

HIP AND KNEE IMPLANTATIONS AMONG PATIENTS WITH OSTEOARTHRITIS AND RISK OF CANCER: A RECORD-LINKAGE STUDY FROM DENMARK

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A nationwide cohort study of hip and knee replacement patients in Denmark was undertaken to assess any carcinogenic potential of these implants. A cohort of 22,997 osteoarthritis patients who received hip replacements and of 4,771 osteoarthritis patients who received knee replacements during the period 1977 through 1989 were identified using the nationwide Danish Hospital Discharge Registry. These patients were followed for cancer occurrence through 1993, using the Danish Cancer Registry. There was no overall excess of cancer in either the hip implant cohort [standardized incidence ratio (SIR) = 0.94; 95% confidence interval (CI) = 0.91–0.98] or the knee implant cohort (SIR = 0.97; 95% CI = 0.89–1.06). The risk reduction in both groups of patients reflected for the most part reduced risks for cancers of the respiratory system and the digestive tract, particularly stomach cancer (SIR = 0.69; 95% CI = 0.50–0.81 for hip replacement patients; SIR = 0.46; 95% CI = 0.20–0.91 for knee replacement patients). Elevated risks were observed for melanoma of the skin in both groups of patients. There was no clear excess risk for lymphohematopoietic cancers or malignant neoplasms of the bone or connective tissue among implant patients in either implant group. Contrary to an earlier study in Sweden, we did not find an excess risk for kidney or prostate cancers. In summary, these nationwide results indicate no overall cancer hazard among hip and knee implant patients, but limited follow-up warrants continued surveillance of individuals undergoing these increasingly common surgical procedures. *Int. J. Cancer* 81:719–722, 1999.

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Although concern has been expressed over the carcinogenic potential of metallic implants such as hip and knee replacements, there has been relatively limited epidemiologic research on this topic (Sunderman, 1989; Coleman, 1996). A number of the materials used in hip and knee implants are considered to be carcinogenic in humans, including chromium, beryllium, nickel and cadmium, while other materials such as cobalt, zinc and titanium have been found to cause cancer in animal models (Sunderman, 1989; Snow, 1992; Dunn and Maxian, 1994; Park *et al.*, 1995). There has also been concern about tumor formation at or near the joint replacement, based solely on case reports (Apley, 1989; Goodfellow, 1992).

In earlier epidemiologic studies, an excess of hematopoietic cancers was reported among implant recipients (Gillespie *et al.*, 1988; Visuri and Koskenvuo, 1991), although more recent and larger studies have not confirmed this observation (Nyren *et al.*, 1995; Mathieson *et al.*, 1995; Visuri *et al.*, 1996; Gillespie *et al.*, 1996). In the largest study to date, a nationwide investigation of hip replacement patients in Sweden, Nyren *et al.* (1995) reported a statistically significant reduction in risk for stomach cancer and significantly elevated risk ratios for cancers of the prostate and kidney.

Due to the increasing use of joint replacement prostheses and the increasing length of time they are in place in the body and the subsequent longer exposure to wear and corrosion products of prosthetic devices, evaluation of any potential carcinogenic risk is of growing public health concern (Sunderman, 1989; Galante *et al.*, 1991; Snow, 1992; Coleman, 1996). In order to assess any long-term cancer risk associated with hip and knee implants, we

examined 2 nationwide cohorts of Danish patients, one which received hip replacements and the other knee replacements due to osteoarthritis during the period 1977–1989.

MATERIAL AND METHODS

The Danish Hospital Discharge Registry (HDR), established in 1977, is a centralized register that keeps information on virtually all non-psychiatric hospitalizations in Denmark. Each admission record includes the personal identification number of the individual, a code for hospital department, dates of admission and discharge, surgical procedures performed during the admission, classified according to the Danish Classification of Surgical Procedures and Therapies and up to 20 discharge diagnoses, classified according to the Danish modified version of the International Classification of Diseases, 8th Revision (ICD-8). The personal identification number, which is unique to every Danish citizen, incorporates sex and date of birth and permits accurate linkage of information between registers, including the Central Population Register, which supplies information on vital status and migration of all inhabitants of the country. The use of the personal identification number also ensures that a full in-patient history can be established for any individual notified to the HDR.

