Cancer after Total Joint Arthroplasty: A Meta-analysis

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Abstract

Background: **Some epidemiologic and laboratory studies have suggested that total joint arthroplasty could increase the risk of cancer. In this meta-analysis, we attempt to clarify the association of joint arthroplasty with subsequent cancer incidence.**
Methods: **We identified population-based studies reporting standardized incidence ratios (SIR) for cancer following large joint arthroplasty. After summing the observed and expected numbers of cases across all qualifying studies, we calculated SIRs for all cancers, and for those at 28 anatomic sites. Latency analysis involving 175,166 patients characterized short-term and long-term cancer associations.**
Results: **The analyses included 1,435,356 person-years of follow-up and 20,045 cases of cancer. Overall cancer risk among patients with arthroplasty was equal to that for the general population. The relative risk of lung cancer, reduced in the first 5 years after arthroplasty, increased significantly over time to approach that of the general population. Risks for all sites in the luminal gastrointestinal tract were significantly reduced by 10% to 20%; with relative risks that were generally stable over time. Increased risks were seen for cancer of the prostate (SIR, 1.12; 95% confidence interval, 1.08-1.16); similar relative risks were seen in each time period after the procedure. For melanoma, relative risks increased with follow-up to a SIR of 1.43 (95% confidence interval, 1.13-1.79) for 10 or more years after arthroplasty. There was a similar delayed emergence of increased risks for cancers of the urinary tract and oropharynx. The relative risk for bone cancer decreased with time after the procedure.**
Conclusions: **There does not seem to be an overall increased risk of cancer following total joint arthroplasty. Although the risks of prostate cancer and melanoma seem to be elevated, there is no obvious mechanism for these associations. Reductions in risk for some malignancies may not be causal.** (Cancer Epidemiol Biomarkers Prev 2006;15(8):1532–7)

Introduction

Total joint arthroplasty (TJA) of the hip and knee rank among the most commonly done major surgical procedures in the U.S. and Europe (1). As arthroplasties are done earlier in life, and the patients receiving them are, in general, living longer, joint prostheses have increasing residence times *in situ* (2). Many of the materials in joint prostheses (and in the debris particles) are known or suspected to be carcinogenic, including chromium, beryllium, nickel, zinc, titanium, and polymethylmethacrylate (3-9). In addition to local effects at the site of implantation, corrosion and wear of implants may lead to systemic distribution of metallic alloy, synthetic polymer, or ceramic matter (10, 11). Indeed, case reports have suggested associations of joint prostheses with adjacent soft tissue or bone sarcomas (12, 13), and some epidemiologic studies have associated TJA with an increased risk of specific malignancies (14, 15).

Early epidemiologic studies suggested an increased risk of hematopoietic cancers following TJA of the hip or knee (16, 17). Although the majority of subsequent studies have not confirmed this association (14, 18-24), excess risks of melanoma, multiple myeloma, lymphoma, and cancer of the prostate and bladder have been reported in some studies (15, 25), as well as a reduced risk of stomach cancer (14, 23). A recent meta-analysis investigated site-specific cancer risk among Nordic cohorts and found reductions in risk of several cancers and elevations in a few others (26). However, this analysis did not consider the patterns of cancer occurrence over time, and so did not take into account the latency associated with the effects of most cancer risk factors (26). Because most cancers are thought to require years or decades to develop, associations that emerge very soon after the surgery may well reflect the characteristics and previous exposures of the patients who have TJA, rather than the effects of the procedure itself. In contrast, those that emerge later are more likely to reflect the effect of the arthroplasty.

To investigate the possibility of delayed effects of TJA (or overall effects at uncommon cancer sites), we combined data from seven primary studies to provide overall and time-specific summary estimates of relative risk. We also conducted separate analyses for total hip replacement, total knee replacement, as well as analyses stratified by gender.

