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Increased cancer risks among arthroplasty patients: 30 year follow-up of the Swedish Knee Arthroplasty Register

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ABSTRACT

Background: An increasing number of young patients are undergoing knee arthroplasties. Thus, the long-term risks of having a knee prosthesis must be evaluated. This study focuses on the potential carcinogenic effects of the prosthesis; it is a long-term follow-up of all patients in Sweden between 1975 and 2006.

Methods: The incidence of cancer in a total population of operated individuals was compared to the overall national cancer incidence in Sweden by means of standardised incidence ratios. Analysis of cancer latency period was performed to identify potential aetiological factors.

Results: For male and female patients with rheumatoid arthritis (RA) or osteoarthritis (OA), the overall cancer risks were elevated, ranging from 1.10 (95% confidence interval (CI): 1.03–1.18) for men with OA to 1.26 (1.23–1.29) for men with RA. The greatest increases in risk were observed for the leukaemia subtypes, myelodysplastic syndromes (MDS) and essential thrombocytosis (ET), ranging from 3.31 (1.24–8.83) for ET in men with OA to 7.38 (1.85–29.51) for ET in women with RA. Increases in risk were also observed for breast cancer, prostate cancer and melanoma. The latency analysis revealed elevated risks late in the study period for both solid and haematopoietic cancers. However, only increases in MDS and possibly prostate cancer and melanoma rates appeared to be connected to the operation.

Conclusion: This study showed that OA and RA arthroplasty patients have a significantly higher risk of cancer than the general population. Elevated risks of MDS and possibly prostate cancer and melanoma indicated a potential connection to exposure to metals in the implant. The observed excessive incidence of ET was likely associated with the inflammatory disease.

1. Introduction

The number of knee arthroplasties has steadily increased since they were introduced six decades ago. The number of operations has even surpassed the number of hip arthroplasties in the high-income countries.[1] In addition, improved long-term prosthetic survival coupled to high patient satisfaction has led to younger patients being operated. It has, therefore, become essential to address the concern raised by several researchers that degradation of prostheses may increase the risk of developing cancer.[2–17]

A link has been suggested, from *in vivo* studies, between the orthopaedic implant and haematopoietic and lymphatic neoplasms.[15] It is well known that polymer and metal

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particles can be found in significant amounts in the tissues, lymph nodes and lungs of knee arthroplasty patients through corrosion and wear of the prosthesis. Serum levels of cobalt and chromium are up to five times that in the average patient under normal circumstances and up to 50–300 times greater during prosthesis failure.[6] If particles released from the joint prosthesis contribute to an increased risk of cancer, one would expect to be able to detect this above all in the urinary, lymphatic and haematopoietic systems. There is already evidence[16,17] and some indications[2,3,5,7,9,12] of elevated incidence rates for haematopoietic cancers following knee and hip arthroplasties. However, some studies have shown little or no increase with respect to this risk.[8,10,14]

If there is a causal relationship, arthroplasty patients with advanced rheumatoid arthritis (RA) may be exposed to an even greater risk of developing leukaemia and lymphoma than the increased cancer risk already established that stems from their inflammatory disease.[6,18–20]

In this study, we investigated the cancer incidence in knee arthroplasty patients in Sweden from 1st January 1975 to 31st December 2006. The study was based on a total population of operations done during this period and it thereby involves the longest follow-up of cancer risks thus far. Because of the long latency associated with environmental exposure, we believed that our study might reveal a link between joint arthroplasty and cancer risks not previously reported.

2. Patients and methods

The patient cohort used for the study was derived from the Swedish Knee Arthroplasty Register, which was established in 1975. The Swedish Knee Arthroplasty Register is the oldest national arthroplasty register and covers all clinics in Sweden during the period from 1975 to 2006. From the registry, all patients who had received a unilateral knee arthroplasty (UKA) or total knee replacement (TKR) were selected for the study. Information about the registry can be obtained from the website (http://www.knee.nko.se).

Table 1 – International Classification of Diseases version 7 (ICD 7) classification of cancer types studied.

Cancer site	ICD 7
Gastrointestinal	150–154
Liver	155–156
Airways	162–164
Kidney/bladder	180, 181
Central nervous system (CNS)	193
Lymphatic/haematopoietic tissue	200–204
Leukaemia	205–207
Acute leukaemia	205.0, 206.0, 207.0
Chronic leukaemia	205.1, 206.1, 207.1
Essential thrombocytosis (ET)	207.9
Myelodysplastic syndromes (MDS)	205.9
Unspecified monocytic leukaemia (UML)	206.9
Prostate	177
Malignant melanoma of skin	190
Breast	170

Each knee arthroplasty is entered in the register as a separate operation. However, cancer risks apply to patients rather than knees. Thus, all patients were considered to be at risk after their first operation.

The number of cancers observed in the cohort was compared to the expected number by means of ratios, given the Swedish national data on cancer incidence[21] with respect to sex, age and calendar year. National data on observed incidence were collected from the National Cancer Register.[22] The ratios, referred to as standardised incidence ratios (SIRs)[23], were calculated for different cancer types (see Table 1) as well as for all cancer types pooled together. These particular cancer types were selected partly because they were previously part of other studies on cancer risk following arthroplasty and partly because they were possibly related to a carcinogenic effect of exposure to prosthetic metal debris. Cancer types were defined according to the International Classification of Diseases version 7 (ICD-7).[24]

Due to the expected difference in cancer risk between osteoarthritis (OA) and RA patients, analyses of these patient cohorts were done separately.

