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July 10, 2001

Office of Device Evaluation  
Document Mail Center (HFZ 401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
9200 Corporate Boulevard  
Rockville, MD 20850

Ladies and Gentlemen:

Re: **Reclassification for Metal/Metal Semi-Constrained Hip Joint Prostheses with Cemented and Uncemented Acetabular Components; 21 CFR 888.320 and 888.330, Amendment 3**

This letter is in response to a phone conversation on June 21, 2001, between the petitioners and Mr. Mark Melkerson and Mr. Glenn Stiegman, pertaining to patient follow-up in Studies A, B, and C of our previous amendment dated May 23, 2001. A "Key for Data Appraisal" was provided by the FDA to OSMA on June 29, 2001, and is provided in Table 1. Revised patient accounting tables were generated according to these definitions in Table 2. According to these definitions, the follow-up compliance for the 24-month interval at the time of the database lock were 87%, 54%, and 76% for the metal/metal treatment in Studies A, B, and C respectively. We would like to point out that both Studies A and C are IDE studies that have resulted in 510(k) clearances for their respective companies. Study B reflects a European Study on the same device that is being studied in Study A. Since the results of Study B are consistent with the results of Study A, we believe it (Study B) to provide relevant clinical experience.

In response to our discussion, the patients from studies A and C that were "Not Yet Overdue" or "Past Due" in the 24-month window in Table 2 were identified, and the current databases were queried for 24-month or later data for these patients. To account for those patients who were "Not Yet Overdue" and "Past Due" at 24 months at the time of database closure, the categories of "Seen since D.B. Lock" and "Received after D.B. Lock" have been added to Table 2. For Study C, an additional category of "Status since D.B. Lock" has been included representing those patients who did not return for evaluation, but whose status was ascertained via telephone at 24 months or later. For those patients who had been evaluated since the database was locked, the overall Harris Hip rating results are summarized in Table 3. There were no additional revisions

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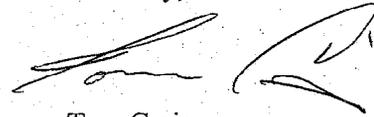
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or loose components reported in the metal/metal group in either Study A or Study C. There was one additional revision in the poly/metal group in Study A due to a deep infection, but no reports of loosening. There were no additional reports of revision or loosening in the poly/metal group in Study C. Study B had been concluded prior to the reclassification petition and no additional data has been received. At present, the databases reflect an overall compliance rate at 24 months of 325/384 (85%) which is the target for 2-year data for FDA approved studies of prosthetic joint replacement.

Also included in this amendment are two additional copies of Amendment 2, Volume 2, requested by FDA, and a recent article pertaining to cancer risks which includes an analysis of the risk of cancer following a Metal/Metal Hip prosthesis arthroplasty. Twenty copies of the Tables with additional follow-up and the paper have been provided to be supplied to the Panel by FDA.

Sincerely,

A handwritten signature in black ink, appearing to read 'Tom Craig', written in a cursive style.

Tom Craig  
President

TC/es  
Encl.

## Table 1

### Key for Data Appraisal

1. Theoretical Due – Patients who entered the follow-up window.
2. Deaths – The number of patients who died within the current or previous windows.
3. Failures – The number of patients who were determined to be study failures within the current or previous windows, e.g. revisions.
4. Not Yet Overdue – Patients who have not been seen, but who are not overdue. That is, patients who have entered the follow-up window, but have not passed through the window.
5. Number Past Due – The number of evaluations not completed and/or reported by investigators that have moved beyond the window end-point of the interval.
6. Actual Number on File – The number of evaluations completed and reported by investigators within the interval.
7. Expected Due – The value of (Theoretical – Deaths – Failures – Not Yet Overdue).
8. Follow-Up Rate – (Actual/Expected), expressed as a percentage.

Metal/Metal Hip Reclassification Petition  
 Distribution of Clinical Evaluations Across Time  
 Study A with Metal Liner Device Type  
 Table 2

13:01 Friday, May 18, 2001

Patient Status	Pre-Op Eval	6 Week Eval	6 Month Eval	12 Month Eval	24 Month Eval	36 Month Eval	48 Month Eval	60 Month Eval
Theoretical Due	219	219	203	179	109	25	0	0
Deaths	0	0	0	0	0	0	0	0
Failures	0	0	0	0	0	0	0	0
Not Yet Overdue	0	6	21	45	63	24	0	0
- Seen since D.B. Lock					47			
Number Past Due	0	18	33	22	6	0	0	0
- Received after D.B. Lock					3			
Actual Number on File	219	195	149	112	40	1	0	0
Expected Due	219	213	182	134	46	1	0	0
Follow-up Rate	0	92	82	84	87	100	-	-

Of the 69 hips that were Not Yet Overdue or Past Due in the 24 Month Interval, 50 were seen since the Database Lock (D.B. Lock) for a follow-up rate of  $90/96 = 94\%$ .