The 2 study cohorts were identified from the HDR for the period 1977–1989: (i) 25,968 patients notified under the combined codes for idiopathic osteoarthritis of the hip (ICD-8 code 713.00) and hip implantation (op-code 8274, 70032 or 70033); and (ii) 5,903 patients notified under the combined codes of osteoarthritis of the knee (ICD-8 code 713.01) and knee implantation (op-code 8280, 70042 or 70043). Excluded from the hip and knee replacement cohorts, respectively, were 788 and 183 patients (3.0% and 3.1%) who died within 1 year from the replacement operation, 1,427 and 741 patients (5.5% and 12.6%) who prior to the operation were admitted to hospital for a connective tissue disease, rheumatoid arthritis included, and 756 and 208 patients (2.9% and 3.5%) admitted to hospital for bone fracture of the hip, knee or ankle prior to the date of replacement operation, leaving 22,997 patients with hip replacement and 4,771 patients with knee replacement for follow-up (Table I). Patients with rheumatoid arthritis and other connective tissue diseases were excluded because of the link reported between these diseases and malignant lymphomas (Gridley *et al.*, 1993; Mellemkjaer *et al.*, 1996, 1997), while patients with bone fracture of lower limbs were excluded in order to avoid a possible confounding effect of tobacco smoking and alcohol abuse, as bone fractures are linked with these exposures and with increased risk for subsequent osteoarthritis (Pinals, 1993; Cumming *et al.*, 1997).

Also from the files of the HDR during the same period, 2 nationwide non-implant comparison cohorts were established,

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TABLE I—DESCRIPTIVE CHARACTERISTICS OF PATIENTS WITH OSTEOARTHRITIS OF THE HIP OR KNEE WHO UNDERWENT JOINT REPLACEMENT SURGERY, 1977–1989

Characteristic	Replacement of ¹	
	Hip	Knee
Patients notified in the HDR	25,968 (100)	5,903 (100)
Exclusions due to		
Death during 1st year of follow-up	788 (3.0)	183 (3.1)
Connective tissue disease prior to entry	1,427 (5.5)	741 (12.6)
Bone fracture prior to entry	756 (2.9)	208 (3.5)
Number of persons at entry	22,997 (88.6)	4,771 (80.8)
Both sexes	22,997 (100)	4,771 (100)
Male	10,574 (46)	1,262 (26)
Female	12,423 (54)	3,509 (74)
Age at joint replacement surgery (years)		
<60	4,317 (19)	580 (12)
60–69	8,070 (35)	1,440 (30)
70–79	9,029 (39)	2,302 (48)
>80	1,581 (7)	449 (9)
Year of joint replacement surgery		
1977–1980	4,783 (21)	500 (10)
1981–1984	7,899 (34)	1,142 (24)
1985–1989	10,315 (45)	3,129 (66)

¹Data are presented as numbers with percentages in parentheses.

composed of 16,661 patients with osteoarthritis of the hip but without alloplastic surgery and 22,696 with osteoarthritis of the knee, also without alloplastic surgery. The same exclusion criteria used in the formation of the 2 implant replacement cohorts were used in identifying the non-implant cohorts.

Information on cancer occurrence among cohort members was obtained through linkage to the Danish Cancer Registry, which collects information on all individuals in Denmark with cancer, including benign brain tumors and bladder papillomas; cancers were classified according to the modified Danish version of the International Classification of Diseases, 7th Revision (ICD-7) (National Board of Health, 1997). The follow-up in the hip and knee replacement cohorts began 1 year after the date of hospital discharge for the implantation surgery and ended at the date of hospital discharge with a connective tissue disease, date of death, or 31 December 1993, whichever occurred first. The follow-up in the 2 comparison cohorts began 1 year after the date of hospital discharge for hip or knee osteoarthritis and ended at the date of a hip or knee implantation (if any), date of death, or 31 December 1993, whichever occurred first. The numbers of cancer cases observed in each of the implant cohorts were compared with the numbers expected on the basis of age-, sex- and calendar year-specific rates from the Danish Cancer Registry. Standardized incidence ratios (SIRs) were calculated as the ratio of the observed to the expected numbers of cancer cases, and 95% confidence intervals (CIs) were calculated assuming a Poisson distribution of the observed cancers (Bailar and Ederer, 1964).

RESULTS

As shown in Table I, there were more women than men included in both the hip and knee implant study cohorts. For the hip replacement patients, a total of 180,000 person-years of follow-up were accrued (average: 6.9 years; range: 1–17 years). For patients receiving knee replacements, 31,000 person-years were accrued (average: 5.3 years; range: 1–17 years). The median age at implant was 68 years for hip and 70 years for knee replacements.