In order to determine whether elevated risks were related to the arthroplasty itself or associated with other factors, such as the already established elevated risk of lymphoma in RA patients, a latency analysis was preformed by dividing the follow-up time into 5-year intervals. Since latency for cancers associated with metal exposure is usually long[25], an elevated risk late in the follow-up period would indicate metal exposure caused by implant debris as a possible aetiological factor.

An additional, more detailed, latency analysis was performed using statistical modelling of the SIR over a follow-up period covering 10 years before and after the operation, to enable further differentiation between potential aetiological factors.

2.1. *Statistical methods*

P-values and confidence intervals (CI) for the SIRs were calculated using Poisson analysis.[23] *P*-values below the standard limit of 0.05 were considered statistically significant. Additional latency analysis was done by means of Poisson modelling, using restricted cubic splines and corresponding 95% confidence bands. The commercial software package STATA[26] was used for the statistical calculations.

3. Results

The study cohort yielded 712,867 person-years, representing 91,291 patients, for the SIR calculations. The median follow-up period was 6.05 years (25th percentile (Q1) = 2.7, 75th percentile (Q2) = 10.3, range 0–30.2) and median patient age at operation was 71.1 years (Q1 = 64.4, Q2 = 76.4, range 14.1–96.2). Women constituted 65% of the cohort; 90% of individuals were OA patients and 10% were RA patients. Person-years accumulated by the cohort patients are presented as background characteristics in Table 2. The results of the SIR calculations are presented in Tables 3–5 and see web appendix Table 6 and 7.

Table 2 – Cohort person-years by sex, diagnosis, age at operation, and year of operation.

Category	Person-years	Category	Person-years	Category	Person-years
Sex		Year of operation		Year of operation	
Women	487,869	1975	1645	1995	32,574
Men	224,998	1976	10,710	1996	39,999
		1977	12,382	1997	38,140
Diagnosis		1978	12,645	1998	36,646
Osteoarthritis (OA)	618,211	1979	11,507	1999	29,374
Rheumatoid arthritis (RA)	94,656	1980	12,686	2000	28,480
		1981	12,676	2001	27,369
Types of prosthesis		1982	13,517	2002	26,145
Total knee replacement (TKR)	498,325	1983	14,062	2003	21,199
Unilateral knee arthroplasty (UKA)	214,542	1984	16,345	2004	17,272
		1985	17,698	2005	10,997
Age at operation		1986	16,511	2006	4172
⩽55	52,215	1987	21,126		
55–59	59,965	1988	21,341		
60–64	99,305	1989	21,164		
65–69	144,840	1990	26,363		
70–74	168,371	1991	35,014		
75–79	128,488	1992	46,849		
80–84	49,824	1993	40,866		
⩾85	9863	1994	35,396		
				Total	712,867

As seen in Table 3, overall cancer risks were significantly elevated for the entire OA and RA cohorts, with excess cancer incidence ranging from 10% to 26% compared to the general population. Leukaemia consistently showed the highest risk out of the different cancer types. Here in risks were doubled in all subgroups, except for men with RA, where it was elevated by 50%. Elevated rates were caused exclusively by the subtypes essential thrombocytosis (ET) and myelodysplastic syndromes (MDS). Both ET and MDS rates showed ranges of 3–5 times the incidence in the general population for all subgroups. Incidence rates for acute and chronic leukaemia subtypes were also elevated for some cohort subgroups. Increases were overall not statistically significant, except for in men with OA, who exhibited almost doubled risks for chronic subtypes compared to the general population.

Risks of breast cancer and melanoma were elevated in women, and risk of prostate cancer and melanoma were elevated in men. Risks of central nervous system (CNS), liver and urinary tract were consistently lower than expected, although only significantly so for urinary tract in men with OA. Risks of gastrointestinal tract were significantly lower than expected in RA patients but significantly higher than those expected in men with OA. The results are shown in Table 3. All statistically significant changes in risk, as indicated by confidence intervals that excluded one, exhibited *P*-values less than 0.003.

The latency analysis showed that overall risks for all subgroups in the arthroplasty cohort had an almost immediate onset. They then remained at approximately the same elevated level for at least 15–20 years when compared to the general population. For the following years statistical power was lacking and the study was, therefore, inconclusive with respect to possible risk increases beyond 20 years after the operation. This was also true for risk of leukaemia in patients with OA, which was significantly elevated and close to double for the first 5–15 years. The reason for this was the markedly high incidence of MDS alone. ET did not add to the elevated risk of leukaemia beyond the interval of 10 years after operation.

For melanoma risks, similar patterns of consistently elevated risks were observed in all subgroups, except for in men with RA. It was additionally observed for breast cancer in women and prostate and gastrointestinal cancers for men with OA. The results are shown in Tables 4 and 5.

Because the patterns of risk increase appeared to be similar for both OA and RA patients and the statistical power of the study was lacking with respect to rare cancer types in small subgroups and for detailed latency analyses, all available data were pooled for the additional latency analysis.

The additional latency analysis, shown in Fig. 1, showed an initial risk that was approximately equal to that in the general population for melanoma, MDS and ET. For prostate cancer, however, a reduction in the incidence rate was observed before the time of operation.

