were alive but who had been diagnosed with cancer (prevalent cancer cases). The number of observed events was divided by the number of expected events, producing a standardized incidence ratio (SIR) with 95% confidence intervals (CIs) calculated assuming that the observed events followed a Poisson probability distribution *(11)*. SIRs were calculated for all cancers combined as well as separately for each cancer type. A chi-square test for linear trend in SIRs was used to evaluate dose–response relationships by duration of follow-up. The indication for the hip implant operation was determined from the diagnostic codes (ICD codes) provided in the Inpatient Register. When more than one indication was listed, the one listed first was considered to be the principal diagnosis. Separate subanalyses were performed with the use of the group of patients with rheumatoid arthritis as their indication for hip replacement, because patients with this disease are hypothesized to have a somewhat different cancer risk profile. All *P* values presented in this report are two-sided, and the results were considered to be statistically significant at *P* less than .05.

RESULTS

The 116 727 patients who received hip implants during the period from 1965 through 1994 were followed for a mean of nearly 7 years (range, 1 day to 31 years) (Table 1). The reason for hip implant surgery was mainly osteoarthritis (67%), while 20% of the cohort had a fracture indication, 5% rheumatoid arthritis, and 8% some other indication.

The cohort generated more than 10 000 cases of cancer during follow-up, excluding those that occurred during the first year. SIRs for major cancer types are shown in Table 2, stratified by sex. Compared with the general population, we observed no excess of cancer overall (SIR = 1.01; 95% CI = 0.99 to 1.03). The incidence of the major digestive cancers was reduced (stomach cancer: SIR = 0.83 [95% CI = 0.75 to 0.92]; colon cancer: SIR = 0.95 [95% CI = 0.89 to 1.02]; and rectal cancer: SIR = 0.90 [95% CI = 0.82 to 0.99]). Among subjects with all indications for implants, lung cancer rates were 16% lower than expected for men (SIR = 0.84; 95% CI = 0.75 to 0.93), but they were 14% higher than expected for women (SIR = 1.14; 95% CI = 0.99 to 1.29). The excess lung cancer among female patients was, however, statistically significant only among those with a fracture indication for hip implant surgery (SIR = 1.52; 95% CI = 1.16 to 1.94). Men with fractures also had a statistically significant excess risk of lung cancer (SIR = 1.80; 95% CI = 1.35 to 2.35), despite the fact that an overall reduced risk was seen for males.

SIRs for both melanoma and nonmelanoma skin cancer were statistically significantly elevated, with the excess of melanoma being more pronounced among men and nonmelanoma skin cancer more pronounced among women. We also observed statistically significant excesses

Table 1. Characteristics of the 116 727 hip replacement patients and their follow-up

Characteristic	Men	Women	Total
Hip replacement patients, No.	45 249	71 478	116 727
Diagnosis at index surgery, No. of patients			
Osteoarthritis	36 263	42 357	78 620
Late sequelae after fracture	2573	9601	12 174
Acute fracture	1842	8970	10 812
Rheumatoid arthritis	1524	4077	5601
Other	3047	6473	9520
Mean age at entry, y	67.7	70.7	69.5
Median calendar year at entry	1987	1987	1987
Total person-years at risk	264 493	429 460	693 954*
Mean years of follow-up	6.8	7.0	6.9
No. of cancer cases during follow-up	4941	5082	10 023†
Mean age at cancer diagnosis, y	75.6	76.3	76.0

*Excludes 113 659 person-years observed during the first year of follow-up.
†Excludes 1377 cases of cancer diagnosed during the first year of follow-up.