Overall, 3,304 cancers were reported in patients with hip implantation, a total significantly less than the 3,498 cancers expected based on rates from the general population (SIR = 0.94; 95% CI = 0.91–0.98) (Table II). The observed deficit in total cancer was due mainly to significantly reduced risks of cancers of

the stomach, colon, larynx and lung. Risk for breast cancer was close to expectation, while those for cancers of the corpus uteri and ovary were elevated. The SIR for malignant melanoma of the skin was also significantly elevated. There were 4 bone cancers observed vs. 2 expected and 10 connective tissue tumors compared with 8.4 expected. None occurred at or near the site of implant. Cancers of the lymphohematopoietic system were slightly in excess, mostly due to an elevated risk of non-Hodgkin's lymphoma. Risks of multiple myeloma and leukemia were slightly below and above expectation, respectively (Table II).

Table II also presents results for patients with knee replacement surgery due to osteoarthritis. Overall, cancer occurrence in this cohort was slightly below expectation (574 cancers observed vs. 590.3 expected; SIR = 0.97; 95% CI = 0.89–1.06). Reduced SIRs were seen for cancers of the buccal cavity and pharynx, esophagus, stomach, colon and rectum, with the SIR for stomach cancer being significantly low. Risks were also reduced for cancers of the lung, kidney and brain, although none was statistically significant. In contrast to hip replacement patients, the risk for ovarian cancer was reduced, although the risk for cancer of the corpus uteri was significantly elevated, consistent with the elevated risk observed among hip replacement patients. Also elevated was the risk for malignant melanoma, paralleling the risk in hip replacement patients. No cancers of the bone were observed (0.3 expected) and 2 connective tissue cancers were seen compared with 1.4 expected. Neither connective tissue tumor occurred at or near the site of implant. Overall there was no excess of hematopoietic tumors, despite some increased risk of Hodgkin's disease based on 2 cases, and reduced SIRs for multiple myeloma and leukemia.

In a further examination of the reduced risks for cancers of the stomach, colon and rectum, we combined patients from both implant cohorts (Table III). For all patients combined, the risk of stomach cancer was lowered by 38%, with significantly reduced SIRs for each latency period and the lowest risk 10–16 years after joint implantation. In patients with a discharge diagnosis of osteoarthritis of the hip or knee but without joint replacement surgery, there was no reduced risk of stomach cancer (SIR = 1.00). Among implant patients, there was no clear pattern of risk reduction over time for cancers of the colon or rectum. There was also no clear temporal pattern of changing risk for the slightly increased risks of lymphohematopoietic cancers, or for the significantly elevated risks of cutaneous melanoma or ovarian cancer (data not shown).

DISCUSSION

The results of this nationwide study of Danish patients who received hip and knee replacements are reassuring, since both cohorts of implant patients had an overall cancer risk below expectation. Both implant groups also had reduced risks of several cancers of the digestive tract, particularly of the stomach. On the other hand, the risks among hip replacement recipients were significantly elevated for malignant melanoma of the skin and cancer of the ovary, while the risks among knee replacement patients were also increased for melanoma, but reduced for ovarian cancer. Cancer of the corpus uteri was elevated in both groups, reaching statistical significance among knee replacement patients. Cancers of the lymphohematopoietic system, although significantly elevated in 2 earlier studies (Gillespie *et al.*, 1988; Visuri and Koskenvuo, 1991), were not materially increased in the present investigation.

Our observation of a marked reduction in the risk of stomach cancer in both implant cohorts supports the findings by Nyrén *et al.* (1995) and Visuri *et al.* (1996) in their studies of hip replacement patients in Sweden and Finland. In the nationwide study from Sweden, the risk of stomach cancer decreased with time since implant surgery. We also found the lowest risk among those patients with the longest time since implant. Nyrén *et al.* (1995) hypothesized that this decreased risk may be due to the prophylac-

TABLE II – SIR AND 95% CI FOR CANCER OCCURRENCE AMONG OSTEOARTHRITIS PATIENTS WHO UNDERWENT HIP OR KNEE REPLACEMENT SURGERY

