Cancer incidence after total knee arthroplasty

A nationwide Finnish cohort from 1980 to 1996 involving 9,444 patients

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A nationwide, computer-based survey of all total joint arthroplasties performed in Finland has been carried out since January 1980. From these records, a cohort of 9,444 patients, with 51,756 person-years, after primary operation with a total polyethylene-on-metal knee arthroplasty (TKA) was followed up for cancer through the Finnish Cancer Register up to December 31, 1996. During the follow-up, 706 cancers were observed. The expected number, based on national rates, was 719; therefore, the standardized incidence ratio (SIR) for all cancers was 0.98.

The SIRs for non-Hodgkin's lymphoma (1.40), Hodgkin's disease (1.24) and multiple myeloma (1.54) were increased, but only that of non-Hodgkin's lymphoma was statistically significant 3–10 years after the operation. The numbers of observed cases of prostate cancer exceeded that of expected, with a SIR value of 1.49.

A low SIR of lung cancer was observed among men, especially during the first 3 years (0.61), but not in women. The SIR for colon cancer was below unity in women only (SIR 0.70). The SIR for cancer of the urinary organs was close to unity (0.97).

SIR relating to soft tissue and bone cancer did not differ significantly from unity, and none of the 6 sarcomas was observed at the site of a prosthesis.

The overall cancer risk after TKA done for primary osteoarthrosis seems not to be increased. The increases in lymphoma and prostate cancer risk, however, are observations that could be related to TKA and justify further follow-up of the cohort.

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National arthroplasty records, e.g., in Sweden, Finland and Norway, show that the annual numbers of knee replacements have increased over the last decade to substantial levels (Havelin et al. 1993, Knutson et al. 1994, Paavolainen et al. 1995, Robertsson et al. 1997), and in the United States, the number of TKAs performed exceeds that of THAs. Bilateral operations have become more popular. The long-term survival of TKA already exceeds that of THA; the probability of an implant being in situ at 10 years is 95–97% (Ritter et al. 1989, Rand and Ilstrup 1991, Gill et al. 1997, Robertsson et al. 1997), and it may function for 20–30 years (Landy and Walker 1988).

It is not known whether patients as a consequence of prosthetic joint replacement are at an increased risk of developing cancer. All the materials used in the prosthetic joint replacement, i.e., metallic alloys (stainless steel- or crome-cobalt-alloys), plastic polymers (polyethylene), and cement (polymethylmethacrylate) have a potential carcinogenic effect (Rock 1993, Merrit and Brown 1996). So far, most such reports have dealt with the THA patients (Gillespie et al. 1988, Visuri and Koskenvuo 1991, Mathiesen et al. 1995, Nyren et al. 1995, Coleman 1996, Gillespie et al. 1996, Visuri et al. 1996, Paavolainen et al. 1999).

In cohorts who have undergone operations before 1973, presumably for fitting of metal-on-metal hip prostheses, there was a slight but significant excess risk of all-site cancers 10 or more years after THA and a sustained increase in the risk of lymphoma and leukemia following THA (Gillespie et al. 1988, Visuri and Koskenvuo 1991). Subsequent studies have not confirmed these initial findings (Mathiesen et al. 1995, Nyren et al. 1995, Gillespie et al. 1996, Visuri et

al. 1996). Similarly, the recent nationwide cohort from Finland, with more than 31,000 patients and more than 200,000 person-years found no association between THA and an increased incidence of cancer at any specific sites (Paavolainen et al. 1999). The only cohort study on TKA patients, with an arthroplasty done either for osteoarthrosis (OA) or rheumatoid arthritis (RA), showed a lower than expected total cancer incidence (Lewold et al. 1996).

We used the Finnish National Register of Arthroplasties and the Finnish Cancer Register to determine whether the pattern of risk of cancer in Finnish knee-replacement patients with total knee endoprostheses, because of primary arthrosis, was differed from the expected numbers based on national rates.

Patients and methods

TKA cohort

All TKA patients who underwent operation in Finland between 1980 and 1995 were identified in the National Register of Arthroplasties, maintained by the National Agency for Medicines (Paavolainen et al. 1991, 1995). Since 1 January 1967, each person resident in Finland has been given a unique personal identification number. These were obtained from the Finnish Population Register Center for all TKA patients. Dates of death or emigration were obtained from the same source.