All the cancer sites examined exhibited increases in incidence rate in the 10 years preceding the arthroplasty. This was most pronounced for ET, reaching its peak just before the time of operation, but it was also evident for melanoma and prostate cancer. The increase in MDS incidence rates, however, happened close to the time of operation. The rate of melanoma was elevated for the entire time period, while the rate of prostate cancer reached levels above that of the general population approximately 2 years before the operation.

After the operation, the incidence rates of prostate cancer exhibited a temporary decline for 5 years, followed by a significant increase. Melanoma incidence rates appeared to peak about 5 years postoperatively. ET rates showed a rapid decline, reaching levels comparable with that of the general

Table 3 – Standardised incidence ratios (SIRs) for the knee register cohort presented by sex and diagnosis.

Site	Women				Men			
	Obs.	Exp.	SIR	95% CI	Obs.	Exp.	SIR	95%CI
OA								
All	6560	5222	1.26	(1.23–1.29)	5027	4247	1.18	(1.15–1.22)
Leukaemia	102	59	1.74	(1.43–2.11)	79	41	1.95	(1.56–2.43)
Acute	47	41	1.15	(0.86–1.53)	36	27	1.33	(0.96–1.84)
Chronic	6	7.4	0.82	(0.37–1.82)	10	5.4	1.87	(1.00–3.47)
MDS	35	7.5	4.67	(3.35–6.51)	26	6.3	4.14	(2.82–6.09)
ET	13	2.5	5.26	(3.05–9.06)	4	1.2	3.31	(1.24–8.83)
UML	0	0.2	0	–	1	0.1	13.10	(1.84–92.87)
CNS	94	100	0.94	(0.78–1.16)	48	51	0.95	(0.71–1.26)
Liver	146	162	0.9	(0.77–1.06)	80	91	0.88	(0.70–1.09)
Airways	198	297	0.67	(0.58–0.77)	262	338	0.78	(0.69–0.88)
Lymphatic/haematopoietic tissue	330	319	1.03	(0.93–1.15)	214	238	0.9	(0.77–1.03)
Gastrointestinal	1061	1015	1.05	(0.98–1.11)	842	724	1.16	(1.08–1.25)
Kidney/bladder	272	295	0.92	(0.82–1.04)	367	409	0.9	(0.81–0.99)
Malignant melanoma	245	145	1.69	(1.49–1.91)	195	110	1.78	(1.55–2.05)
Prostate	–	–	0	–	1680	1459	1.15	(1.10–1.21)
Breast	1439	1153	1.25	(1.19–1.31)	8	6.8	1.18	(0.59–2.36)
RA								
All	903	821	1.1	(1.03–1.18)	406	335	1.21	(1.10–1.34)
Leukaemia	15	8.8	1.7	(1.02–2.81)	5	3.4	1.48	(0.61–3.55)
Acute	7	6.2	1.13	(0.54–2.37)	5	2.3	2.2	(0.92–5.29)
Chronic	2	1.4	1.41	(0.35–5.64)	0	0.6	0	–
MDS	4	0.9	4.57	(1.72–12.18)	0	0.4	0	–
ET	2	0.3	7.38	(1.85–29.51)	0	0.1	0	–
UML	0	0.03	0	–	0	0.01	0	–
CNS	21	20	1.04	(0.67–1.59)	3	5.5	0.54	(0.18–1.68)
Liver	24	27	0.89	(0.59–1.32)	6	8.3	0.72	(0.32–1.60)
Airways	29	47	0.62	(0.43–0.89)	36	31	1.17	(0.84–1.62)
Lymphatic/haematopoietic tissue	63	47	1.32	(1.03–1.69)	24	20	1.21	(0.81–1.81)
Gastrointestinal	103	147	0.7	(0.58–0.85)	44	60	0.74	(0.55–0.99)
Kidney/bladder	36	46	0.79	(0.57–1.09)	33	34	0.97	(0.69–1.36)
Malignant melanoma	39	23	1.73	(1.27–2.37)	11	8.6	1.28	(0.71–2.31)
Prostate	0	0	0	–	107	106	1.01	(0.83–1.22)
Breast	180	196	0.92	(0.79–1.06)	0	0.5	0	–

MDS – myelodysplastic syndrome, ET – essential thrombocytemia, UML – unspecified monocytic leukaemia, and CNS – central nervous system.

population about 4–5 years after the operation. MDS rates appeared to reach a temporary steady level up until 5–6 years postoperatively and then continued to increase.

The Poisson modelling of the SIRs also showed differences in incidence of ET between TKR and UKA patients. The SIR for TKR patients was estimated to be 3.81 times higher (95% CI: 1.35, 10.80).

4. Discussion

In the entire arthroplasty cohort, there was a significant overall cancer risk. Latency analysis results showed an almost immediate onset of considerably elevated rates of haematopoietic malignancies and of some solid tumours. Excess risks were sustained for at least 15 years after the operation. In addition, risks were greatly increased for ET, both before and after operation.

4.1. *Statistical power of the study*

Even though the 30 years of follow up yielded great statistical power for the study with respect to some cancer risks, it was still lacking when studying rare cancer types in smaller subgroups, such as men with RA. The power was then further reduced when dividing the follow-up time into smaller 5-year intervals. This becomes especially evident when studying the width of the confidence intervals corresponding to the latter part of the follow-up period. The explanation for the lack of power is primarily that patients were generally between the ages of 60 and 70 when operated and that the number of operations was considerably lower 15–30 years ago. This was unfortunate when studying solid tumours due to their long latency period, but was sufficient for studying haematopoietic malignancies as well as detecting trends in risks of solid cancers.