Site of cancer	Hip replacement			Knee replacement		
	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)
All malignant neoplasms	3,304	3,498.0	0.94 (0.91–0.98)	574	590.3	0.97 (0.89–1.06)
Buccal cavity and pharynx	53	59.9	0.88 (0.66–1.16)	4	8.9	0.45 (0.12–1.16)
Esophagus	31	35.5	0.87 (0.59–1.24)	2	5.4	0.37 (0.04–1.33)
Stomach	71	110.9	0.64 (0.50–0.81)	8	17.2	0.46 (0.20–0.91)
Colon	281	333.9	0.84 (0.75–0.95)	59	61.4	0.96 (0.73–1.24)
Rectum	153	170.6	0.90 (0.76–1.05)	26	27.8	0.94 (0.61–1.37)
Liver	45	35.5	1.27 (0.93–1.70)	7	5.7	1.23 (0.49–2.54)
Biliary tract	33	35.5	0.93 (0.64–1.31)	9	7.0	1.29 (0.59–2.45)
Pancreas	105	108.4	0.97 (0.79–1.17)	23	19.2	1.20 (0.76–1.80)
Larynx	17	28.1	0.60 (0.35–0.97)	1	3.3	0.30 (0.00–1.68)
Lung	322	438.7	0.73 (0.66–0.82)	47	60.2	0.78 (0.57–1.04)
Breast	289	280.3	1.03 (0.92–1.16)	83	67.4	1.23 (0.98–1.53)
Cervix uteri	37	35.6	1.04 (0.73–1.43)	10	8.2	1.21 (0.58–2.23)
Corpus uteri	84	70.3	1.20 (0.95–1.48)	28	16.6	1.68 (1.12–2.44)
Ovary	75	58.9	1.27 (1.00–1.60)	9	13.9	0.65 (0.30–1.23)
Prostate	280	274.6	1.02 (0.90–1.15)	28	27.7	1.01 (0.67–1.46)
Testis	6	3.1	1.96 (0.72–4.27)	0	0.3	—
Kidney	87	93.9	0.93 (0.74–1.14)	10	15.5	0.65 (0.31–1.19)
Bladder	219	230.2	0.95 (0.83–1.09)	37	31.4	1.18 (0.83–1.63)
Melanoma of skin	80	54.6	1.47 (1.17–1.83)	15	9.8	1.53 (0.85–2.52)
Other skin	555	538.1	1.03 (0.95–1.12)	90	94.0	0.96 (0.77–1.18)
Brain	55	57.1	0.96 (0.73–1.25)	7	10.0	0.70 (0.28–1.44)
Thyroid	6	9.4	0.64 (0.23–1.40)	3	1.9	1.62 (0.32–4.72)
Bone	4	2.0	2.01 (0.54–5.15)	0	0.3	—
Connective tissue	10	8.4	1.20 (0.57–2.20)	2	1.4	1.42 (0.16–5.12)
All hematopoietic neoplasms	226	201.7	1.12 (0.98–1.28)	32	34.3	0.93 (0.63–1.31)
Non-Hodgkin's lymphoma	86	71.9	1.20 (0.96–1.48)	13	12.8	1.01 (0.54–1.73)
Hodgkin's disease	8	6.3	1.27 (0.55–2.50)	2	1.0	2.01 (0.23–7.27)
Multiple myeloma	38	39.8	0.96 (0.68–1.31)	6	6.7	0.89 (0.33–1.94)
Leukemia	94	83.7	1.12 (0.91–1.37)	11	13.8	0.80 (0.40–1.43)

TABLE III – SIR AND 95% CI FOR CANCER OF THE STOMACH, COLON AND RECTUM AMONG COHORTS OF PATIENTS WITH OSTEOARTHRITIS OF THE HIP OR KNEE BY TREATMENT, SEX AND LATENCY PERIOD

Site sex and latency	Osteoarthritis and surgery			Osteoarthritis, no surgery		
	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)
<i>Stomach</i>						
Total	79	128.1	0.62 (0.5–0.8)	149	148.9	1.00 (0.9–1.2)
Men	49	73.0	0.7 (0.5–0.9)	66	63.8	1.0 (0.8–1.3)
Women	30	55.1	0.5 (0.4–0.8)	83	85.1	1.0 (0.8–1.2)
Latency (years)						
1–4	37	62.5	0.6 (0.4–0.8)	93	89.7	1.0 (0.8–1.3)
5–9	34	49.3	0.7 (0.5–1.0)	44	45.4	1.0 (0.7–1.3)
10–16	8	16.3	0.5 (0.2–1.0)	12	13.8	0.9 (0.5–1.5)
<i>Colon</i>						
Total	340	395.2	0.86 (0.8–1.0)	372	397.0	0.94 (0.8–1.0)
Men	156	168.7	0.9 (0.8–1.1)	116	125.5	0.9 (0.8–1.1)
Women	184	226.5	0.8 (0.7–0.9)	256	271.4	0.9 (0.8–1.1)
Latency (years)						
1–4	141	177.2	0.8 (0.7–1.0)	209	216.3	1.0 (0.8–1.1)
5–9	138	159.9	0.9 (0.7–1.0)	117	132.0	0.9 (0.7–1.1)
10–16	61	58.1	1.0 (0.8–1.4)	46	48.6	0.9 (0.7–1.3)
<i>Rectum</i>						
Total	179	198.3	0.90 (0.8–1.0)	159	189.5	0.84 (0.7–1.0)
Men	95	108.8	0.9 (0.7–1.1)	66	82.8	0.8 (0.6–1.0)
Women	84	89.5	0.9 (0.8–1.2)	93	106.7	0.9 (0.7–1.1)
Latency (years)						
1–4	85	91.6	0.9 (0.7–1.2)	93	104.6	0.9 (0.7–1.1)
5–9	64	78.8	0.8 (0.6–1.0)	46	61.8	0.7 (0.5–1.0)
10–16	30	28.0	1.1 (0.7–1.5)	20	23.1	0.9 (0.5–1.3)