Only patients who had undergone primary TKA and in whom primary arthrosis was the indication for operation were included in the final analysis. Patients who had undergone bilateral TKA were not studied separately (Mathiesen et al.1995). Since it has been reported that persons suffering from rheumatoid arthritis and other autoimmune diseases are at increased risk of non-Hodgkin's lymphoma and leukemia (Isomäki et al. 1978, Prior et al. 1984, Porter et al. 1991, Santana and Rose 1992), and since substantial consumption of antirheumatic drugs may also affect the risk of cancer (Gridley et al. 1993, Muscat et al. 1994, Kauppi et al. 1996), patients with rheumatoid arthritis were excluded.

Almost 80% of primary TKA patients were women. Over the 16-year period for which register data were studied, the annual incidence of TKAs increased in men twelvefold (from 2 to 23/100,000) and in women eightfold (from 10 to 76/100,000). Over 40% of those who underwent operation were below 65 years of age.

Implant-related factors

From 1980 to 1995, 15,189 primary TKAs were done for primary arthrosis. The 10 most popular designs of TKAs covered about 80% of those used during that time: Duracon (Howmedica) 2642, AGC2000 (Biomet) 2249, PCA-Modular (Howmedica) 1132, Miller-Galante I (Zimmer) 1115, P.F.C. (Johnson & Johnson) 1096, PCA (Howmedica) 1061, Miller-Galante II (Zimmer) 904, Synatomic (DePuy) 588, Townley (DePuy) 585, TCIV (Kirschner) 449. All of the prostheses, except Miller-Galante I and II, incorporate cobalt-chrome- (stainless-steel-) or cobalt-chrome-molybdenum- (vitallium-) alloys against polyethylene. No metal-on-metal articulations have been used since 1980. The percentage of the cemented component fixation on the femoral side was 46, and that of the tibial side 57. Palacos-with-Gentamyicin cement was used in 57% of the cases.

Follow-up and incidence of cancer

Follow-up for cancer was undertaken, using the files in the population-based, nationwide Finnish Cancer Register, employing personal identification numbers. Follow-up for cancer started on the date of first knee replacement and ended on emigration, death, or 31 December 1996, whichever occurred first. No subject was lost to follow-up. The 306 cancers diagnosed before TKA were left out of account.

The numbers of cases observed and person-years at risk were counted for 5-year age groups, separately for 3 periods (1980–85, 1986–1990 and 1991–1996). Expected numbers of cases of cancer overall and of specific types of cancer were calculated, by sex, and by 5-year age group, by multiplying numbers of person-years in each category by the corresponding average incidence of cancer in Finland as a whole. Data were further grouped by time since operation (0–2, 3–9 and 10 or more years). Specific types of cancer selected for analysis included cancers at sites in relation to which risk was known or suspected to be exceptional on

Table 1. Numbers of male and female knee-replacement patients in 1980 by age at operation, and numbers of person-years to 31 December 1996

Age at operation	Men		Women	
	n	Person-years	n	Person-years
30–44	15	47	20	69
45–59	249	818	562	1,786
60–74	1,294	5,581	4,929	21,804
+75	443	3,570	1,932	18,081
Total	2,001	10,016	7,443	41,740

the basis of results of previous studies of hip- or knee-replacement patients, and other common types of cancer.

Standardized incidence ratios (SIRs) were calculated by dividing observed numbers of cases by expected numbers. 95% confidence intervals (95% CIs) for SIRs were calculated, assuming that the number of cases observed followed a Poisson distribution.

Results

There were 2,001 men and 7,443 women left in the cohort to be followed up. The numbers of person-years were 10,016 and 41,740, respectively (Table 1). The mean duration of follow-up per person was therefore 5.5 years. Follow-up in relation to 52% of person-years was for less than 3 years after operation; 4% of person-years were more than 10 years after operation. At operation, there were 6,223 patients in the age category 60–74 years, and 2,375 patients in the category of more than 75 years.