Materials and Methods

We attempted to identify all published articles containing quantitative population-based data on TJA and cancer through MEDLINE database searches and review of references. We searched the database for articles published between January 1966 and to October 2004, using the keywords, ''joint, arthroplasty, joint prosthesis, total knee replacement, total hip replacement, and cancer, neoplasm, hematopoietic, tumor, or sarcoma.'' We also scanned previous reviews and the bibliographies of candidate articles to widen our search. The search revealed 15 articles, which were independently reviewed by the authors to determine eligibility for the meta-analysis (14-28). Studies were included if they ascertained essentially all total hip arthroplasties (THA) or total knee arthroplasties (TKA) in a population, and reported site-specific cancer standardized incidence ratios (SIR) compared with the corresponding general population, or the data needed to calculate those values. We required the data to take into account the age and sex structure of the population by

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applying age- and sex-adjusted population rates in the computations of the expected numbers of cases.

Six studies were excluded for the following reasons: (*a*) patient population partially included in a subsequently published larger study (14, 21, 24), (*b*) arthroplasty on a joint(s) other than the hip or knee (27), (*c*) meta-analysis (26, 28). For latency analyses, we included only studies from which we were able to obtain data corresponding to latency periods of 1 to 4 years, 5 to 9 years, and >10 years of follow-up. In total, data from >242,000 hip and knee arthroplasties were included in our analyses of cancer risk by site, and >175,000 for the latency analyses (Table 1).

Statistical Methods. We abstracted the observed and expected number of cancer cases by cancer site (or groups of sites) from the articles included. If the number of expected cases was not reported, we calculated those values by dividing the number of observed cases by the reported SIR. Pooling available data by cancer site, we compiled the number of observed and expected cases separately. SIRs were calculated by dividing the number of observed cases by the number expected; 95% confidence intervals (CI) were calculated for each SIR assuming a Poisson distribution of the number of observed cases. When the observed number of cases was <1,000, we used tabulated values of 95% confidence limits to estimate the CIs (29), whereas a standard approximation calculation was used with >1,000 observations (30).

Across studies, some cancer sites were reported with differing nomenclature, or grouped with related anatomic or physiologic sites. To address these inconsistencies, we used International Classification of Disease codes (ICD-7) when available, and did analyses on a general anatomic or physiologic category when necessary (e.g., ''hepatobiliary'' for liver, gallbladder, and bile duct). Also, we contacted authors to clarify ambiguities, classifications, and in some instances, to receive additional data.

Separate analyses were done to assess risks by gender, and after THA and TKA. SIRs were compared between male and female populations using a two-sample z test based on the gender-specific SIRs and their SEs. Data were insufficient to compare unilateral versus bilateral TJA, TJA for rheumatoid arthritis versus that for osteoarthritis, or metal-on-metal prostheses versus those containing synthetic polymers.

We did a latency analysis over three time periods for all sites containing at least five observations in two or more time periods of observation. Only cancer of the uterus other than the corpus, and testicular cancer were excluded based on this criterion. Poisson regression was used to test the hypothesis of no trend over the three time periods after surgery (1-4, 5-9, and 10 or more years), with an offset equal to the total person-years during the time period.

In addition to the approach described above, we also aggregated studies using the conventional Cochrane paradigm of meta-analysis (http://www.cochrane.org/). That is, we weighted studies by the inverse of the square of the reported SE, and tested for heterogeneity using Cochrane's Q as well as calculating I^2, which is now used by *Cochrane Reviews*, and measures the percentage of variation across all studies due to heterogeneity rather than chance (31). When heterogeneity was evident, we calculated SIRs using random effects models (32). These methods yielded SIR estimates that were very similar to those calculated using the approach described above and are not presented.