Moreover, the lack of power imposed some variation on the rate estimates and somewhat distorted the patterns of the SIRs beyond 15 years after the operation. It also made it difficult to draw conclusions from SIR and latency analyses regarding men with RA, and the latency analysis for women with RA, since these subgroups were comparatively small.

An additional contributing factor that potentially distorted the observed latency analysis patterns was that significance

Table 4 – Latency analysis for women and men with OA. SIRs were calculated for each 5-year interval after the first operation.

Site		Women				Men			
	Interval	Obs.	Exp.	SIR	95% CI	Obs.	Exp.	SIR	95% CI
All	0–5	3316	2742	1.21	(1.17–1.25)	2676	2355	1.14	(1.09–1.18)
	5–10	2155	1614	1.34	(1.28–1.39)	1576	1271	1.24	(1.18–1.30)
	10–15	877	671	1.31	(1.22–1.40)	607	480	1.27	(1.17–1.37)
	15–20	215	188	1.14	(1.00–1.31)	130	115	1.13	(0.95–1.34)
	20–25	54	48	1.14	(0.87–1.48)	27	31	0.87	(0.60–1.27)
	25–30	8	8.3	0.96	(0.48–1.92)	6	5.7	1.05	(0.47–2.34)
Leukaemia	0–5	54	30	1.82	(1.40–2.38)	44	22	1.97	(1.46–2.64)
	5–10	34	18	1.86	(1.33–2.61)	19	12	1.56	(1.00–2.44)
	10–15	11	7.9	1.4	(0.77–2.52)	14	4.6	3.05	(1.80–5.14)
	15–20	1	2.2	0.45	(0.06–3.17)	2	1.1	1.81	(0.45–7.25)
	20–25	2	0.6	3.49	(0.87–13.9)	0	0.3	0	–
	25–30	0	0.1	0	–	0	0.1	0	–
MDS	0–5	17	3.7	4.64	(2.88–7.46)	15	3.3	4.58	(2.76–7.60)
	5–10	9	2.4	3.74	(1.95–7.19)	8	2	4.06	(2.03–8.11)
	10–15	7	1	6.79	(3.24–14.25)	3	0.8	3.91	(1.26–12.11)
	15–20	1	0.3	3.34	(0.47–23.73)	0	0.2	0	–
	20–25	1	0.1	12.61	(1.78–89.49)	0	0.1	0	–
	25–30	0	0.01	0	–	0	0.01	0	–
ET	0–5	8	1.13	7.1	(3.55–14.17)	3	0.7	4.34	(1.40–13.44)
	5–10	3	0.8	3.9	(1.26–12.08)	1	0.3	2.97	(0.42–21.07)
	10–15	2	0.4	4.79	(1.20–19.16)	0	0.1	0	–
	15–20	0	0.1	0	–	0	0.03	0	–
	20–25	0	0.03	0	–	0	0.01	0	–
	25–30	0	0.01	0	–	0	0	0	–
Malignant melanoma	0–5	135	75	1.8	(1.52–2.13)	112	61	1.84	(1.53–2.21)
	5–10	74	44	1.68	(1.33–2.10)	55	32	1.71	(1.31–2.23)
	10–15	32	19	1.7	(1.20–2.40)	23	12	1.86	(1.23–2.79)
	15–20	2	5.3	0.37	(0.09–1.50)	3	3	1.01	(0.33–3.13)
	20–25	1	1.4	0.71	(0.10–5.04)	1	0.8	1.21	(0.17–8.58)
	25–30	1	0.3	3.83	(0.54–27.19)	1	0.2	5.92	(0.83–42.00)
Prostate	0–5	0	0	0	–	950	813	1.17	(1.10–1.25)
	5–10	0	0	0	–	489	437	1.12	(1.03–1.22)
	10–15	0	0	0	–	199	161	1.23	(1.07–1.42)
	15–20	0	0	0	–	28	38	0.74	(0.51–1.07)
	20–25	0	0	0	–	9	10	0.87	(0.45–1.68)
	25–30	0	0	0	–	3	1.8	1.67	(0.54–5.17)
Breast	0–5	779	623	1.25	(1.17–1.34)	5	3.6	1.38	(0.57–3.32)
	5–10	433	342	1.27	(1.15–1.39)	1	2.1	0.49	(0.07–3.45)
	10–15	176	138	1.27	(1.10–1.48)	2	0.8	2.4	(0.60–9.60)
	15–20	48	38.4	1.25	(0.94–1.66)	0	0.2	0	–
	20–25	5	9.8	0.51	(0.21–1.23)	0	0.06	0	–
	25–30	2	1.7	1.16	(0.29–4.64)	0	0.01	0	–

MDS – myelodysplastic syndrome and ET – essential thrombocytemia.

testing of each interval risk estimate gave rise to multiplicity issues. The risk of falsely detecting a statistically significant change in risk in any of the intervals, when none was present, was roughly 26%, or one in four, for the six time intervals in the present study.

4.2. *Selection bias*

The national Knee Arthroplasty Register has a coverage of about 96%. Since little is known about the characteristics of the patients and operations not registered, it is not possible to estimate the influence of selection bias. However, even if the 4% not covered did not show an elevated risk, this would not affect our findings. For instance, an observed SIR of 1.3 would only be reduced by 0.01, to 1.29, by inclusion of this 4% with no increase in risk.