During the 17-year follow-up period, 220 cases of cancer occurred in the men. The expected number was 213. In the women, 486 cases of cancer were observed vs. 506 expected.

When the data for men and women were combined, the SIR for cancer at all sites was 0.98 (Table 2). SIRs were significantly lower in relation to cancers of the lung (0.68), and colon (0.78). The less-than-expected incidence of lung cancer related particularly to male subjects, especially in the first three years following TKA (SIR 0.73, 95% CI 0.33–1.38); after that the risk ratio returned to unity. The incidence of risk of colon cancer was lower than would have been expected only in women (SIR 0.70, 95% CI 0.47–1.01); in the men, the SIR was 1.08 (95% CI 0.56–1.88).

Table 2. Observed (Obs) and expected (Exp) numbers of cancer cases and standardized incidence ratios (SIRs) with 95% confidence intervals (95% CI) in 9,444 Finnish knee-replacement patients followed from the date of first knee-replacement to the end of 1996

Primary site of cancer	Obs	Exp	SIR	95% CI
All sites	706	719	0.98	0.91–1.05
Lip	7	5	1.34	0.54–2.76
Stomach	43	44	0.98	0.71–1.31
Colon	41	52	0.78	0.56–1.06
Rectum	27	32	0.84	0.55–1.21
Liver	6	10	0.58	0.21–1.26
Gallbladder	9	14	0.62	0.28–1.18
Pancreas	26	33	0.78	0.51–1.13
Lung	45	66	0.68	0.50–0.90
Breast	124	103	1.20	1.00–1.41
Cervix uteri	4	6.3	0.64	0.17–1.63
Corpus uteri	36	29	1.23	0.86–1.70
Ovary	21	22	0.93	0.57–1.41
Prostate	86	58	1.48	1.19–1.84
Kidney	27	25	1.07	0.71–1.56
Bladder	24	27	0.88	0.57–1.31
Skin melanoma	13	13	0.98	0.52–1.67
Other skin [a]	27	33	0.82	0.54–1.19
Brain, nervous system	21	16	1.28	0.79–1.96
Thyroid gland	6	7	0.81	0.30–1.76
Bone	2	0.7	2.71	0.33–9.79
Soft tissue	4	4	1.00	0.27–2.56
Non-Hodgkin's lymphoma [b]	25	18	1.40	0.90–2.06
Hodgkin's disease	2	1.6	1.24	0.15–4.49
Multiple myeloma	17	11	1.54	0.89–2.45
Leukemia	12	14	0.84	0.44–1.47

[a] Excludes basal-cell carcinoma
[b] Extranodal lymphomas are included in the primary sites of their origins

As far as cancers of the urinary organs is concerned, the SIR was within unity (SIR 0.97, 95% CI 0.73–1.28). The incidence of prostate cancer was significantly elevated throughout the follow-up, with a total SIR of 1.49 (95% CI 1.19–1.84).

The overall incidence of non-Hodgkin's lymphoma (extranodal sites included) was elevated, but not significantly (SIR 1.40, 95% CI 0.90–2.06). However, in the follow-up category of 3–10 years postoperatively, there was a significant two-fold increase in the incidence of non-Hodgkin's lymphoma (SIR 1.90, 95% CI 1.09–3.08) (Table

Table 3. Observed (Obs) and expected (Exp) numbers of cancers, standardized incidence ratios (SIR), and 95% confidence intervals (95% CI) by follow-up period