Results

A total of 173,166 patients who had received hip replacements and 58,777 patients who had knee replacements were included in the analyses. Together, they generated 1,365,959 person-years of follow-up and 20,045 cases of cancer. In the studies that reported the relevant data, 63% of TJA patients were female (145,865 women and 84,730 men). Four studies that provided data which permitted the computation of SIRs by gender included a combined follow-up of 1,094,191 person-years, 70,974 arthroplasties and 5,862 cancers for men, and 118,173 arthroplasties and 6,493 cancers for women. The mean age at surgery was 69.7 years, with only minimal differences between men and women. Latency data were available from five studies that included 192,976 arthroplasty patients (15, 18, 19, 22, 23, 25), 1,293,608 person-years of observation, and 15,178 cancers.

The combined data yielded an overall cancer SIR of 0.98 (95% CI, 0.96-0.99) (Table 2). Risk for all cancers combined was not significantly different than expected within any latency period (Table 2). However, there was a modest but highly statistically significant positive trend across the three periods, with the SIR after 10+ years of follow-up equal to 1.02 (95% CI, 0.98-1.06).

Overall, there were apparent reductions in the risk of several malignancies. The most prominent were for three smoking-related cancers: lung cancer (overall SIR, 0.78; 95% CI, 0.74-0.82), cancer of the esophagus (overall SIR, 0.81; 95% CI, 0.68-0.95), and cancer of the larynx (overall SIR, 0.62; 95% CI, 0.43-0.88; Table 2). For lung cancer, there were trends of increasing SIRs over time, such that by 10 or more years after TJA, risks were similar to those for the general population. However, for cancer of the larynx, the low SIRs were present in each of the time periods post-TJA. Cancer of the mouth and pharynx showed a significantly increasing trend across time, rising to a SIR of 1.32 (95% CI, 1.02-1.72) 10 or more years after TJA (Table 2).

In the luminal gastrointestinal tract, cancer risks were significantly reduced following TJA; the SIRs were ~0.81 for cancers of the stomach, and ~0.90 for cancers of the colon and rectum (Table 2). These low SIRs were seen soon after TJA, and were more or less stable over follow-up (Table 2).

Risk of prostate cancer was increased after TJA (overall SIR, 1.12; 95% CI, 1.08-1.16); this modest increase was present

Table 1. Characteristics of studies included in the meta-analysis

Study	Total	Men	Women	Person-years	Period of arthroplasty	End of follow-up period	Mean follow-up time, years per patient
THA							
(15)	116,727	45,249	71,478	693,954	1965-1994	1995	6.9
(23)	31,651	11,591	20,060	199,996	1980-1995	1995	6.4
(22)	22,997	10,574	12,423	180,000	1977-1989	1993	6.9
(18)	1,358	Not given	Not given	14,286	1966-1973	1983	10.5
(17)	433	164	279	5,729	1967-1973	1981	9.6
TKA							
(20)	10,120	3,184	6,936	40,000	1975-1989	1989	4.0
(22)	4,771	1,262	3,509	31,000	1977-1989	1993	5.3
(25)	9,444	2,001	7,443	51,756	1980-1995	1996	5.5
(18)	30,011	9,629	20,382	122,616	1980-1984	1995	4.3

Table 2. Overall postarthroplasty cancer risk and trend in cancer risk over three latency periods