It has been reported that there is considerable non-random under-reporting concerning certain cancer types in the National Cancer Register.[27] It is suspected that cases not reported are those that are less treated and investigated, lacking histology and cytology verification. The cancers most affected are lymphoma and leukaemia. This could possibly explain part of the elevated SIRs in the RA patients, because these patients are better investigated then the general population.

Table 5 – Latency analysis for women and men with RA. SIRs were calculated for each 5-year interval after the first operation.

Site	Interval	Women				Men			
		Obs.	Exp.	SIR	95% CI	Obs.	Exp.	SIR	95% CI
All	0–5	357	339	1.05	(0.94–1.17)	158	148	1.07	(0.91–1.25)
	5–10	249	247	1.01	(0.89–1.14)	138	103	1.34	(1.13–1.58)
	10–15	184	141	1.3	(1.13–1.51)	78	55	1.43	(1.15–1.79)
	15–20	76	65	1.16	(0.93–1.46)	24	21	1.12	(0.75–1.68)
	20–25	31	25	1.25	(0.88–1.78)	7	7.2	0.97	(0.46–2.03)
	25–30	8	5.2	1.55	(0.78–3.11)	0	1.4	0	–
Leukaemia	0–5	4	3.6	1.1	(0.41–2.93)	2	1.5	1.3	(0.33–5.21)
	5–10	5	2.7	1.88	(0.78–4.51)	2	1	1.93	(0.48–7.71)
	10–15	4	1.5	2.66	(1.00–7.09)	1	0.5	1.9	(0.27–13.50)
	15–20	1	0.7	1.41	(0.20–10.03)	0	0.2	0	–
	20–25	1	0.3	3.72	(0.52–26.40)	0	0.1	0	–
	25–30	0	0.1	0	–	0	0.01	0	–
MDS	0–5	0	0.3	0	–	0	0.2	0	–
	5–10	1	0.3	3.97	(0.55–28.17)	0	0.1	0	–
	10–15	2	0.2	12.3	(3.08–49.18)	0	0.1	0	–
	15–20	0	0.1	0	–	0	0.03	0	–
	20–25	1	0.04	24.5	(3.45–173.6)	0	0.01	0	–
	25–30	0	0.01	0	–	0	0	0	–
ET	0–5	0	0.1	0	–	0	0.04	0	–
	5–10	1	0.1	12.36	(1.74–87.73)	0	0.03	0	–
	10–15	1	0.1	18.33	(2.58–130.1)	0	0.02	0	–
	15–20	0	0.03	0	–	0	0.01	0	–
	20–25	0	0.01	0	–	0	0	0	–
	25–30	0	0.0	0	–	0	0	0	–
Malignant melanoma	0–5	19	9.2	2.08	(1.32–3.25)	3	3.8	0.8	(0.26–2.48)
	5–10	12	6.7	1.79	(1.02–3.15)	2	2.6	0.76	(0.19–3.05)
	10–15	2	3.9	0.51	(0.13–2.05)	4	1.4	2.86	(1.07–7.62)
	15–20	4	1.9	2.14	(0.80–5.71)	2	0.6	3.53	(0.88–14.11)
	20–25	2	0.8	2.68	(0.67–10.71)	0	0.2	0	–
	25–30	0	0.2	0	–	0	0.04	0	–
Prostate	0–5	0	0.0	0	–	45	45	1	(0.75–1.34)
	5–10	0	0.0	0	–	35	33	1.06	(0.76–1.48)
	10–15	0	0.0	0	–	19	18	1.05	(0.67–1.65)
	15–20	0	0.0	0	–	7	7.2	0.97	(0.46–2.04)
	20–25	0	0.0	0	–	1	2.5	0.4	(0.06–2.81)
	25–30	0	0.0	0	–	0	0.5	0	–
Breast	0–5	83	83	1	(0.80–1.24)	0	0.2	0	–
	5–10	44	58	0.76	(0.56–1.01)	0	0.2	0	–
	10–15	35	33	1.07	(0.77–1.49)	0	0.1	0	–
	15–20	16	15.0	1.06	(0.65–1.74)	0	0.03	0	–
	20–25	4	5.8	0.69	(0.26–1.84)	0	0.01	0	–
	25–30	0	1.2	0	–	0	0	0	–

MDS – myelodysplastic syndrome and ET – essential thrombocytemia.

It is not likely to explain the corresponding increase in SIRs in the OA population, however. Registration of solid tumours is good and coverage is reported to be about 96%.

4.3. *Confounding*

Another possible issue with the current study is that of confounding. In the SIR analysis the standardisation takes care of possible confounding due to differences in gender and age distribution between the arthroplasty cohort and the general population, as well as effects caused by variations in cancer incidence over calendar years. The latency analysis then allows us to differentiate between effects of the underlying condition leading to the operation and that of the operation itself.