Primary site	< 3 years				3–9.9 years				10 years or more			
	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI
All sites	341	349.5	0.98	0.87–1.08	329	334.9	0.98	0.98–1.09	36	34.6	1.04	0.73–1.44
Stomach	16	21	0.76	0.43–1.22	25	21.0	1	0.78–1.77	2	2.2	0.91	0.11–3.29
Colon	21	24	0.86	0.53–1.31	17	25.0	0.68	0.40–1.08	3	2.8	1.08	0.22–3.14
Lung	19	34.4	0.55	0.33–0.86	25	29.4	0.85	0.55–1.25	1	2.5	0.39	0.01–2.19
Prostate	45	28.4	11.59	1.16–2.20	37	26.8	1.38	0.97–1.90	4	2.5	1.61	0.44–4.11
Kidney	6	12.6	1.27	0.73–2.06	8	6.5	1.24	0.53–2.44	1	1.1	0.91	0.02–5.64
Bladder	10	13.2	0.76	0.37–1.40	11	12.8	0.86	0.45–1.54	3	1.3	2.26	0.47–6.61
Soft tissue	3	1.93	1.55	0.32–4.53	1	1.86	0.54	0.01–2.99	0	0.2	0.00	0.00–19.1
Non-Hodgkin's lymphoma	9	8.6	1.05	0.48–1.98	16	8.4	1.90	1.09–3.08	0	0.9	0.00	0.00–4.22
Hodgkin's disease	1	0.81	1.23	0.07–6.65	1	0.73	1.38	0.03–7.68	0	0.1	0.00	0.00–53.4
Multiple myeloma	11	5.4	2.05	1.02–3.60	6	5.2	1.16	0.43–2.52	0	0.5	0.00	0.00–7.00
Leukemia	7	6.9	1.01	0.41–2.08	4	6.6	0.60	0.16–1.54	1	0.7	1.45	0.04–8.08

3). The SIR value for multiple myeloma was 1.54 (95% CI 0.89–2.45) , and that for leukemia was almost within unity (Tables 2 and 3).

There were only 6 bone and soft-tissue sarcomas, and none of these tumors was observed at the prosthesis sites.

Discussion

Nationwide recording of all types of total joint arthroplasty in Finland began in 1980 (Paavolainen et al. 1991, 1995). The unique personal identification number given to each Finn allows national arthroplasty data to be linked with data in other national records relating to health and welfare. The Finnish National Register of Arthroplasties is unselected in terms of subsequent events, and its coverage is acceptable. In comparison to the Finnish Hospital Discharge Register which records data on discharges from all public and private hospitals in the country, fewer than 5% of the total joint arthroplasties was found not to be recorded in the Finnish National Register of Arthroplasties (Keskimäki and Aro 1991, Paavolainen et al. 1995).

The Finnish Cancer Register has been found to cover solid cancers adequately (Teppo et al. 1994). Between 1985 and 1988, recording was somewhat incomplete or delayed only in relation to benign neoplasms of the central nervous system, chronic lymphatic leukemia, and multiple myeloma. It is unlikely that the slight underreporting of such cancers would have any association with TKA, i.e., observed and expected numbers of cases should be subject to similar errors. The SIRs calculated can therefore be considered free from bias. Recording of deaths in and migration of the Finnish population is comprehensive. Computerized record linkage on the basis of personal identification numbers eliminates possibilities of error (Pukkala 1992).

There is a considerable variation in the incidence of cancer between social classes in Finland; the overall incidence of cancer in Finnish men of working age is inversely related to social class. In women of working age, it is directly related to social class (Pukkala 1995). In addition to these lifestyle factors, access to care might bias the results of such register-based studies, too. However, health care in all Nordic countries is free for all, and patients who have undergone TKA are therefore likely to be evenly distributed throughout the socioeconomic strata (Hermanson et al. 1994). The average incidence of cancer in the population as a whole ought therefore to be suitable for purposes of comparison (Nyren et al. 1995).

There are several published studies comparing

cancer rates in cohorts of THA patients with national rates (Gillespie et al. 1988, Visuri and Koskenvuo 1991, Nyren et al. 1995, Mathiesen et al. 1995, Gillespie et al. 1996, Visuri et al. 1996, Paavolainen et al. 1999). Only one of the studies (Nyren et al. 1995) found an increased total cancer incidence (3%) after total hip replacement. Two studies found an increased incidence of tumors in the lymphatic and hematopoietic systems (Gillespie et al. 1988, Visuri and Koskenvuo 1991). Both of these research groups have later published second and larger cohorts, which did not confirm these results when modern metal-on-polyethylene types of endoprosthesis were used (Gillespie et al. 1996, Visuri et al. 1996). This was true also in the 3 later large Scandinavian cohorts studied by Mathiesen et al. (1995), Nyren et al. (1995), and Paavolainen et al. (1999). The significantly lower SIRs for colon and lung cancers was evident in most of the earlier reports.