Studies	Overall (n = 9)		1-4 years (n = 5)		5-9 years (n = 5)		10+ years (n = 5)		P value for trend
Primary cancer site	Observed	SIR (95% CI)	Observed	SIR (95% CI)	Observed	SIR (95% CI)	Observed	SIR (95% CI)	
Total (all sites)	20,045	0.98 (0.96-0.99)	7,188	0.97 (0.96-1.00)	5,262	1.02 (0.99-1.05)	2,728	1.02 (0.98-1.06)	0.0033
Upper aerodigestive tract									
Mouth, pharynx	356	0.99 (0.89-1.10)	111	0.98 (0.81-1.18)	83	0.96 (0.77-1.20)	60	1.32 (1.02-1.72)	0.0085
Esophagus	149	0.81 (0.68-0.95)	60	0.99 (0.76-1.29)	31	0.65 (0.44-0.93)	17	0.79 (0.46-1.27)	0.1003
Gastrointestinal tract									
Stomach	737	0.82 (0.76-0.88)	297	0.83 (0.74-0.93)	225	0.82 (0.71-0.93)	101	0.75 (0.62-0.92)	0.2177
Colon	1,618	0.91 (0.87-0.96)	614	0.90 (0.83-0.98)	524	0.94 (0.86-1.03)	261	0.93 (0.82-1.05)	0.2912
Rectum	895	0.90 (0.84-0.96)	355	0.91 (0.82-1.01)	276	0.89 (0.79-1.01)	146	0.96 (0.81-1.13)	0.3745
Hepatobiliary	508	1.00 (0.91-1.09)	170	0.98 (0.84-1.14)	133	0.99 (0.83-1.18)	65	0.90 (0.70-1.16)	0.3264
Pancreas	649	0.96 (0.89-1.04)	187	0.92 (0.79-1.06)	154	0.96 (0.82-1.13)	73	0.86 (0.68-1.09)	0.3936
Respiratory tract									
Lung	1,369	0.78 (0.74-0.82)	429	0.77 (0.70-0.84)	333	0.83 (0.75-0.93)	175	0.95 (0.82-1.11)	0.0110
Larynx	32	0.62 (0.43-0.88)	5	0.65 (0.21-1.52)	5	0.74 (0.24-1.73)	2	0.66 (0.08-2.38)	0.4721
Reproductive tract									
Breast	2,247	0.98 (0.94-1.02)	684	0.95 (0.88-1.02)	498	0.94 (0.86-1.02)	307	1.08 (0.96-1.21)	0.0681
Cervix	149	0.98 (0.84-1.16)	55	1.05 (0.79-1.37)	31	0.88 (0.60-1.25)	14	0.81 (0.44-1.36)	0.1685
Corpus Uterus	455	1.00 (0.91-1.10)	180	1.06 (0.92-1.23)	110	0.89 (0.73-1.07)	47	0.73 (0.54-0.97)	0.0057
Ovary	407	1.02 (0.93-1.13)	150	1.11 (0.94-1.31)	75	0.79 (0.63-1.00)	46	0.98 (0.72-1.31)	0.0778
Prostate	3,009	1.12 (1.08-1.16)	1,175	1.13 (1.07-1.19)	954	1.18 (1.10-1.25)	468	1.10 (1.01-1.21)	0.4602
Urinary tract									
Kidney	553	1.05 (0.96-1.14)	182	1.07 (0.93-1.24)	137	1.07 (0.90-1.27)	78	1.22 (0.97-1.53)	0.2266
Bladder, ureters	1,031	1.02 (0.96-1.09)	282	0.97 (0.86-1.09)	261	1.13 (1.00-1.28)	146	1.15 (0.98-1.36)	0.0256
Skin									
Malignant melanoma	470	1.18 (1.08-1.29)	137	1.04 (0.87-1.23)	106	1.06 (0.87-1.29)	77	1.43 (1.13-1.79)	0.0401
Nonmelanoma	1,540	1.06 (1.00-1.11)	318	1.15 (1.03-1.29)	248	1.00 (0.88-1.13)	179	1.12 (0.96-1.30)	0.2643
Brain	371	1.03 (0.93-1.14)	151	1.11 (0.95-1.31)	91	0.90 (0.73-1.12)	33	0.83 (0.57-1.17)	0.0314
Thyroid	92	0.91 (0.74-1.12)	29	0.78 (0.52-1.12)	28	1.02 (0.68-1.48)	16	1.33 (0.76-2.15)	0.0582
Bone/Connective tissue	117	0.99 (0.82-1.19)	53	1.10 (0.83-1.45)	29	0.88 (0.59-1.26)	13	0.37 (0.20-0.63)	0.0000
Hematologic									
All hematopoietic	1,510	0.98 (0.93-1.03)	417	0.95 (0.86-1.05)	348	1.01 (0.91-1.12)	162	0.87 (0.74-1.02)	0.2389
Lymphoma	639	1.00 (0.93-1.08)	241	1.00 (0.88-1.14)	181	1.02 (0.88-1.18)	73	0.81 (0.64-1.02)	0.0778
Multiple myeloma	333	1.08 (0.97-1.20)	121	1.03 (0.86-1.23)	100	1.20 (0.98-1.46)	49	1.19 (0.88-1.57)	0.1401
All leukemia	434	0.95 (0.86-1.04)	145	0.89 (0.75-1.05)	110	0.96 (0.79-1.16)	45	0.79 (0.57-1.05)	0.3156
Leukemia or lymphoma	817	0.94 (0.87-1.00)	66	0.89 (0.69-1.14)	74	0.94 (0.74-1.18)	28	0.64 (0.42-0.93)	0.0778