However, consideration is not given to possible confounding factors acting in the time between diagnosis and operation, such as lifestyle changes due to the underlying condition. For instance, it is known that being overweight is an important risk factor for getting OA. It has also been shown that an increase in body-mass index (BMI) is associated with elevated cancer risks of, for instance, colon, rectal, breast cancer, melanoma, leukaemia, multiple myeloma and non-Hodgkin lymphoma.[28] Therefore, if changes in BMI occur in close relation to the operation, it would introduce a potential bias in the latency analysis when estimating cancer risks

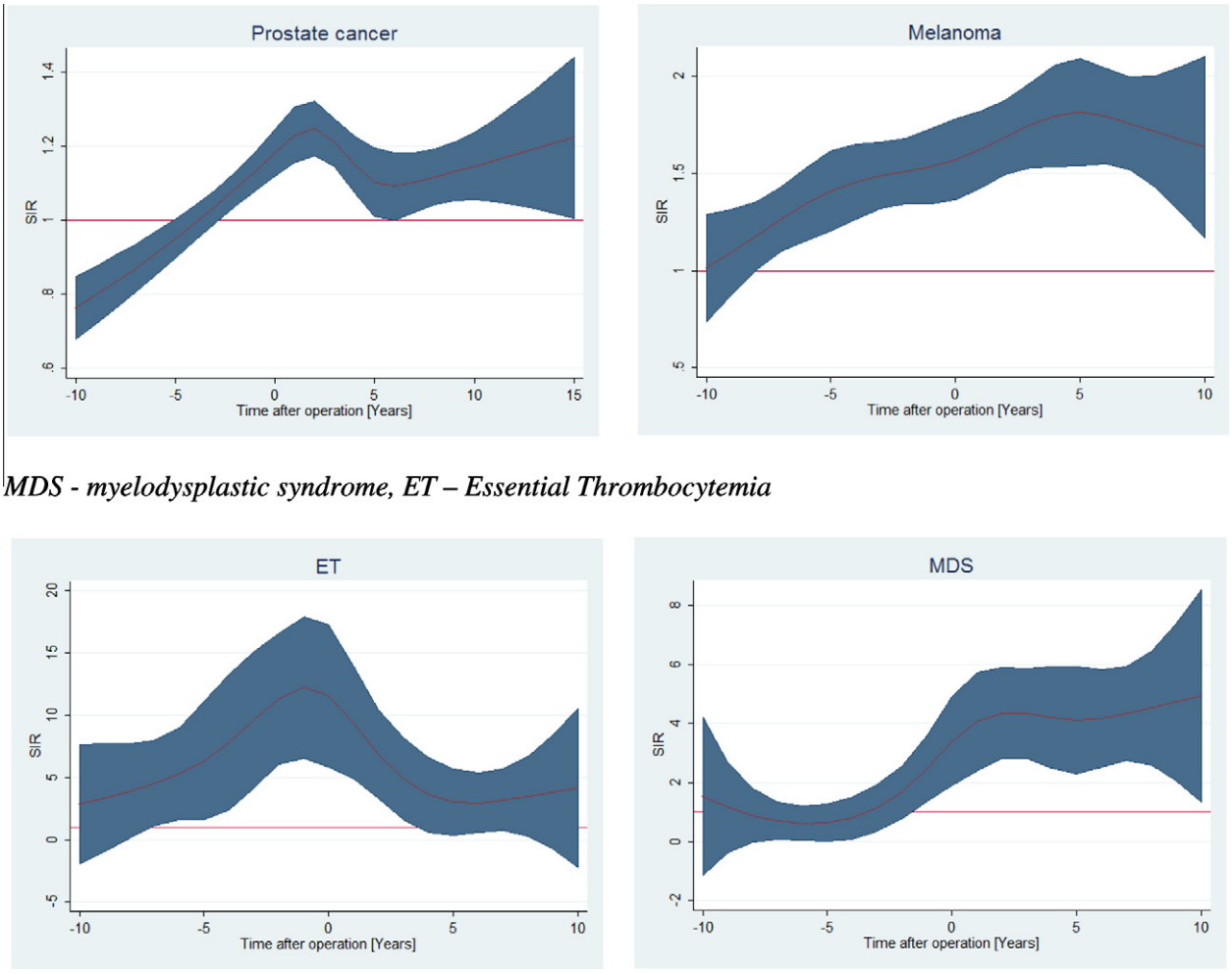

Fig. 1 – Additional latency analysis. Starting 10 years before operation, we observe the change in standardised incidence ratios (SIRs) up to 10 years after operation. Zero on the time axis indicates the time of operation. Blue areas represent 95% confidence bands. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

for the OA subgroup. It may not have influenced the estimates of leukaemia and melanoma risks, as effects induced by changes in BMI are shown to be of a considerably lesser magnitude than those observed in the present study, but may very well explain the increase in gastrointestinal cancer observed for men with OA.

The bias is not likely to have affected the risk estimates of the RA subgroup, since it has been reported that the distribution of BMI in RA populations are usually quite similar to that of the general population.[29] Although, the literature on this subject is quite sparse.

4.4. *Overall risks*

For RA patients, the elevated overall rates might have been expected because of the link already established between autoimmune diseases and risks of developing lymphoma. Moreover, the recently introduced disease-modulating drugs may also contribute to elevated risks in RA patients. For the OA patients in this study cohort, however, there was an excess overall cancer risk, which to our knowledge has not been reported previously with respect to OA patients, with or without prosthesis.