Table 2. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) for cancer occurrence among hip replacement patients, stratified by sex

	Men			Women			Total		
Cancer type (ICD-7 code*)	No. observed	SIR	95% CI	No. observed	SIR	95% CI	No. observed	SIR	95% CI
All sites (140–209)	4941	1.02	1.00 to 1.05	5082	0.99	0.96 to 1.02	10 023	1.01	0.99 to 1.03
Buccal cavity (140–148)	104	1.00	0.82 to 1.22	83	1.11	0.88 to 1.37	187	1.05	0.90 to 1.21
Esophagus (150)	41	0.74	0.53 to 1.01	34	0.96	0.66 to 1.34	75	0.83	0.65 to 1.04
Stomach (151)	209	0.85	0.74 to 0.97	168	0.81	0.69 to 0.94	377	0.83	0.75 to 0.92
Stomach excluding cardia (151)	166	0.78	0.67 to 0.91	157	0.82	0.70 to 0.96	323	0.80	0.72 to 0.89
Colon (153)	371	1.02	0.92 to 1.13	478	0.90	0.82 to 0.98	849	0.95	0.89 to 1.02
Rectum (154)	207	0.84	0.73 to 0.96	248	0.96	0.84 to 1.08	455	0.90	0.82 to 0.99
Primary liver and bile duct (155)	98	1.03	0.84 to 1.26	175	0.98	0.84 to 1.14	273	1.00	0.89 to 1.13
Pancreas (157)	123	1.00	0.83 to 1.19	169	0.93	0.80 to 1.08	292	0.96	0.85 to 1.07
Lung (162–163)	353	0.84	0.75 to 0.93	231	1.14	0.99 to 1.29	584	0.94	0.86 to 1.01
Breast (170)	12	1.59	0.82 to 2.77	1113	0.96	0.90 to 1.01	1125	0.96	0.90 to 1.02
Cervix (171)	—	—	—	78	0.91	0.72 to 1.14	—	—	—
Corpus uteri (172)	—	—	—	249	0.96	0.84 to 1.08	—	—	—
Ovary (175)	—	—	—	219	1.04	0.90 to 1.18	—	—	—
Prostate (177)	1789	1.16	1.11 to 1.22	—	—	—	—	—	—
Kidney (180)	129	1.02	0.86 to 1.22	156	1.26	1.07 to 1.48	285	1.14	1.01 to 1.28
Bladder (181)	358	1.02	0.92 to 1.13	169	1.15	0.98 to 1.33	527	1.06	0.97 to 1.15
Malignant melanoma of skin (190)	126	1.24	1.04 to 1.48	129	1.06	0.89 to 1.27	255	1.15	1.01 to 1.30
Skin (nonmelanoma) (191)	278	1.03	0.91 to 1.16	296	1.19	1.05 to 1.33	574	1.11	1.02 to 1.20
Brain (193)	71	1.05	0.82 to 1.32	101	1.04	0.85 to 1.26	172	1.04	0.89 to 1.21
Thyroid (194)	7	0.54	0.22 to 1.11	37	0.93	0.66 to 1.29	44	0.84	0.61 to 1.12
Bone (196)	2	0.53	0.06 to 1.93	6	1.25	0.46 to 2.71	8	0.93	0.40 to 1.84
Connective tissue (197)	26	0.99	0.65 to 1.45	29	0.93	0.62 to 1.34	55	0.96	0.72 to 1.25
All hematopoietic (200–209)	329	0.97	0.87 to 1.08	359	0.97	0.87 to 1.07	688	0.97	0.90 to 1.04
Lymphoma (200–202, 205)	147	0.97	0.82 to 1.15	159	0.93	0.79 to 1.09	306	0.95	0.85 to 1.06
Multiple myeloma (203)	91	1.17	0.94 to 1.44	90	1.04	0.84 to 1.28	181	1.10	0.95 to 1.28
All leukemia (204–207)	91	0.82	0.66 to 1.00	110	0.96	0.79 to 1.16	201	0.89	0.77 to 1.02

*World Health Organization (WHO): International Classification of Diseases (ICD). 7th revision. Geneva (Switzerland): WHO; 1957.

of prostate cancer (SIR = 1.16; 95% CI = 1.11 to 1.22) and of kidney cancer in women (SIR = 1.26; 95% CI = 1.07 to 1.48). Stratification by indication showed that the excess risk for kidney cancer among women was most prominent for those with underlying rheumatoid arthritis (SIR = 1.88; 95% CI = 0.97 to 3.29). Among women with osteoarthritis, the SIR for kidney cancer was 1.28 (95% CI = 1.05 to 1.55).