during the first few years after the procedure, and did not vary substantially with follow-up (Table 2). There was also an increased risk of melanoma, but here the relative risks steadily increased with follow-up, to a SIR of 1.43 (95% CI, 1.13-1.79) 10+ years after TJA (P for trend = 0.04). Risks of bladder/ureter cancer also tended to increase over time to a SIR ~1.2 (Table 2).

For endometrial cancer, there were decreasing relative risks such that 10 or more years after TJA, the SIR was 0.73 (95% CI, 0.54-0.97; P for trend = 0.006; Table 2). Risks of bone/connective tissue cancer also decreased with time, to a SIR of 0.37 (95% CI, 0.20-0.63; P for trend < 0.0001) for 10+ years after surgery.

Patterns were broadly similar after THA and TKA (Table 3). However, in contrast to THR, there was an increased risk of cancer of the corpus uterus after TKA (SIR, 1.40; 95% CI, 1.09-1.81), as well as an increased risk of all hematopoietic cancers combined (SIR, 1.16; 95% CI, 1.03-1.29) and lymphomas (SIR, 1.20; 95% CI, 1.01-1.42). No latency data were available for TKA or THR separately, so the time patterns of these associations could not be assessed.

The SIR for all cancers in men (1.01; 95% CI, 0.99-1.04) was similar to that in women (0.99; 95% CI, 0.97-1.02; Table 4). However, for several cancers of the aerodigestive tract (oropharynx, esophagus, and lung) and urinary tract (kidney and bladder), the SIRs tended to be lower among men than among women. The differences were statistically significant for cancers of the lung and bladder. The decreased risk for colon cancer was specific to women, whereas that for the rectum was specific to men (Table 4). For women, the risk for non–melanoma skin cancer was elevated (SIR, 1.21; 95% CI, 1.09-1.34).

Tests for heterogeneity among the studies included in the SIR estimates showed a high degree of consistency for most cancers, and all three approaches of SIR estimation yielded similar results. Cochrane's Q test statistics suggested that the study-specific SIR's for most cancers were relatively homogenous ($P > 0.05$). The exceptions were cancers of the lung and oropharynx, with Cochrane's Q test P values of 0.02 and 0.00, respectively. I^2 values indicated a low proportion (<40%) of variance due to heterogeneity in cancer risk across almost all cancer sites (data not shown). However, for lung, oropharynx, and all hematopoietic (combined) cancers, 82%, 62%, and 48%, respectively, of the variation among studies was ascribed to heterogeneity. The results of these tests of heterogeneity suggest that SIR estimates in our meta-analysis are reasonably reliable for most sites, but confidence in the lung, oropharynx, and combined hematopoietic cancer SIR estimates may be lower.

Discussion

In this large meta-analysis, we found that overall cancer risk after THA or TKA is comparable to that in the general population. However, we found an early and persistent excess risk of prostate cancer after TJA, and an increased risk of melanoma that became evident 10 years postarthroplasty. There were beneficial associations for lung and laryngeal cancers as well as for luminal gastrointestinal tract cancers. For several of these, the risk reductions were most apparent soon after the procedure, and became less marked over time. The relative risk for cancers of the endometrium and bone were reduced after a latency of 10 years. With a few exceptions, overall patterns of cancer risk were broadly similar for hip and knee replacements. Differences in risk patterns between men and women were notable for cancers of the lung, skin, and urinary tract.