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Metal/Metal Hip Reclassification Petition  
 Distribution of Clinical Evaluations Across Time  
 Study A with Poly Liner Device Type  
 Table 2

13:01 Friday, May 18, 2001

Patient Status	Pre-Op Eval	6 Week Eval	6 Month Eval	12 Month Eval	24 Month Eval	36 Month Eval	48 Month Eval	60 Month Eval
Theoretical Due	206	206	189	162	100	20	0	0
Deaths	0	0	0	0	0	0	0	0
Failures	0	0	1	1	1	1	1	1
Not Yet Overdue	0	10	23	41	52	20	0	0
- Seen since D.B. Lock					31			
Number Past Due	0	11	28	16	2	0	0	0
- Received after D.B. Lock					1			
Actual Number on File	206	185	137	104	46	0	0	0
Expected Due	206	196	165	120	47	0	0	0
Follow-up Rate	100	94	83	87	98	-	-	-

Of the 54 hips that were Not Yet Overdue or Past Due in the 24 Month Interval, 32 were seen since the Database Lock (D.B. Lock) for a follow-up rate of  $78/79 = 99\%$ .

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Metal/Metal Hip Reclassification Petition  
 Distribution of Clinical Evaluations Across Time  
 Study B with Metal Liner Device Type  
 Table 2

13:01 Friday, May 18, 2001

Patient Status	Pre-Op Eval	6 Week Eval	6 Month Eval	12 Month Eval	24 Month Eval	36 Month Eval	48 Month Eval	60 Month Eval
Theoretical Due	87	87	87	87	87	60	0	0
Deaths	0	0	0	0	0	0	0	0
Failures	0	0	0	1	1	1	1	1
Not Yet Overdue	0	0	0	0	17	49	0	0
Number Past Due	0	2	15	19	32	0	0	0
Actual Number on File	87	85	72	67	37	10	0	0
Expected Due	87	87	87	86	69	10	0	0
Follow-up Rate	0	98	83	78	54	100	0	0

No additional patients followed since database lock due to study being closed.

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Metal/Metal Hip Reclassification Petition  
 Distribution of Clinical Evaluations Across Time  
 Study C with Metal Liner Device Type  
 Table 2

13:01 Friday, May 18, 2001

Patient Status	Pre-Op Eval	6 Week Eval	6 Month Eval	12 Month Eval	24 Month Eval	36 Month Eval	48 Month Eval	60 Month Eval
Theoretical Due	97	97	97	94	72	45	23	0
Deaths	0	1	1	2	2	2	2	2
Failures	0	0	0	0	0	0	0	0
Not Yet Overdue	0	0	2	14	25	17	19	0
- Seen since D.B. Lock					18			
- Status since D.B. Lock					3			
Number Past Due	0	96	9	11	11	6	0	0
- Received after D.B. Lock					6			
- Status since D.B. Lock					3			
Actual Number on File	97	0	85	67	34	20	2	0
Expected Due	97	96	94	78	45	26	2	0
Follow-up Rate	100	0	90	86	76	77	100	-

Of the 36 hips that were Not Yet Overdue or Past Due in the 24 Month Interval, 30 were seen or had a status since the Database Lock (D.B. Lock) for a follow-up rate of  $64/75 = 85\%$ .

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Metal/Metal Hip Reclassification Petition  
 Distribution of Clinical Evaluations Across Time  
 Study C with Poly Liner Device Type  
 Table 2

13:01 Friday, May 18, 2001

Patient Status	Pre-Op Eval	6 Week Eval	6 Month Eval	12 Month Eval	24 Month Eval	36 Month Eval	48 Month Eval	60 Month Eval
Theoretical Due	97	97	97	87	66	44	17	0
Death	0	1	1	2	2	2	2	2
Failure	0	0	0	0	0	0	0	0
Not Yet Overdue	0	0	10	17	18	19	13	0
- Seen since D.B. Lock					9			
- Status since D.B. Lock					4			
Number Past Due	0	96	14	15	9	1	0	0
- Received after D.B. Lock					4			
- Status since D.B. Lock					2			
Actual Number on File	97	0	72	53	37	22	2	0
Expected Due	97	96	86	68	46	23	2	0
Follow-up Rate	100	0	84	78	80	96	100	-

Of the 27 hips that were Not Yet Overdue or Past Due in the 24 Month Interval, 19 were seen or had a status since the Database Lock (D.B. Lock) for a follow-up rate of 56/65 = 86%.