No association was observed for connective tissue cancer (SIR = 0.96; 95% CI = 0.72 to 1.25). Eight cases of bone cancer were identified in the cohort, slightly less than the 8.6 expected. The report forms received by the Cancer Register were reviewed for each of these eight cases. Five were chordomas (three located in the sacrum/coccyx area and two in the vertebral column excluding the sacrum and coccyx), and three were chondrosarcomas (located in the tibia [n = 1], distal femur [n = 1], and proximal femur [n = 1]). Five of the bone cancer cases were diagnosed in the patient within 5 years of receiving the implant, and all were diagnosed within 7 years (mean, 4.4 years after implantation).

Almost 1900 incident cancer cases were identified among cohort members followed at least 10 years after their surgeries (Table 3). For all cancers combined, we observed a borderline statistically significant excess risk between 10 and 14 years after surgery (SIR = 1.06; 95% CI = 1.00 to 1.12), but not in any other time period. The deficit of stomach cancer became more pronounced with increasing follow-up time (particularly after the exclusion of cardia cancers), with a 30% reduction in risk after 10 years' latency. The largest excess of melanoma was seen after a latency period of 15 years or more (SIR = 1.83; 95% CI = (1.10–2.86), and our analysis revealed a clear and statistically significant trend of increasing SIRs over time for this cancer (P for trend = .01). In contrast, the association with nonmelanoma skin cancer was inconsistent across latency periods and disappeared after 15 years of follow-up. The highest SIR for prostate cancer was seen during the period 5–9 years after implant surgery (SIR = 1.21; 95% CI = 1.12 to 1.31), although some excess was still apparent at a latency of 15 or more years (SIR = 1.15; 95% CI = 0.92 to 1.43). The incidence of kidney cancer was 54% higher than expected 10–14 years after surgery (SIR = 1.54; 95% CI = 1.13 to 2.04), but this excess was attenuated and statistically nonsignificant with longer follow-up. The risks of multiple myeloma and bladder cancer were higher than expected after a latency of 15 years or more, but not in earlier time periods. We could not assess patterns of cancer risk by latency and surgical indication jointly, because the number of cancer events became too small in the later follow-up years.

In the subgroup of patients with rheumatoid arthritis, we found statistically nonsignificantly elevated SIRs for hematopoietic malignancies (Table 4). We also observed a strong and statistically significant deficit of colon cancer, a nonsignificant deficit of rectal cancer, and stomach cancer risk close to that expected in the general population. In contrast, among patients who had osteoarthritis or a fracture as their surgical indication, we observed no association with hematopoietic cancers (SIR = 0.95; 95% CI = 0.88 to 1.03) or colon cancer (SIR = 0.97; 95% CI = 0.91 to 1.04), a modest deficit in rectal cancer (SIR = 0.90; 95% CI = 0.82 to 0.99), and a substantial reduction in stomach cancer (SIR = 0.82; 95% CI = 0.74 to 0.91) (data not shown).

Separate analyses of the original cohort who received hip implants during the period from 1965 through 1983 (36 774 patients; 364 882 person-years) and the newer cohort who received implants dur-

Table 3. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) for cancer occurrence among hip replacement patients, stratified by latency period