The knee is the largest synovial joint in the human body. The contact area between prosthesis and tissue is larger than in the hip, as also is the clearing capacity of the joint. The destructive and wear mechanisms of the artificial articulating surfaces may differ between these two joints. Gillespie et al. (1966) published a case-referent study anoted on a cohort of 1,034 patients who had undergone joint replacement of the knee. A relative risk of 0.45 (95% CI 0.10–1.93) was noted for leukemia or lymphoma; no other specific sites were detected.

A large nationwide TKA cohort, based on the material of the Swedish Arthroplasty Register with 14,551 patients matched with the Swedish National Cancer Register, was published by Lewold et al. (1996). The cohort was followed for a total of 66,622 person-years, but done separately for the patients operated on for osteoarthrosis (OA) and rheumatoid arthritis (RA); the mean follow-up was only 4.6 years. According to our findings, and earlier studies on THA materials, both male and female patients with OA had a slightly decreased incidence of malignant tumors (SIR 0.8 and 0.9, respectively). Colorectal cancer had a lower incidence than expected (SIR 0.7), as also did respiratory neoplasms (SIR 0.5). Among the OA patients, the incidence of malignant lymphoma revealed no deviation from the expected, but according to the earlier reports, an increased risk was found among RA patients (Porter et al. 1991). This is in good agreement with our preliminary analyses of all the TKA operations, including those done for RA; SIR for non-Hodkin's lymphoma was significantly elevated (SIR 1.57, 95% CI 1.07–2.21), and that for all lymphomas exceeded 2.0 during the 4th and 10th years after TKA (SIR 2.07, 95% CI 1.33–3.08) (Paavolainen et al., unpublished data). These observations indicate that the high incidence of lymphoma seems to be related more to the basic disease than to the TKA per se.

Further, individuals suffering from RA and other autoimmune diseases are at increased risk of non-Hodgkin's lymphoma and leukemia (Isomäki et al. 1978, Prior et al. 1984, Porter et al. 1991, Santana and Rose 1992), and substantial consumption of antirheumatic drugs can also affect the risk of cancer (Gridley et al. 1993, Kauppi et al. 1996). It seems likely that RA patients are physically inactive because of the disease. Low joint forces are produced, which is reflected in most of the survival materials with TKA (Paavolainen et al. 1995, Robertsson et al. 1997). This source of bias in the present paper was obviated by concentrating only on OA patients.

A plausible explanation of the low incidence of lung cancer in our study of patients who underwent TKA is that some candidates for operation may have stopped smoking or may have been excluded from the study cohort because they had a smoking-related disease (Visuri et al. 1996). Further, the high prevalence of regular NSAID use may be reflected by the constantly low incidence of colon cancer (Muscat et al. 1994); we saw a low SIR of 0.78 for colon cancer, which agrees with our earlier report on THA patients (Paavolainen et al. 1999). The increased risk of prostate cancer in the present material (SIR 1.59) seems to be coincidental. It has no significant support in the literature; only a slight increase in this type of cancer has been reported in some of the earlier THA cohorts (SIRs 1.13–1.05) (Nyren et al. 1995, Visuri et al. 1996, Paavolainen et al. 1999), and SIR was within unity in the only TKA cohort (Lewold et al. 1996).

Many previous reports have tried to link the development of adjacent tumors with the materials

of the prosthetic implants or cement (Bago-Granell et al. 1984, Penman and Ring 1984, Swann 1984), but no association is proven (Hamblen and Carter 1984, Solomon and Sekel 1992). The possible carcinogenic effect of these materials has been connected to local currents and corrosion due to combinations of metallic materials or metal surface, quantity and kind of metallic particles detached from the implant surface, as well as cytotoxicity of these particles (Rock 1993, Howie et al. 1996). The connective tissue in close proximity to steel implants contains cytotoxic elements like iron, cobalt and chromium (Merrit and Brown 1996). The environment of the titanic implants showed titanium of good tissue affinity, too (Agins et al. 1988, Scales 1991, Buly et al. 1992). Although this theoretical background of metal-induced sarcomas is of interest, only five documented cases of metal ion-induced adjacent sarcoma have been reported with TKA (Weber 1986, Himmer et al. 1991, Eckstein et al. 1992, Rock 1993, Iglesias et al. 1994). In our series, the SIR of soft tissue cancer was 1.0 and that of bone cancer 2.7, without any statistical significance. All 6 cases of sarcoma developed during the first 2 years of follow-up; it seems evident that this is pure coincidence.

