Risk of cancer after primary total hip replacement: The influence of bearings, cementation and the material of the stem

A retrospective cohort study of 8,343 patients with 9 years average follow-up from Valdoltra Orthopaedic Hospital, Slovenia

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Background and purpose — Despite the increasing number of total hip replacements (THRs), their systemic influence is still not known. We have studied the influence of specific features of THRs—the bearing surface, the use of bone cement and the material of the stem—on the cancer incidence.

Patients and methods — In a retrospective cohort study we identified 8,343 patients with THRs performed at Valdoltra Hospital from September 1, 1997 to December 31, 2009. Patient data were linked to national cancer and population registries. The standardized incidence ratios (SIR) and Poisson regression relative risks (RR) were calculated for all and specific cancers.

Results — General cancer risk in our cohort was comparable to the population risk. Comparing with population, the risk of prostate cancer was statistically significantly higher in patients with metal-on-metal bearings (SIR = 1.35); with metal-on-polyethylene bearings (SIR = 1.30), with non-cemented THRs (SIR = 1.40), and with titanium alloy THRs (SIR = 1.41). In these last 3 groups there was a lower risk of hematopoietic tumors (SIR = 0.69; 0.66 and 0.66 respectively). Risk of kidney cancer was significantly higher in the non-metal-on-metal, non-cemented, and titanium alloy groups (SIR = 1.30; 1.46 and 1.41 respectively). Risk of colorectal and lung cancer was significantly lower in the investigated cohort (SIR = 0.82 and 0.83, respectively). Risk for all cancers combined as well as for prostate and skin cancer, shown by Poisson analysis, was higher in the metal-on-metal group compared with non-metal-on-metal group (RR = 1.56; 2.02 and 1.92, respectively).

Interpretation — Some associations were found between the THRs' features, especially a positive association between metal-on-metal bearings, and specific cancers.

Total hip replacement (THR) implants are manufactured mainly from metallic materials in combination with polymers and/or ceramics. Since life expectancy is becoming prolonged, more people are being exposed to implanted metallic materials. During the lifetime of an endoprosthesis, dissolved metal ions and solid metal nanoparticles are formed and released into the surrounding tissue and blood (Milošev et al. 2005). Some of the metals used to manufacture THRs are recognized by the International Agency for Research on Cancer (IARC) to be cancerogenic (IARC 1999). Several studies have analyzed the connection between THRs and cancer incidence (Gillespie et al. 1988, Visuri and Koskenvuo 1991, Mathiesen et al. 1995, Nyrén et al. 1995, Visuri et al. 1996, Paavolainen et al. 1999, Signorello et al. 2001, Visuri et al. 2010, Brewster et al. 2013). To our knowledge the present study is the first in which the effect of the characteristics of endoprostheses on the incidence of cancer has been investigated.

Thus, we assessed whether any of the features of the THRs, such as bearing surface between head and cup, cementation, or material of the stem influenced the cancer risk.

Patients and methods

8,343 consecutive patients with primary total THR implanted for the first time in the period from September 1, 1997 to December 31, 2009 were followed from the date of the first THR until the date of each cancer diagnosis (some patients had more than 1 cancer diagnosis in the study period), the date of death or the end of follow-up on January 1, 2015. Non-Slovenian patients, patients undergoing an operation on the contralateral hip, and patients with diagnosis of rheumatoid arthritis were excluded.

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The data on patients were taken from the hospital computer database from September 1, 1997 to January 1, 2002 and, later, from the Valdoltra Arthroplasty Registry. These data are checked by hospital analytics service since payment for the material used is controlled by the State Health Insurance Company. From 2002 the Valdoltra Arthroplasty Registry has been running and its completeness is 100% (Levašič et al. 2009). Using the name, surname, sex, and birth date the cohort was linked with the Slovenian population-based cancer registry (CRS), which is filled by obligatory reporting. The quality and completeness indices are monitored and reported routinely so the CRS adequately covers the entire population (Zadnik et al. 2017). The vital status of the patients was checked by linkage with the Central Population Register, the central repository and processing of data concerning state citizens, which is the basis for establishing e-Government services. Diagnoses of cancer were classified as in the International Classification of Diseases version 10 (ICD-10). The analysis was stratified by cancer site: All sites (C00–C96); Melanoma (C43); Corpus uteri (C54); Prostate (C61); Haematolymphatic cancers (C81–C96); Stomach (C16); Lung and bronchi (C33–C34); Breast (C50); Lymphomas (C81–C85); Gastrointestinal tract (C15–C20); Urotract (C64–C67); Kidney and renal pelvis (C64–C65); Bladder (C67); Liver (C22); Central nervous system (C70–C72); Plasmacytoma (C90); Leukemias (C91–C95); Colon and rectum (C18–C20); Liver and gall bladder (C22–C23); Pancreas (C25); Skin cancer other than melanoma (C44) according to ICD-10.