tic use of antibiotics by patients undergoing implant surgery, thus eradicating *Helicobacter pylori* bacteria, a major risk factor for gastric cancer development (IARC, 1994). We did not have information on the drugs used by the implant recipients, but the duration of antibiotic use both pre- and postoperatively tends to be long and probably sufficient to eliminate *H. pylori* infection in a

number of patients. Nyrén *et al.* (1995) also suggested that the use of non-steroidal anti-inflammatory drugs (NSAIDs) may have contributed to the reduced risk of gastric cancer, but this explanation seems unlikely since we observed no decreased risk among patients with osteoarthritis of the hip or knee who did not undergo replacement even though presumably they continued using NSAIDs

for pain relief for longer periods of time in the absence of joint replacement.

It is possible that NSAIDs contributed to the lowered risks of colon and rectum cancers in both implant cohorts, but the reductions were modest and not statistically significant, except for colon cancer among hip replacement patients. A number of previous studies (Gillespie *et al.*, 1988; Visuri *et al.*, 1996; Lewold *et al.*, 1996), although not all (Nyrén *et al.*, 1995), have reported lowered risks of colon or rectal cancer among implant patients. The reduced SIR for lung cancer in our study is consistent with most previous studies, which have reported slightly to moderately lowered risks (Gillespie *et al.*, 1988; Nyrén *et al.*, 1995; Mathieson *et al.*, 1995; Visuri *et al.*, 1996; Lewold *et al.*, 1996). The reason is unclear, but it is likely that patients who receive implant operations may smoke less than the general population, particularly since we found that most smoking-related cancers were reduced in both implant groups.

Based on clinical and experimental observations (Apley, 1989; Sunderman, 1989; Goodfellow, 1992; Coleman, 1996), implant patients may be prone to cancers of the bone and connective tissue, particularly at the site of implant. In neither cohort were these tumors in significant excess, nor were any tumors located at the site of the implant. In addition, we could not confirm the excess risk of kidney and prostate cancers reported in the nationwide study in Sweden (Nyrén *et al.*, 1995). However, consistent with the Swedish study, we found little evidence of an excess risk for lymphatic and hematopoietic neoplasms as reported earlier in 2 smaller cohorts (Gillespie *et al.*, 1988; Visuri and Koskenvuo, 1991).

The significant increase we observed in ovarian cancer risk among hip replacement patients was not seen among knee replacement recipients, who experienced a 35% reduction in risk. This inconsistency and the fact that earlier studies have not reported such an increased risk for ovarian cancer suggest the play of chance in this result. However, the elevated risks for endometrial cancer among implant patients is probably real and due to confounding by obesity, a known risk factor for this type of cancer (Grady and Ernster, 1996). In addition, our finding of an elevated risk of malignant melanoma of the skin following hip and knee replacement recipients supports the earlier finding of Nyrén *et al.* (1995). The mechanism is unclear, although diagnostic surveillance may play a role.

In conclusion, the overall results of our nationwide study of Danish patients undergoing hip or knee replacement surgery are reassuring, revealing a slight deficit of total cancer. The markedly reduced risk of stomach cancer supports the hypothesis that prophylactic use of antibiotics among implant patients eradicates *H. pylori*, a major etiologic agent for this cancer. The significantly elevated risk for ovarian cancer observed among hip replacement patients was balanced by a reduced risk following knee replacement, suggesting a chance finding. The increased risk for cutaneous melanoma in both implant groups deserves further study, but may be partly related to diagnostic surveillance. Continued monitoring of implant patients is needed to more thoroughly assess the long-term consequences of metallic and other types of implants, which are becoming more common and are remaining in the body for longer periods of time than in the past.

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