Table 3. Postarthroplasty cancer risk for hip and knee prostheses

Primary cancer site	Hip joint prostheses		Knee joint prostheses	
	Observed	SIR (95% CI)	Observed	SIR (95% CI)
Total (all sites)	15,896	0.98 (0.96-0.99)	3,827	0.97 (0.94-1.00)
Upper aerodigestive tract				
Mouth, pharynx	282	1.00 (0.89-1.13)	51	0.94 (0.70-1.24)
Esophagus	130	0.81 (0.68-0.97)	9	0.75 (0.34-1.43)
Gastrointestinal tract				
Stomach	585	0.79 (0.73-0.86)	145	0.85 (0.72-1.00)
Colon	1,278	0.91 (0.86-0.96)	306	0.88 (0.78-0.98)
Rectum	714	0.90 (0.84-0.97)	160	0.84 (0.72-0.99)
Hepatobiliary	430	1.00 (0.91-1.10)	69	0.94 (0.73-1.19)
Pancreas	491	0.93 (0.85-1.01)	144	1.04 (0.88-1.23)
Respiratory tract				
Lung	1,159	0.82 (0.77-0.86)	207	0.70 (0.60-0.80)
Larynx	31	0.70 (0.47-0.99)	1	0.30 (0.01-1.69)
Reproductive tract				
Breast	1,715	0.97 (0.92-1.01)	554	1.04 (0.96-1.13)
Cervix	127	0.95 (0.79-1.13)	14	0.97 (0.53-1.62)
Corpus Uterus	380	1.00 (0.91-1.11)	64	1.40 (1.09-1.81)
Ovary	332	1.08 (0.96-1.20)	70	0.89 (0.70-1.13)
Prostate	2,231	1.13 (1.09-1.18)	475	1.17 (1.07-1.29)
Urinary tract				
Kidney	458	1.06 (0.96-1.16)	88	1.03 (0.83-1.28)
Bladder, ureters	865	1.03 (0.96-1.10)	139	0.98 (0.82-1.16)
Skin				
Malignant melanoma	387	1.20 (1.08-1.32)	78	1.19 (0.95-1.49)
Nonmelanoma	1,234	1.06 (1.00-1.12)	331	0.98 (0.88-1.10)
Brain	286	1.02 (0.91-1.15)	97	1.21 (0.99-1.48)
Thyroid	75	0.87 (0.69-1.10)	13	0.71 (0.38-1.21)
Bone/connective tissue	90	0.96 (0.78-1.20)	28	1.15 (0.76-1.66)
Hematologic				
All hematopoietic	1,114	1.00 (0.94-1.06)	306	1.16 (1.03-1.29)
Lymphoma	483	0.98 (0.89-1.07)	142	1.20 (1.01-1.42)
Multiple myeloma	260	1.07 (0.95-1.21)	70	1.15 (0.90-1.46)
All leukemia	348	0.96 (0.86-1.06)	94	1.10 (0.89-1.35)
Leukemia or lymphoma	530	0.91 (0.84-1.00)	210	1.07 (0.93-1.23)

Total cancer incidence was not statistically different from expectations in any of the time periods included in the latency analysis, but there was a statistically significant trend of increasing risks over time. The trend was modest, and a likely explanation is the waning of an initial decrease in risk related to the selection of healthy patients. The effects of patient selection may also explain the gender differences in SIRs that we observed for some smoking-related cancers. Because in the age groups at risk for TJA, men smoke more than women (33), the corresponding selection effects will also be greater for men.