The characteristics of the THR implants were classified using the Valdoltra Implant Library, which records all the prostheses used in Valdoltra from September 1, 1997 onwards together with their characteristics—the parts of the prosthesis used, cementation use, the material, and size. The prostheses in our cohort were categorized one by one into subgroups according to (1) bearing type—metal-on-metal (MoM), metal-on-polyethylene (MoP), ceramic-on-ceramic (CoC), and ceramic-on-polyethylene (CoP), and then divided into 2 groups: MoM and non-MoM, (2) use of bone cement for fixation and (3) material of the stem components: titanium (Ti) alloy, cobalt chromium (CoCr) alloy or stainless steel (Fe-alloy).

Statistics

The ratio of observed to expected numbers of cancer was expressed as the standardized incidence ratio (SIR). The expected number of cases was calculated by the formula:

$$expected = \sum n_i R_i$$

for each 5-year age-group i, where n_i is the number of person-years at risk in our cohort and R_i is age-specific cancer incidence rate in Slovenia. The person-years were calculated by summing all the follow-up days. The SIR can be interpreted as an estimate of the relative risk of cancer in a particular category in comparison with the national rates. The 95% confidence interval (CI) is reported.

The crude and to bearing surface, cementation, and stem material mutually adjusted relative risks of cancers for relevant sub-cohorts were assessed by Poisson regression analysis. The reference categories were: MoM in bearings, Ti-alloy in stem material, and non-cemented THRs in use of bone cement. The statistical analysis was made using the STATA13 program (StataCorp, College Station, TX, USA). Results with a p-value of less than 0.05 were considered statistically significant.

Ethics, funding, and potential conflicts of interest

The study was approved by the Republic of Slovenia National Medical Ethics Committee on April 5, 2013, N° 117/02/13. The study was funded by the Valdoltra Orthopaedic Hospital but no other support, financial or other, was received for this study. No competing interests declared.

Results

Participants

8,343 patients were included in the study: 3,260 men and 5,083 women. The mean age at the time of THR was 65 years, 63 for men and 67 for women. None of the patients were lost to follow-up. In the follow-up period, 1,405 cancers were observed in this cohort. 2,101 patients died before the end of the follow-up period. The follow-up time ranged from 1 day (death of patient) to 17 years with a mean follow up of 9.0 years. The sub-cohorts for bearing surface analysis included 338 patients with MoM bearings, 5,909 with MoP, 1,323 with CoC, and 773 with CoP bearings. The sub-cohorts for the presence of bone cement included 6,966 patients with non-cemented THR and 1,377 patients with cemented components (900 cemented THR, 257 hybrid, and 220 reverse hybrid THR). The sub-cohorts for stem material included 7,316 patients with stems made of Ti-alloy, 850 of CoCr-alloy, and 177 of Fe-alloy (Table 1).

The numbers of cancer cases and person years by sub-cohort are listed in Table 2. The cumulative follow-up time of the cohort was 77,075.56 person-years.

SIR analysis

For all cancer sites the risk in the whole cohort was the same as that in the general Slovenian population (SIR = 0.98, CI 0.93–1.03). The risk was higher for prostate cancer (SIR = 1.4, CI 1.2–1.6) and for kidney with renal pelvis cancer (SIR = 1.4, CI 1.0–1.8). The risk was lower for lung and bronchi cancers (SIR = 0.83, CI 0.69-0.98), for hematolymphatic cancers due to the lower risk of leukemias (SIR = 0.41, CI 0.24–0.71) and for gastrointestinal tract cancers due to the occurrence of colorectal cancers (SIR = 0.82, CI 0.70–0.96).

In patients fitted with a Ti-alloy stem there was a higher risk of prostate (SIR = 1.4, CI 1.2–1.6) and kidney cancers (SIR = 1.4, CI 1.0–1.9) and a lower risk of leukemia (SIR = 0.34, CI 0.24–0.71) and colorectal cancer (SIR = 0.83, CI 0.71–0.98).