4.5. *Latency analysis*

The latency analysis did not clearly indicate that elevated cancer risks were caused by the prosthesis. Onset of risk of solid tumours, such as prostate and breast cancer, was almost immediate. This is not consistent with the expected latency period of solid cancers of at least 10–20 years.[30]

The pattern observed also showed an almost immediate onset of increased risk of non-solid tumours, such as leukaemia, as well as an increase in risk of solid tumours 10–20 years after operation, as seen in Tables 4 and 5, see web appendix Tables 6 and 7, and in Fig. 1. These observations are consistent with the risk of developing each cancer type when induced by exposure.[30,31]

The mechanisms behind this pattern are unclear, but several explanations have been proposed. It has, for instance, been suggested that when latency is short in comparison to that which is typical of metal-induced cancer caused by

occupational exposure, as in the present study, the early excess risks cannot be attributed to the prosthesis. Instead, detection bias, due to the frequent contacts with the health care system in conjunction with the joint replacement boosting detection rates, or disease-related aetiological factors, would appear likely. However, we found elevated risks that were sustained for more than one decade, which is probably too long for this to be a consequence of a higher frequency of hospital visits by the arthroplasty patients as compared to the general population.

4.6. Prostate cancer and melanoma

Potential causal relationships between metals and prostate cancers, as well as melanoma, have been reported.[4,32] Consequently, both of the previous explanations may hold true. The initial follow-up period may be affected by detection bias and the latter part of the follow-up may reflect a real increase in risk.

The initial decreases in prostate cancer rates observed in the additional latency analysis, seen in Fig. 1, are most likely due to healthy patient selection. A dip in rates is also observed during the first years after operation, which is possibly due to decreasing detection rates as patient hospital visits become less frequent. The following increase in the SIR may reflect a real risk increase and subsequently be attributable to the arthroplasty.

Melanoma rates increased as patients got closer to the operation. This is probably due to the same effect as in prostate cancer rates – although more pronounced, as melanoma is more easily detected. After appearing stable, the rate increased, reaching a peak at 5 years. It was still significantly elevated after 10 years.

The melanoma risk pattern is less clear than for prostate cancer, but the estimated decline in the additional latency analysis, at the end of the studied interval, might be an indication that the effect of the selection and/or confounding bias that caused the two peaks is decreasing. Subsequently, the observed risk increase between 10 and 15 years after the surgery might possibly reflect an excess risk attributable to the operation or the prosthesis.

The increased rate of prostate cancer detected was in accordance with the findings of several other studies[2,5,7,9–11,14], as was the increase in relative rates of malignant melanoma[7,10,11,14] and breast cancer.[5]

In the study by Goldacre and colleagues.[3], no increase in the risk of developing any of the latter cancer types was found. This may further support the hypothesis that the initial part of the follow-up in the present study is affected by detection bias. The study primarily contained patients with relatively short follow-up and hospital patients undergoing treatment unrelated to cancer were used as a reference population. That surveillance effects are of similar magnitude in all hospital patient groups would possibly explain why excess risks were not detected here.

Another indication is that women with RA in the present study appear not to exhibit the same pattern of elevated breast cancer risks as do those with OA. This may be because RA patients are already under thorough medical surveillance due to their disease. Further investigation of the general health of RA patients, after the operation, would not lead to an elevation in observed incidence rates due to increased detection. Naturally, there are other possible explanations such as gene-associated differences.

4.7. Leukaemia

The observed increase in leukaemia rates was possibly related to the joint prosthesis, with *in vivo* results supporting a causal connection. The pattern found, with an instant increase in incidence, has been observed by other researchers[9,16], although one of the findings was not statistically significant.

The short latency period observed in connection with increased risks is consistent with what has been reported previously in relation to exposure.[31,33,34] Elevated rates were present in all subgroups with the exception of males with RA and were mainly due to MDS and ET. That elevated rates were not observed in men with RA was to be expected and is evident from the expected number of cases in the subgroup. This is of course due to MDS and ET being rare diseases and the male RA subgroup being particularly small. Consequently, the study is inconclusive with respect to potentially increased MDS and ET rates in men with RA who have undergone knee arthroplasties.

4.8. Myelodysplastic syndromes

Depending on the type of condition, MDS patients can be at considerable risk of developing acute myeloid leukaemia (AML). The aetiology of MDS is largely unknown, and because possible aetiological factors have not been sufficiently researched, little is known about the importance of different kinds of exposure. However, metal exposure has been implicated as a potential risk factor.[35]

This in connection with the additional latency analysis results, with observed rates at normal levels before the operation followed by a significant increase in risk just a few years later, points to the prosthesis metals as potential aetiological factors.

4.9. Essential thrombocytosis

ET is a rare disease and its aetiology is still poorly understood. In some cases, the condition has been linked to a specific gene mutation. In rare cases ET, just like MDS, develops into AML.

The pattern seen in the additional latency analysis, with risks exceeding five times that in the general population even 4–5 years before the operation, does not support the hypothesis of aetiological factors being related to the operation or prosthesis. The peak in elevated rates almost a year before the time of operation rather points to a relation to disease onset and worsening condition. Moreover, it is known that secondary or reactive thrombocytosis is associated with inflammatory conditions, with an established link to RA[36] and that the differentiation between the primary and secondary conditions may not be trivial.[37] Consequently, elevated risks may partly be due to misclassification when changing between ICD classification systems.

In addition, observations made in other studies[36] of a correlation between reactive thrombocytosis activity and disease activity, at least in RA patients, agree well with two observations made in the present study. The TKR patients, with greater disease activity, had a significantly higher incidence rate than UKA patients. Furthermore, the peak in incidence rate happens just before the time of operation when disease activity is at its peak.