Stresses associated with surface damage in the tibial component of the TKR are much larger than those in the hip replacements. The combination of higher stress and moving contact area is more likely to cause surface damage due to fatigue in tibial UHMWPE-components than in acetabular components (Hood et al. 1983, Bartel et al. 1986, Landy and Walker 1988). Efforts to reduce wear in TKA have been focused on improving implant design, quality of the surface finishing, and polyethylene quality. The design and conformity of TKR plays an important role on femoral-tibial contact conditions (Lewis et al. 1982, Soundry et al. 1986, Zimlich et al. 1998). Therefore, the variety of the TKR designs in the different cohorts might be a risk modifier, too.

Periprosthetic granulomatosis involves an uncoupling of the normal sequence of monocyte-macrophage-mediated clearance of foreign materials and tissue debris that is normally followed by fibroblast-mediated synthesis and remodeling of the extracellular matrix. The s.c. aggressive granulomatosis in association with both cemented (Santavirta et al. 1990a) and uncemented (Santavirta et al. 1990b, 1991) components is a distinct entity with well organized connective tissue containing histiocytic-monocytic and fibroblastic reactive zones. The macrophages, unable to digest the particles they ingest, synthesize and release a large number of cytokines and growth factors, which initiate a complex chain of events (Harris 1994, Takagi 1996). Despite this chronic inflammatory process in the synovia, there is hardly any evidence of local malignant transformation experimentally (Gaechter et al. 1977) or clinically (Miehlke et al. 1981, Himmer et al. 1991, Eckstein et al. 1992, Friedman et al. 1993, Iglesias et al.1994). We observed no such cases.

The exact mechanism of the systemic distribution of the corrosion products in the body remains unknown, but metallic debris can be identified in the lymphatic and bone marrow tissue of the body distant from the hip some years after THA. Tissue necrosis, fibrosis, and sinus histiocytosis are seen in the distant lymph nodes, and macroscopically these nodes may even resemble metastases (Scales 1991, Langkamer et al. 1992, Case et al. 1994). Further, severalfold increments in the chromium and cobolt concentrations in subjects with long-term metal-on-metal TKAs were measured in the serum (Miehlke et al. 1981), as well as in the synovial fluid (Cracchiolo and Revell 1982). Evidently, this means a continuous load on leuco- and lymphopoietic tissues as well as on urinary track organs.

There is emerging evidence that especially the organometallic ions, produced in association with implants, constitute a chronic stress on the immune system (Howie et al. 1996). While this may prove beneficial in the short term, there is the possibility of immune system depletion in the longer term and a resultant increasing incidence of tumors, caused by the innate carcinogenicity of the materials released, as well as increased progression of tumors arising from other sources (Porter et al. 1991, Friedman et al. 1993). As the life spans of the patients continue to increase and the age at the time of TKA declines, these concerns may well become more important (Friedman et al. 1993, Amstutz et al. 1996, Black 1996). Accordingly to our earlier THA cohorts with polyethyl-

ene-on-metal designs (Visuri et al. 1996, Paavolainen et al. 1999), the slightly elevated SIR values with lympho- and hematopoietic cancers did not gain statistical significance. In the present paper, the total SIR for non-Hodgkin's lymphoma (1.40) was not significant. However, after the follow-up of 3–10 years postoperatively, there was an almost twofold significant increase in the incidence of lymphoma. After that, the numbers were too few to draw any conclusions.

We conclude that this large nationwide study found no association between TKA and the overall incidence of remote or adjacent cancers; on the contrary, the incidences of certain cancers were in fact lower than expected on the basis of incidences in the population. However, the period of latency might be long (Rock 1993, Lumb and Sunderman 1994), and the maximum duration of the follow-up (17 years) and the mean duration of follow-up per person is still short. Therefore, further follow-up of the cohort is needed.

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