Table 1. Number of patients in sub-cohorts (bearing surface between head and cup, cementation, material of the stem) by age at operation

Group	Age group						
Subgroup	0–40	40–49	50–59	60–69	70–79	≥ 80	Total
All	131	591	1,631	3,059	2,664	267	8,343
Bearing							
MoM	12	43	141	124	18	0	338
MoP	39	233	763	2,128	2,481	265	5,909
CoC	69	274	535	407	38	0	1,323
CoP	11	41	192	400	127	2	773
Use of bone cement							
Non-cemented	119	580	1,596	2,91	1,713	48	6,966
Cemented	12	11	35	149	951	219	1,377
Stem material							
Ti-alloy	122	585	161	298	194	79	7,316
CoCr-alloy	9	5	21	67	586	162	850
Fe-alloy	0	1	0	12	138	26	177

Table 2. Number of cancer cases and number of person-years according to sub-cohorts (bearing surface between head and cup, cementation, material of the stem)

Group/Subgroup	No. cancers	Person-years
Bearing		
MoM	76	4,378.52
MoP	1,003	51,673.26
CoC	188	13,340.13
CoP	138	7,683.65
Use of bone cement		
Non-cemented	1,156	65,624.09
Cemented	249	11,451.47
Stem material		
Ti-alloy	122	68,694.83
CoCr-alloy	156	6,932.79
Fe-alloy	29	1,447.95

In the MoM and in the MoP bearings groups, analysis showed a significantly higher risk of prostate cancer (SIR = 2.4, CI 1.4–4.1) and (SIR = 1.4, CI 1.2–1.6), respectively. Further, in the non-MoM group there was a significantly higher kidney cancer risk (SIR = 1.3, CI 1.0–1.8). The MoM group for hematolymphatic cancers did not differ from that in the Slovenian population (SIR = 0.45, CI 0.11–1.8) and SIR was even significantly lower in MoP (SIR = 0.76, CI 0.59–0.98) and in all other non-MoM bearings (SIR = 0.69, CI 0.54–0.87). In the MoP group there was also a lower risk of gastrointestinal cancer (SIR = 0.73, CI 0.63–0.86).

In the non-cemented THR cohort there was a higher risk of prostate (SIR = 1.4, CI 1.2–1.6) and of kidney (SIR = 1.5, CI 1.1–2.0) cancers, but a lower risk of hematolymphatic cancers (SIR = 0.66, CI 0.50–0.86), especially of leukemia (SIR = 0.33, CI 0.16–0.65). There was a lower risk in the non-cemented group of colorectal cancers (SIR = 0.83, CI 0.72–0.95). Gastrointestinal cancers were, on the whole, lower in both cemented (SIR = 0.83, CI 0.72–0.95) and non-cemented (SIR = 0.83, CI 0.72–0.95) groups.

Because of the small sample size, it was not possible to calculate the SIR for each cancer site by prosthesis features. This was the case for stem material—CoCr-alloy for liver, Fe-alloy for liver, liver with gall bladder, central nervous system, plasmacytoma and leukemia, and for bearings—MoM for corpus uteri, liver, liver with gall bladder, central nervous system, plasmacytoma, and leukemias (Tables 3 and 4, see Supplementary data).

Poisson analysis

Under Poisson analysis, not mutually adjusted to THRs characteristics, the risk for all types of cancer is shown to be higher in the MoM group (RR = 1.56, CI 1.23–1.95) for prostate cancer (RR = 2.02, CI 1.17–3.48) and for skin cancers other than melanoma (RR = 1.92, CI 1.19–3.10). The risk does not depend on the stem material or bone cement usage (Table 5, see Supplementary data).

As the relative risks for specific cancer sites are mutually adjusted to bearing surface, cementation, and stem material (Table 6, see Supplementary data) the risk for all types of cancer is again significantly higher in the MoM group (RR = 1.54, CI 1.22–1.93), for prostate cancer (RR = 2.01, CI 1.20–3.57) and for skin cancers other than melanoma (RR = 2.01, CI 1.24–3.25). There is less prostate cancer in femoral stems from CoCr-alloy (RR = 0.32, CI 0.12–0.87). A significantly higher risk exists of central nervous system cancer in the cemented THR group (RR = 5.87, CI 1.21–28.46). Similarly to that in the SIR analysis, it was not possible to calculate relative risks for each cancer site using prosthesis features because of small sample size.