The increased risks of prostate cancer and melanoma after TJA are not as easily dismissed. Chromium, which is found in

Table 4. Postarthroplasty cancer risk by gender

Primary cancer site	Men		Women		*P* for interaction
	Observed	SIR (95% CI)	Observed	SIR (95% CI)	
Total (all sites)	5,862	1.01 (0.99-1.04)	6,493	0.99 (0.97-1.02)	0.26
Upper aerodigestive tract					
Mouth, pharynx	120	0.97 (0.81-1.16)	105	1.12 (0.92-1.36)	0.28
Esophagus	45	0.77 (0.56-1.03)	35	0.94 (0.66-1.31)	0.38
Gastrointestinal tract					
Stomach	303	0.83 (0.74-0.93)	240	0.77 (0.67-0.87)	0.39
Colon	593	0.98 (0.90-1.06)	793	0.88 (0.82-0.95)	0.05
Rectum	340	0.84 (0.76-0.94)	398	0.95 (0.86-1.05)	0.09
Hepatobiliary	108	1.03 (0.85-1.25)	196	0.98 (0.85-1.13)	0.68
Pancreas	152	1.03 (0.87-1.21)	227	0.98 (0.86-1.12)	0.64
Lung	422	0.83 (0.75-0.91)	262	0.98 (0.87-1.11)	0.03
Urinary tract					
Kidney	143	0.99 (0.84-1.17)	193	1.28 (1.11-1.48)	0.02
Bladder, ureters	409	1.01 (0.92-1.11)	206	1.16 (1.01-1.34)	0.10
Skin					
Malignant melanoma	143	1.21 (1.03-1.43)	162	1.09 (0.93-1.28)	0.36
Nonmelanoma	308	0.99 (0.88-1.10)	359	1.21 (1.09-1.34)	0.01
Brain	89	1.09 (0.88-1.35)	137	1.06 (0.89-1.26)	0.84
Thyroid	9	0.52 (0.24-0.99)	55	0.92 (0.70-1.21)	0.13
Hematologic					
Lymphoma	185	1.02 (0.88-1.18)	207	0.95 (0.82-1.09)	0.49
Multiple myeloma	106	1.14 (0.94-1.38)	119	1.08 (0.90-1.30)	0.68
All leukemia	114	0.86 (0.71-1.04)	153	1.05 (0.90-1.24)	0.11

some metallic implants, has been shown to induce prostatic tumors in rats (34), but this association has not been clearly seen in epidemiologic studies (35-39). Latency for metal-associated cancers is typically long, at least for occupational exposures (40), so the fact that an increased prostate cancer risk was seen within the first 5 years after the procedure suggests that the excess risk is probably not due to the prosthesis. A more likely explanation for the association is increased surveillance among arthroplasty patients, leading to higher detection rates in this population.

There is also no clear explanation for the trend of significantly increasing risks of melanoma over time. Others have suggested the possibility of heightened physician surveillance after arthroplasty or greater sun exposure in outdoor (and hence physical) occupations, thus being associated with increased osteoarthritis (17, 21). With the assumption that men work outdoors more than women, the latter explanation is consistent with our finding that the increased melanoma risk occurred only in males. However, one would expect these factors to diminish over time, not to increase as would be needed to explain an increasing SIR. Furthermore, there is no concomitant increase in non–melanoma skin cancer risk, as would be expected with a sun-related etiology. Physician surveillance even less plausibly applies to cancer of the mouth and pharynx; other than chance, there is no ready explanation for the delayed increased risk after TJA.

We found risk for cancer of the kidney to be increased beginning 10 years post-TJA, and for bladder cancer as early as 5 to 9 years after the procedure. Urinary excretion of metals provides a possible mechanism for these site-specific cancers (41-43), although there may not be a relationship between urinary output of metals and markers of chromosomal damage (44).

Previous reports linking TJA with increased risk of bone/connective tissue cancers were not corroborated in our overall analysis. Case studies, along with laboratory data, have implicated prosthetic joint materials in local cellular effects that can lead to bone or connective tissue cancers (12, 13, 45). One study in our meta-analysis showed an increase of these cancers in relation to TJA (18), but this excess was based on only three cases. In our pooled data, with 117 cases of bone and connective tissue cancer, there was no significant overall association, and long-term follow-up showed decreased risks after TJA.