	Latency period*											
	1–4 y			5–9 y			10–14 y			⩾15 y		
Cancer type (ICD-7 code†)	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI
All sites (140–209)	4790	1.00	0.97 to 1.03	3339	0.99	0.96 to 1.03	1434	1.06	1.00 to 1.12	460	0.99	0.91 to 1.09
Buccal cavity (140–148)	85	0.97	0.78 to 1.20	60	1.00	0.77 to 1.29	34	1.45	1.00 to 2.02	8	1.01	0.44 to 2.00
Esophagus (150)	45	1.02	0.75 to 1.37	19	0.62	0.37 to 0.97	11	0.90	0.45 to 1.62	0	—	0.00 to 0.91
Stomach (151)	192	0.87	0.75 to 1.00	130	0.85	0.71 to 1.01	41	0.69	0.49 to 0.93	14	0.71	0.39 to 1.19
Stomach excluding cardia (151)	167	0.85	0.72 to 0.98	106	0.78	0.64 to 0.95	39	0.74	0.53 to 1.01	11	0.64	0.32 to 1.14
Colon (153)	400	0.95	0.86 to 1.04	297	0.98	0.87 to 1.10	120	0.96	0.80 to 1.15	32	0.73	0.50 to 1.03
Rectum (154)	213	0.88	0.77 to 1.01	154	0.90	0.76 to 1.05	65	0.94	0.72 to 1.20	23	0.97	0.61 to 1.45
Primary liver and bile duct (155)	139	1.04	0.88 to 1.23	87	0.95	0.76 to 1.17	37	1.02	0.72 to 1.41	10	0.83	0.40 to 1.53
Pancreas (157)	145	0.97	0.82 to 1.14	95	0.93	0.75 to 1.14	43	1.07	0.78 to 1.44	9	0.67	0.31 to 1.28
Lung (162–163)	281	0.90	0.80 to 1.01	191	0.92	0.79 to 1.06	86	1.10	0.88 to 1.35	26	1.07	0.70 to 1.57
Breast (170)	555	0.96	0.88 to 1.04	355	0.92	0.82 to 1.02	163	1.06	0.90 to 1.23	52	0.96	0.72 to 1.26
Cervix (171)	45	1.02	0.75 to 1.37	23	0.83	0.53 to 1.25	4	0.39	0.10 to 0.99	6	1.74	0.64 to 3.78
Corpus uteri (172)	143	1.10	0.93 to 1.30	71	0.83	0.65 to 1.05	32	0.96	0.66 to 1.36	3	0.26	0.05 to 0.76
Ovary (175)	129	1.19	0.99 to 1.41	55	0.80	0.60 to 1.04	25	0.98	0.63 to 1.44	10	1.20	0.57 to 2.20
Prostate (177)	807	1.14	1.07 to 1.22	652	1.21	1.12 to 1.31	244	1.10	0.96 to 1.24	86	1.15	0.92 to 1.43
Kidney (180)	134	1.07	0.89 to 1.26	90	1.09	0.88 to 1.34	48	1.54	1.13 to 2.04	13	1.31	0.70 to 2.24
Bladder (181)	231	0.98	0.86 to 1.11	188	1.11	0.95 to 1.28	75	1.09	0.86 to 1.36	33	1.42	0.98 to 1.99
Malignant melanoma of skin (190)	108	1.00	0.82 to 1.21	87	1.17	0.94 to 1.44	41	1.37	0.98 to 1.85	19	1.83	1.10 to 2.86
Skin (nonmelanoma) (191)	261	1.16	1.02 to 1.31	176	0.98	0.84 to 1.13	105	1.28	1.05 to 1.56	32	1.01	0.69 to 1.43
Brain (193)	99	1.16	0.94 to 1.41	51	0.95	0.71 to 1.25	17	0.86	0.50 to 1.38	5	0.82	0.27 to 1.92
Thyroid (194)	20	0.75	0.46 to 1.16	17	0.98	0.57 to 1.57	6	0.92	0.34 to 2.00	1	0.47	0.01 to 2.62
Bone (196)	5	1.14	0.37 to 2.66	3	1.07	0.22 to 3.12	0	—	0.00 to 3.54	0	—	0.00 to 11.29
Connective tissue (197)	30	1.08	0.73 to 1.54	18	0.93	0.55 to 1.47	5	0.65	0.21 to 1.51	2	0.76	0.09 to 2.74
All hematopoietic (200–209)	330	0.97	0.87 to 1.08	239	0.99	0.87 to 1.13	90	0.93	0.75 to 1.14	29	0.88	0.59 to 1.26
Lymphoma (200–202, 205)	150	0.98	0.83 to 1.15	109	1.00	0.82 to 1.21	38	0.86	0.61 to 1.18	9	0.59	0.27 to 1.11
Multiple myeloma (203)	88	1.12	0.90 to 1.38	57	1.03	0.78 to 1.33	22	0.99	0.62 to 1.50	14	1.86	1.01 to 3.11
All leukemia (204–207)	92	0.84	0.68 to 1.04	73	0.96	0.75 to 1.20	30	0.98	0.66 to 1.41	6	0.59	0.21 to 1.28

*Person-years of observation in each strata: 1–4 years, 353 235; 5–9 years, 226 614; 10–14 years, 85 835; ⩾15 years, 28 269.