Discussion

Key results

Comparing the groups with the general population using SIR analysis showed the general cancer risk in the whole cohort was comparable to that in the population. The prostate cancer risk was higher for the MoM and MoP bearings. The same was true for both the non-cemented THRs and for the Ti-alloy THRs. The risk of kidney cancer was higher in the non-MoM, non-cemented, and Ti-alloy groups. The risks of colorectal cancer and lung cancer were lower for the complete cohort. That for hematolymphatic cancers for MoM SIR was the same while, for the non-MoM, non-cemented, and Ti-alloy groups, SIR was even lower. Poisson analysis showed that risk for all types of cancer was higher in the MoM group compared with non-MoM and so too for prostate cancer and skin cancers. These results suggest that the bearing surface is the main feature of THR influencing the cancer risk.

Possible study improvements

Cohort expansion or follow-up time elongation would improve the power of our analysis for certain less common cancer sites. Inclusion of further confounders (multiple joint replacements, other than RA concomitant diseases…) would give additional strength to the causality results.

Interpretation

The question as to the influence of the hip implant on the human body is probably as old as the THR procedure itself. The toxicity of the metals used in orthopedic prostheses was questioned back in 1981 (Rae 1981). Some bearing surfaces, such as MoM, were investigated by Huk et al. since they generate both metal particles and ions (Huk et al. 2004). Arthroplasty registries, especially in Scandinavian countries, have already been used to obtain a better insight into this problem. Several studies and meta-analyses have been carried out, but with differing results (Visuri and Koskenvuo 1991, Paavolainen et al. 1999, Signorello et al. 2001, Tharani et al. 2001, Visuri et al. 2003, Onega et al. 2006, Visuri et al. 2010, Smith et al. 2012, Wagner et al. 2012, Brewster et al. 2013, Mäkelä et al. 2014). The surrounding tissue reacts to wear debris by undergoing a local tissue reaction in which the aseptic loosening is thought to be due to the response of macrophages and to involve hypersensitivity (Milošev 2006). There is a growing consensus that metal-induced DNA damage may lead to carcinogenesis. Keegan et al. (2007) analyzed many kinds of systemic toxicology, especially of Al, Cr(VI), Co, Ni, and V(V) and outlined the 'potential hazards' of circulating metals that include potential harmful effects on immunity, reproduction, the kidney, developmental toxicity, the nervous system, and carcinogenesis.

The International Agency for Research on Cancer (IARC) has classified Cr-(VI) and Ni-(II) as being carcinogenic, metallic Ni and soluble Co as possible carcinogens, and metallic Cr, Cr-(III) compounds and implanted orthopedic alloys as being unclassifiable. Possible pathogenetic mechanisms could involve direct mutagenic effects of metal ions or, in cases of hematolymphatic cancers, chronic antigenic stimulation of lymphocytes (IARC 2006). Ni is a highly allergenic element, Co is directly toxic, while bone cement has methylmethacrylate (MMA) as one of the main substances—not classifiable as to its carcinogenicity to humans by IARC 1994 (IARC 1994). But the monomer MMA is a lipid solvent and therefore could pass the hemato-encephalic membrane and affect the central nervous system. This would explain one of our results of Poisson analysis which indicates that use of cement increases risk of cancer in the central nervous system. Some local neurotoxicity has been diagnosed in dental technicians from contact exposure (Seppäläinen and Rajaniemi 1984).

Willert and Semlitsch (1977) reported the development of a foreign-body reaction to wear debris, consisting of macrophages and foreign-body giant cells. It is possible that the bearing type influences local and, eventually, also systemic host defenses (Trebše et al. 2014). In the study of Milošev (2006) the histological picture of periprosthetic tissue of revised THR patients showed lymphocytic aggregates in MoP patients, but they were less frequent and of much lower intensity than those in MoM patients. MoM implants are associated with more adverse events because of metal-ion-induced, T-cell-mediated delayed-type hypersensitivity (Konttinen and Pajarinen 2012). Adverse tissue reactions in MoM THRs can be systemic or local. Higher serum and solid organ metal ion levels may, theoretically, have carcinogenic and teratogenic potential (Lohmann 2014). Metal ions can activate toll-like receptor signaling, so they can also function as haptens, activating the adaptive immune system (Pajarinen et al. 2014).