Patients with osteoarthritis of the knee tend to be more overweight than those with osteoarthritis of the hip (46, 47). Because high body weight is a strong risk factor for endometrial cancer (48, 49), these patterns may explain the increased risk of that malignancy after TKA but not THA. However, there is no obvious mechanism to explain the decreasing risk over time after TJA. Increased activity after the procedure might plausibly decrease body weight, but that would be expected to decrease risk only to an average level, not below it.

Some laboratory studies have suggested a link between prosthetic biomaterials and risk of hematopoietic and lymphatic neoplasms (6), and several individual studies have found elevated SIRs for multiple myeloma (15), lymphoma (25), leukemia and lymphoma (24), or hematopoietic and lymphatic cancers in general after TJA. In individual studies, chance may account for these associations because different malignancies were identified in each study. Our meta-analysis does not support an association with hematopoietic cancers in general, although multiple myeloma showed a borderline significant, but consistent, increased risk beginning 5 years after TJA. Given the large number of associations examined in this report, it is quite possible that this is a chance finding.

There were decreased risks of several cancers after TJA. Some authors have speculated that the decreased risk of lung cancer after TJA may be attributed to a link between greater physical activity and lower lung cancer incidence or to a possible connection between postarthroplasty antibiotic use and lower incidence due to eradication of *Chlamydia pneumoniae* infection (26). Risk reduction could conceivably be due to reduced inflammation and less oxidative stress following TJA. However, it seems unlikely that these effects could act so rapidly that a marked reduction in risk of lung cancer could emerge as early as a few years after the procedure. Rather, the early emergence of the reduced risk suggests that it reflects the characteristics of those who undergo the procedure, in particular, the selection of healthy, non–smoking individuals for surgery. This selection bias may account for the observed risk reduction for lung cancer in men, but not in women, although further examination of this apparent difference is needed. The modest reductions in colon and stomach cancer risk we found have been previously noted (16, 20, 22, 23, 26) and explained by the high use of nonsteroidal antiinflammatory drugs in this patient population or (for stomach cancer) by the eradication of *Helicobacter pylori* in the stomach by postoperative antibiotics after TJA (23, 26). Our trend analysis is consistent with the former because the risk reductions for these gastrointestinal cancers were observed soon after TJA. It is not clear if the prophylactic antibiotics used after TJA would successfully eradicate *H. pylori*, and if so, whether the effect would be seen so soon after the procedure. Indeed, one study found little difference in the level of *H. pylori* antibodies between THA and control patients (50).

This meta-analysis has the advantage of using data from several large studies, each of which were able to assess TJA done on entire populations and follow-up subjects through high-quality cancer registries. Thus, the associations we observed are likely to reflect those that hold for TJA in general, rather than for a selection of patients.

However, several limitations were inherent in our study. Some TJA patients in our analysis probably had advanced rheumatoid arthritis, which is known to be associated with elevated risks of non–Hodgkins lymphoma and leukemia (51-55). At least two groups have reported an increased risk of lymphoma in rheumatoid arthritis after TJA, and the consistent elevation over latency periods suggests a link to the underlying disease, rather than to the arthroplastic intervention (20, 23). Also, heterogeneity among studies may limit the reliability of the pooled estimates for cancers of the lung and oropharynx. Furthermore, some findings in our latency analysis may be due, at least in part, to variability created by small numbers of subjects observed for various intervals. Finally, because we analyzed 28 specific cancer sites, some of the associations we observed are likely to have been due to chance.

This meta-analysis, which included all data available to date with site-specific cancer risk following TJA, was generally reassuring regarding cancer risk following the procedures. Reductions in risk for specific cancers can largely be explained by biases of various sorts, as can most of the findings of increased risk. Nonetheless, although the delayed increases in risk for melanoma and cancers of the urinary tract and oropharynx are likely to be the result of chance or bias, further long-term data would be welcome.

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