†World Health Organization (WHO): International Classification of Diseases (ICD). 7th revision. Geneva (Switzerland): WHO; 1957.

Table 4. Hematopoietic and digestive cancers among hip implant patients with a rheumatoid arthritis indication*

Cancer type	Obs	Exp	SIR	95% CI
Hematopoietic cancer				
All hematopoietic	34	24.56	1.38	0.96 to 1.93
All leukemia	11	7.43	1.48	0.74 to 2.65
All lymphoma	18	11.68	1.54	0.91 to 2.44
Hodgkin's disease	3	0.92	3.25	0.67 to 9.51
Non-Hodgkin's lymphoma	15	10.6	1.41	0.79 to 2.33
Multiple myeloma	5	5.46	0.92	0.30 to 2.14
Acute lymphocytic leukemia	1	0.25	4.01	0.10 to 22.35
Chronic lymphocytic leukemia	4	3.17	1.26	0.34 to 3.24
Acute nonlymphocytic leukemia	6	2.28	2.63	0.97 to 5.73
Chronic nonlymphocytic leukemia	0	0.69	—	0.00 to 5.37
Major digestive cancers				
Colon	16	29.18	0.55	0.31 to 0.89
Rectum	13	16.57	0.78	0.42 to 1.34
Stomach	14	12.92	1.08	0.59 to 1.82

*Obs = observed number of cases; Exp = expected number of cases; SIR = standardized incidence ratio; CI = confidence interval.

ing the period from 1984 through 1994 (79 953 patients; 329 071 person-years) produced, on the whole, similar results. The exception was with respect to kidney cancer. The overall SIR for kidney cancer in the original cohort was 1.35 (95% CI = 1.15 to 1.56; 177 cases observed versus 131.6 expected) with excesses of varying magnitudes seen for patients with all indications, while in the newer cohort the SIR for kidney cancer was 0.92 (95% CI = 0.75 to 1.11; 108 cases observed versus 117.9 expected) with an excess seen only for patients with rheumatoid arthritis (SIR = 2.66; 95% CI = 1.38 to 4.65).

DISCUSSION

In summary, overall cancer risk among hip implant patients was close to expectation. However, we observed these patients to have a statistically significant excess of melanoma and prostate cancer and, after a latency of 15 years or more, of multiple myeloma and bladder cancer. In contrast, we noted a statistically significant deficit of stomach cancer and suggestive evidence for decreased colorectal cancer risk. The incidence of bone and connective tissue cancers was not statistically significantly higher than expected for either sex in any follow-up period.

In our earlier report *(9)*, the rate of kidney cancer was found to be statistically significantly elevated among hip implant recipients, whereas this finding is not confirmed in the newer cohort of patients who received implants during the period from 1984 through 1994. It is possible that hip implants from the earlier time period (more commonly metal on metal than polyethylene on metal) could influence renal cancer risk via properties that

are not shared by newer implants. Also, hip implant patients are high consumers of analgesics, and the older cohort of patients had more opportunity to take phenacetin, an analgesic that was linked to both kidney failure *(12)* and kidney cancer *(13)* and, therefore, withdrawn from the Swedish market in the early 1970s. If one considers the number of associations examined in the analysis, it is also possible that the elevated SIR for kidney cancer in the 1965–1983 cohort was due to chance. In line with findings from our expanded cohort, Olsen et al. *(14)* found no excess of kidney cancer in a large cohort of Danish patients who had hip implant surgery during the period from 1977 through 1989 (SIR = 0.93; 95% CI = 0.74 to 1.14).

The excess risk of melanoma that we observed is also consistent with the Danish study *(14)*, which found a nearly 50% excess risk and a trend of increasing SIRs with increasing follow-up. The biologic rationale linking hip implants to melanoma is not clear, and other studies *(15–17)* have not reported this association. However, a large Swedish cohort study *(18)* has reported that persons with physically demanding occupations, particularly involving outdoor work, are at statistically significantly elevated risk of being hospitalized for osteoarthritis. Thus, individuals with high sun exposure may be over-represented among hip implant patients with osteoarthritis.