To our knowledge, this is the first time the observation of elevated incidence rates of ET and MDS have been reported for arthroplasty patients. The reason that it has not been observed previously is possibly because its rare nature demands very large cohorts in order to detect a significant increase in incidence rates. Secondly, in most other studies, groupings of cancer sites have been kept fairly wide, probably drowning out the effect of incidence rates of ET and MDS. Lastly, the observation was only made possible by the inclusion of more recent ICD classifications in the Swedish National Cancer Register, since both conditions were classified as unspecified leukaemia types in the ICD 7 classification system.

The latter consideration may have caused underestimation of the SIRs of both conditions in the present study, as reference population data for the SIRs were based on ICD 7 classifications, where the categories for unspecified leukaemia may contain additional types of malignancies.

4.10. *Lymphoma*

Excess numbers of lymphomas were present mainly in RA patients, where an elevated risk has already been established. Although the risk was significantly lower than that reported for a general RA population[6], the latency analysis showed that the risks reached the reported levels by 10–15 years after the operation. Consequently, the lower risk observed in the present study may have been caused by healthy patient selection.

4.11. *Gastrointestinal cancer*

A reduction in the incidence of gastrointestinal cancers, as observed in similar studies[7–12,14,16], was also found in the present study but only for RA patients. In previous studies, two possible explanations were offered for the reduction observed. It was explained by the long-term use of non-steroid anti-inflammatory drugs and/or by the elimination of *Helicobacter pylori* due to peroperative and postoperative administration of antibiotics as prophylaxis. This may very well explain the difference in risk observed between OA and RA patients in the present study, as RA patients are more frequent users of anti-inflammatory drugs. Moreover, the difference regarding the OA patients in the present study may then be due to variations in the use of anti-inflammatory drugs between countries, as well as within Sweden over time. The excess risk observed for men with OA may furthermore be due confounding, as suggested earlier in the discussion. An observation that supports this claim is that excess risks due to BMI increases tend to be greater for men, at least for colon cancer.[28]

4.12. *Cancer of the respiratory system*

The markedly low incidence of cancer in the respiratory organs was present in all subgroups with the exception of men with RA and may be attributed to the fact that many patients may stop smoking before surgery or even that patients with lung-related diseases are less likely to be candidates for surgery. Support for these explanations can be found in the reduction of other smoke-related cancers shown in other studies.[7–9] It has even been suggested that the result may be due to confounding[7], as physical exercise is thought to reduce the risk of lung cancer.

This risk reduction was also noted in several other studies done on the possible association between knee and/or hip arthroplasty and cancer.[2,5,7,9,12,16]

4.13. *Consistency*

In order for excess risks to be attributable to operation related factors, they would have to be consistent over all subgroups and agree with the expected latency pattern. In the present study some risk estimates may vary considerably between groups due to lacking statistical power pertaining to rare cancer types, especially in small subgroups. However, in spite of this issue excess risks of MDS, ET, melanoma and prostate cancer were reasonably consistent over all subgroup analyses. MDS rates furthermore exhibited the expected pattern in the additional latency analysis. The prostate cancer rate pattern did not agree with what was expected, but the additional latency analysis showed that this might be due to detection bias. The increase late in the study period could still possibly be attributed to operation related factors. A similar, but less clear, pattern was observed for melanoma rates. Subsequently, cancer types that could be connected to exposure to operation related factors on grounds of consistency were MDS, ET, prostate cancer and possibly melanoma.

Other cancer types were clearly not consistent over subgroups. These were the reduced number of kidney/bladder cancers in men with OA, the risk increase in breast cancer in women with OA, chronic leukaemia in men with OA, gastrointestinal cancer in men with OA and lymphatic/haematopoietic cancers in the RA subgroup. The latter three may be explained by confounding due to the underlying condition and/or risk factors related to it, as discussed in the paragraph on confounding. But the reduction in kidney/bladder cancer may possibly have been a product of multiple testing. As previously mentioned, the elevation of breast cancer risks in women with OA may also be due to detection bias.

5. Conclusion

We found significantly elevated overall cancer risks in male and female. OA and RA subgroups of the knee arthroplasty cohort, which were sustained for over 15 years. However, only increases in specific cancer types can potentially be attributed to operation related factors.

The increased incidence of MDS, in connection with its established link with exposure indicates a carcinogenic effect of factors related to the operation and maybe of the implant.

The incidence rate patterns of prostate cancer and melanoma are possibly additional evidences of carcinogenic effects of factors related to the operation, with laboratory studies supporting a causal relationship with the implant.

Lastly, we observed a significant increase in the incidence rate of essential thrombocytosis that has not, to our knowledge, been reported previously in connection with arthroplasty patients. We conclude that its aetiology is more likely to be connected to the inflammatory disease than to the arthroplasty or prosthesis and it could be related to the degree of disease activity.

However, even if all excess cancers could be attributed to operation related factors the absolute risk of developing cancer due to the operation would still be rather low. Approximately 550 patients would then have to be operated for one to develop cancer due to the operation. Roughly 3000 patients would have to be operated in order for one to develop MDS.

The results are, therefore, not likely to change the indication for operation, but may guide researchers to develop alternative procedures with less impact on cancer incidence. Additionally, it may call for closer monitoring of prosthesis patients.

Authors' contribution

PW and JR designed the study. All authors analysed the results. PW wrote the first draft, which was then actively improved and revised by all the authors.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2010.11.023.

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