The metal nanoparticles that are released from both MoM and MoP bearings result in a postoperative increase in metal ion levels at various organ sites. It is hypothesized that metal-induced DNA damage may lead to hematopoetic, prostate endometrial cancer as well as malignant melanoma (Polyzois et al. 2012).

A meta-analysis by Visuri et al. (2003) of 6 Nordic cohorts showed that the overall incidence of cancer was reduced in gastrointestinal (GIT) cancers (stomach, colon, and rectum). All cohorts showed a reduced incidence of lung cancer. The incidence was increased for endometrial cancer; prostate cancer was slightly increased in all cohorts. All forms of hematopoietic cancers, except leukemia, were slightly increased. GIT cancers are affected by use of nonsteroidal anti-inflammatory drugs (NSAIDs), which can prevent the development of colorectal cancers (Muscat et al. 1994, Hawk et al. 1999). Patients who are treated with joint replacement have often, for many years, consumed NSAIDs and, in many cases, continue to take them as painkillers for pain from other locations as well. The higher risk for prostate cancer resulting in our SIR analysis also has also been found in other studies (Signorello et al. 2001, Visuri et al. 2010, Brewster et al. 2013). Possible reasons could be found in Watson et al. (2010). These authors claim that certain metal ions have the ability to bind to estrogen receptors. These xenestrogens (metalloestrogens) can facilitate both synthesis and regulated secretion of prolactin, a growth factor for target tissues such as breast and prostate. The incidence of prostate cancer could increase by detection bias and in the latter part of the follow-up may reflect a real increase in risk (Wagner et al. 2011). Another hypothesis is that metal-induced DNA damage may lead to carcinogenesis, including hematopoetic, prostate, and endometrial cancer and malignant melanoma (Lewis and Sunderman Jr 1996). Obesity is a risk factor for endometrial cancer, renal parenchyma cancer, and gallbladder cancer in women (Olsen et al. 1999). Since the average BMI of patients at the Valdoltra hospital is in the range of overweight people, this could affect the final result (Levašič and Milošev 2017). Ni and Co are rapidly excreted by the kidney, but Cr is concentrated in the epithelial cells of the proximal renal tubules, so this could harm the kidney tissue (Oliveira et al. 2006).

The reduction in the number of respiratory tract cancers could be explained by reduced smoking, assuming that people who decide to undergo the THR have a healthier lifestyle (inclusion bias). One of the connections could be that the risk of osteoarthritis of the hip is lower in male smokers than in non-smokers (Makela et al. 2012). As smaller numbers of cases of lung cancer have been found in several studies, another mechanism not yet proven could provide the explanation alternatively (Mathiesen et al. 1995, Lewold et al. 1996, Visuri et al. 1996, Paavolainen et al. 1999, Signorello et al. 2001, Goldacre et al. 2005, Visuri et al. 2010, Makela et al. 2012). Hematolymphatic cancers—leukemic cancers and lymphomas—have been associated with McKee-Farrar (MoM) prostheses but the risk decreased after the first year following surgery (Visuri and Koskenvuo 1991). The incidence of lymphoma and of leukemia can be associated with rheumatoid arthritis (RA) or its treatment (Gillespie et al. 1988). SIR analysis in our cohort showed fewer leukemias and, in consequence, fewer hematolymphatic cancers, but only in non-MoM bearings, non-cemented THR, and the Ti-stem. This is most probably due to the exclusion of patients with RA from the cohort to avoid the bias of the higher percentage of RA patients since they are more prone to receive artificial joints than the normal population.

Unlike in some other studies, as reported by Makela et al. (2012), we did not find a higher incidence of sarcomas. In the whole cohort we found 5 sarcomas, none of which was at the site of endoprosthesis.

Generalizability

From all the features of THRs we studied the main associations were found between the bearing surface, especially metal-on-metal bearings, and specific cancers. Absolute causality remains to be confirmed by other means; however, MoM bearings should be used only in individually chosen cases. Our results are transferrable to other countries, since the Slovenian cancer incidence rates applied in our analysis are comparable to the population rates in other European countries (Zadnik et al. 2017).

Supplementary data

Tables 3–6 are available as supplementary data in the online version of this article, http://dx.doi.org/10.1080/17453674.2018.1431854

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