Increased rates of multiple myeloma and of bladder cancer have not been observed in earlier studies, possibly because the follow-up periods were too short for such evaluation. The etiology of multiple myeloma is poorly understood, but chronic immune stimulation is thought to play a role *(19)*. Foreign-body implants provoke a variety of immune responses *(20–23)* that persist for the life of the implant; thus, a causal relationship may be plausible. With regard to bladder cancer, no information was available on risk factors, such as cigarette smoking, phenacetin-containing analgesics, and a number of occupational exposures *(24);* therefore, confounding by these variables cannot be ruled out as an explanation for the excess risk.

Confounding seems a likely explanation for the inverse association with stomach cancer, which could be due to incidental *Helicobacter pylori* eradication via antibiotic prophylaxis used at the time of hip implant surgery *(9,25,26)* and/or to frequent use of nonsteroidal anti-inflammatory drugs (NSAIDs) for arthritis and other pain *(27,28)*. It is noteworthy that, in our study, the protective effect was greater for stomach cancer than for colorectal cancer. An antibiotic effect on *H. pylori* infection should be specific for stomach cancer, while NSAIDs have been shown to protect against both stomach and colorectal cancers *(27,29,30)*. Further evidence suggesting an antibiotic effect comes from a study in Denmark *(14)*, where a lowered risk of stomach cancer was found among patients with osteoarthritis who underwent hip implant surgery (presumably exposed to both NSAIDs and antibiotics) but not among those who did not have surgery (presumably exposed only to NSAIDs). Also, Akre et al. *(26)* recently showed a dose–response reduction in stomach cancer risk with increasing weight-adjusted prophylactic antibiotic dose among hip implant patients.

An excess of lung cancer was seen only among implant patients with a hip fracture indication, probably because cigarette smoking is a risk factor for low bone density and associated hip fractures *(31,32)*. A reason for the excess risk of prostate cancer is less clear. Increased contact with the medical system due to hip surgery could increase detection rates for prostate cancer, although we did exclude cancers that were found during the first year of follow-up and it is unlikely that detection bias would be sustained over one to two decades. Confounding by obesity is possible, although the association between obesity and prostate cancer is weak *(33)*. If the association between hip implants and prostate cancer is causal in nature, it could be via exposure to cadmium *(34)*.

Patients with rheumatoid arthritis have been shown to have higher rates of hematopoietic cancers and lower rates of colorectal and possibly stomach cancers *(35–37)*. This study provided the opportunity to test these associations in a large group of hip implant patients with rheumatoid arthritis as an underlying condition. Despite the small number of cases, we did find that leukemia and lymphoma were related (albeit statistically nonsignificantly) to hip implantation only among this subgroup of patients. Earlier studies *(38,39)* have reported associations between hip implantation and hematopoietic cancers. A relatively small (14 286 person-years of observation) cohort study by Gillespie et al. *(38)* found a statistically significant 68% increased risk of lymphoma/hematopoietic cancer, but patients with a prior diagnosis of cancer were included in the analysis, and the association was primarily seen in the first 2 years of follow-up. Visuri and Koskenvuo *(39)* reported a statistically significant threefold excess risk of lymphoma/leukemia among hip implant patients with osteoarthritis after 5729 person-years of observation, but again the first year of follow-up largely contributed to the excess. Later studies by the same authors of these early studies *(15,17,40)*, as well as other studies *(9,16)*, have not found evidence linking hip implants to hematopoietic cancers beyond the first year after implantation, although Olsen et al. *(14)* noted a marginally significant 10% excess. We observed a substantial deficit of colon and rectal cancers, consistent with other studies of patients with rheumatoid arthritis *(35,36)*. High NSAID use among these patients may account for these associations *(29–30)*.

Overall, the results of our study are largely reassuring that hip implant patients have similar rates of most types of cancer as the general population. We did find evidence, however, that hip replacement may be associated with an increased risk of melanoma and prostate cancer and with an excess of multiple myeloma and bladder cancer after long-term follow-up. If these associations were causal in nature, they would represent serious public health issues, but we note that causal inference is hindered by the limitations of our study design (and that of other previous record linkage studies that lack information on confounding factors). Still, general impressions can be offered on the basis of an assessment of the overall state of the evidence. Except for our earlier report *(9)*, there is almost no other evidence linking hip implants to prostate cancer risk, and there is no consistency regarding an association with melanoma; given the lack of proposed biologic hypotheses and the multiple comparisons that we performed, chance or confounding bias is a likely explanation for the melanoma and prostate cancer results. However, because this investigation provided the first opportunity to adequately evaluate the long-term cancer-related effects of hip implants, the associations that we observed with bladder cancer and multiple myeloma, while also potentially attributable to chance or bias, should be considered

carefully and require further in-depth study.

REFERENCES

(1) International Agency for Research on Cancer (IARC). Surgical implants and other foreign bodies. IARC Mongr 1999;74:303–11.

(2) International Agency for Research on Cancer (IARC). Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. IARC Monogr 1993;58:41–237.

(3) Sinibaldi K, Rosen H, Liu SK, DeAngelis M. Tumors associated with metallic implants in animals. Clin Orthop 1976;118:257–66.

(4) Memoli VA, Urban RM, Alroy J, Galante JO. Malignant neoplasms associated with orthopedic implant materials in rats. J Orthop Res 1986;4:346–55.

(5) Laskin DM, Robinson IB, Weinman JP. Experimental production of sarcomas by methylmethacrylate implants. Proc Soc Exp Biol Med 1954;87:329–32.

(6) International Agency for Research on Cancer (IARC). Surgical implants and other foreign bodies. IARC Monogr 1999;74:132–61.

(7) Jacobs JJ, Rosenbaum DH, Hay RM, Gitelis S, Black J. Early sarcomatous degeneration near a cementless hip replacement. A case report and review. J Bone Joint Surg Br 1992;74:740–4.

(8) Goodfellow J. Malignancy and joint replacement [editorial]. J Bone Joint Surg Br 1992;74: 645.

(9) Nyren O, McLaughlin JK, Gridley G, Ekbom A, Johnell O, Fraumeni JF Jr, et al. Cancer risk after hip replacement with metal implants: a population-based cohort study in Sweden. J Natl Cancer Inst 1995;87:28–33.

(10) Mattson B, Wallgren A. Completeness of the Swedish Cancer Registry. Non-notified cancer cases recorded on death certificates in 1978. Acta Radiol Oncol 1984;23:305–13.

(11) Breslow NE, Day NE. Statistical methods in cancer research. Volume II—The design and analysis of cohort studies. IARC Sci Publ 1987;82:1–406.

(12) Henrich WL. Analgesic nephropathy. Am J Med Sci 1988;295:561–8.

(13) McLaughlin JK, Lipworth L. Epidemiologic aspects of renal cell cancer. Semin Oncol 2000; 27:115–23.

(14) Olsen JH, McLaughlin JK, Nyren O, Mellemkjaer L, Lipworth L, Blot WJ, et al. Hip and knee implantations among patients with osteoarthritis and risk of cancer: a record-linkage study from Denmark. Int J Cancer 1999;81: 719–22.

(15) Visuri T, Pukkala E, Paavolainen P, Pulkkinen P, Riska EB. Cancer risk after metal on metal and polyethylene on metal total hip arthroplasty. Clin Orthop 1996;(329 Suppl):S280–9.

(16) Mathiesen EB, Ahlbom A, Bermann G, Lindgren JU. Total hip replacement and cancer. A cohort study. J Bone Joint Surg Br 1995; 77:345–50.

(17) Paavolainen P, Pukkala E, Pulkkinen P, Visuri T. Cancer incidence in Finnish hip replacement patients from 1980 to 1995: a nationwide cohort study involving 31,651 patients. J Arthroplasty 1999;14:272–80.

(18) Vingard E, Alfredsson L, Hogstedt C, Goldie I. Increased risk of arthrosis of the knee and hip among workers with heavy weight on the legs. Lakartidningen 1990;87:4413–6.

(19) Herrinton LJ, Weiss NS, Olshan AF. Multiple myeloma. In: Schottenfeld D, Fraumeni JF Jr, editors. Cancer epidemiology and prevention. 2nd ed. New York (NY): Oxford University Press; 1996. p. 946–70.

(20) Tang L, Lucas AH, Eaton JW. Inflammatory responses to implanted polymeric biomaterials: role of surface-adsorbed immunoglobulin G. J Lab Clin Med 1993;122:292–300.

(21) Dorr LD, Bloebaum R, Emmanual J, Meldrum R. Histologic, biochemical, and ion analysis of tissue and fluids retrieved during total hip arthroplasty. Clin Orthop 1990;261:82–95.

(22) Wilkinson JD. Nickel allergy and orthopedic prostheses. In: Maibach HI, Menne T, editors. Nickel and the skin: immunology and toxicology, Boca Raton (FL): CRC Press; 1989. p. 187–93.

(23) Takagi M, Konttinen YT, Santavirta S, Kangaspunta P, Suda A, Rokkanen P. Cathepsin G and alpha 1-antichymotrypsin in the local host reaction to loosening of total hip prostheses. J Bone Joint Surg Am 1995;77:16–25.

(24) Silverman DT, Morrison AS, Devesa SS. Bladder cancer. In: Schottenfeld D, Fraumeni JF Jr, editors. Cancer epidemiology and prevention. 2nd ed. New York (NY): Oxford University Press; 1996. p. 1156–72.

(25) Graham DY. *Helicobacter pylori* infection is the primary cause of gastric cancer. J Gastroenterol 2000;35 Suppl 12:90–7.

(26) Akre K, Signorello LB, Engstrand L, Bergstrom R, Larsson S, Eriksson BI, et al. Risk for gastric cancer after antibiotic prophylaxis in patients undergoing hip replacement. Cancer Res 2000;60:6376–80.

(27) Farrow DC, Vaughan TL, Hansten PD, Stanford JL, Risch HA, Gammon MD, et al. Use of aspirin and other nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. Cancer Epidemiol Biomarkers Prev 1998;7:97–102.

(28) Thun MJ, Namboodiri MM, Calle EE, Flanders WD, Heath CW Jr. Aspirin use and risk of fatal cancer. Cancer Res 1993;53:1322–7.

(29) Arber N, DuBois RN. Nonsteroidal anti-inflammatory drugs and prevention of colorectal cancer. Curr Gastroenterol Rep 1999;1: 441–8.

(30) Smalley WE, DuBois RN. Colorectal cancer and nonsteroidal anti-inflammatory drugs. Adv Pharmacol 1997;39:1–20.

(31) Deal CL. Osteoporosis: prevention, diagnosis, and management. Am J Med 1997;102: 35S–39S.

(32) Lauritzen JB, McNair PA, Lund B. Risk factors for hip fractures. A review. Dan Med Bull 1993;40:479–85.

(33) Kolonel LN. Nutrition and prostate cancer. Cancer Causes Control 1996;7:83–94.

(34) Waalkes MP, Rehm S. Cadmium and prostate cancer. J Toxicol Environ Health 1994;43: 251–69.

(35) Gridley G, McLaughlin JK, Ekbom A, Klareskog L, Adami HO, Hacker DG, et al. Incidence of cancer among patients with rheumatoid arthritis. J Natl Cancer Inst 1993;85: 307–11.

(36) Mellemkjaer L, Linet MS, Gridley G, Frisch M, Moller H, Olsen JH. Rheumatoid arthritis and cancer risk. Eur J Cancer 1996;32A: 1753–7.

(37) Isomaki HA, Hakulinen T, Joutsenlahti U. Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. J Chronic Dis 1978;31:691–6.

(38) Gillespie WJ, Frampton CM, Henderson RJ, Ryan PM. The incidence of cancer following total hip replacement. J Bone Joint Surg Br 1988;70:539–42.

(39) Visuri T, Koskenvuo M. Cancer risk after McKee-Farrar total hip replacement. Orthopedics 1991;14:137–42.

(40) Gillespie WJ, Henry DA, O'Connell DL, Kendrick S, Juszczak E, McInneny K, et al. Development of hematopoietic cancers after implantation of total joint replacement. Clin Orthop 1996;(329 Suppl):S290–6.

NOTES

Funded by the International Epidemiology Institute.

Manuscript received February 13, 2001; revised July 17, 2001; accepted July 19, 2001.