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**Table 3**

**Harris Hip Overall Ratings  
For Hips "Not Yet Overdue" or "Past Due" in the 24 Month Interval at the  
Time of Database Lock Who Were Subsequently Evaluated**

Study	Device Type	Harris Hip Overall Rating								N
		Excellent		Good		Fair		Poor		
		N	Percent	N	Percent	N	Percent	N	Percent	
A	Metal Liner	46	92.0	3	6.0	1	2.0	0	0.0	50
A	Poly Liner	30	93.8	2	6.2	0	0.0	0	0.0	32
C	Metal Liner	21	87.5	2	8.3	0	0.0	1	4.2	24
C	Poly Liner	11	84.6	2	15.4	0	0.0	0	0.0	13

# THE RISK OF CANCER FOLLOWING TOTAL HIP OR KNEE ARTHROPLASTY

BY RAVI THARANI, BS, FREDERICK J. DOREY, PHD, AND THOMAS P. SCHMALZRIED, MD

The first well-documented case of cancer associated with total joint replacement was in a patient in whom a malignant fibrous histiocytoma developed three and one-half years after a McKee-Farrar total hip replacement that was performed in December 1969<sup>1</sup>. At least twenty-four additional cases of malignant disease occurring in association with a total hip or knee prosthesis have been reported in the English-language literature<sup>2-20</sup>. On the basis of this small number of case reports, there is no apparent relationship between any specific implanted material and cancer.

The carcinogenic properties of the metals used in joint prostheses have been studied. Cobalt and chromium wear particles have been shown to induce carcinoma in animal models<sup>21</sup>, giving rise to the concern that such alloys could have the same effect in human tissue if present in sufficient amounts for a sufficient length of time. Elevated levels of chromium and cobalt have been found in human tissues surrounding orthopaedic implants and in tissues at remote sites<sup>22</sup>. There also has been concern that metal-on-metal bearings used in total hip arthroplasty may pose a higher risk of malignant degeneration because of an increased exposure to metal particles and ions. Although metal particles and ions have been the prominent concern, there also have been reports of cancer induction in association with polymethylmethacrylate (bone cement)<sup>23</sup> and polyethylene<sup>24</sup> in animal models.

The speculation that total hip and total knee replacements could cause malignancy has inspired epidemiological studies aimed at evaluating this concern. Of the twenty-five reported cases of cancer following a total hip or knee

replacement, twenty-one<sup>1-9,11-16,18-20</sup> involved sarcomas. Because the prevalence of such cancers is low in the general population, combining the available data enhances the ability to examine the relative risk of cancer in association with total hip or knee arthroplasty. The available epidemiological studies regarding this question encompass more than 140,000 total hip and knee replacements<sup>25-33</sup>.

While there has been much research on the local effects of total joint arthroplasty, such as osteolysis, there has been comparatively little investigation of systemic effects, such as cancer. If a goal of research is to develop prostheses that will function for thirty years or more, it is increasingly important to understand the systemic consequences of joint arthroplasty. This review presents the available data on cancer associated with total joint arthroplasty in order to (1) define the current state of knowledge, (2) identify limitations of the available data, and (3) direct future studies.

## Epidemiological Studies

With use of MEDLINE via PubMed, the Internet database of the National Library of Medicine, all articles published between January 1966 and October 1999 in the English-language literature that include the key words *joint, hip, knee, replacement, prosthesis, arthroplasty, implant, cancer, sarcoma, lymphoma, leukemia, histiocytoma, hematopoietic, tumor, polyethylene, cobalt, chromium, ions, toxicity, stainless steel, titanium, and UHMWPE (ultra-high molecular weight polyethylene)* were reviewed.

The search revealed nine studies<sup>25-33</sup> that included the following data: (1) the relative risk of cancer in patients undergoing elective total hip

or knee arthroplasty compared with that in the general population of the study or a control group and (2) a standard incidence ratio (SIR) or relative risk and the data needed to calculate these values. The pooled data from the nine studies encompassed 110,792 total hip replacements and 29,800 total knee replacements. Seven of the studies were from Scandinavia<sup>27-33</sup>; one, from New Zealand<sup>25</sup>; and one, from Seattle, Washington<sup>26</sup>.

Relative risk was calculated by dividing the sum of the observed number of cancer cases associated with hip or knee arthroplasty by the sum of the expected number of cases in the general population from each of the nine relevant studies. The expected number of cases in the general population was derived from reported data from that geographical region as cited in each study. A 95% confidence interval was calculated with use of these data through a Poisson model.

## Total Hip Replacement Risk of All Cancers

A combined total of 12,052 observed and 12,435.4 expected cases of cancer were identified following total hip replacement (relative risk, 0.97; 95% confidence interval, 0.95 to 0.99) (Fig. 1-A). Mathiesen et al.<sup>28</sup> separately evaluated the data for bilateral and revision total hip arthroplasty to obtain the relative risk for each procedure. Among the 2005 patients who underwent bilateral total hip replacement, there were 117 observed and 138.7 expected cases of cancer (relative risk, 0.84; 95% confidence interval, 0.70 to 1.01). Among the 1258 patients who underwent revision total hip replacement, there were ninety observed and 86.8 expected cases of cancer (relative risk, 1.04; 95% confi-

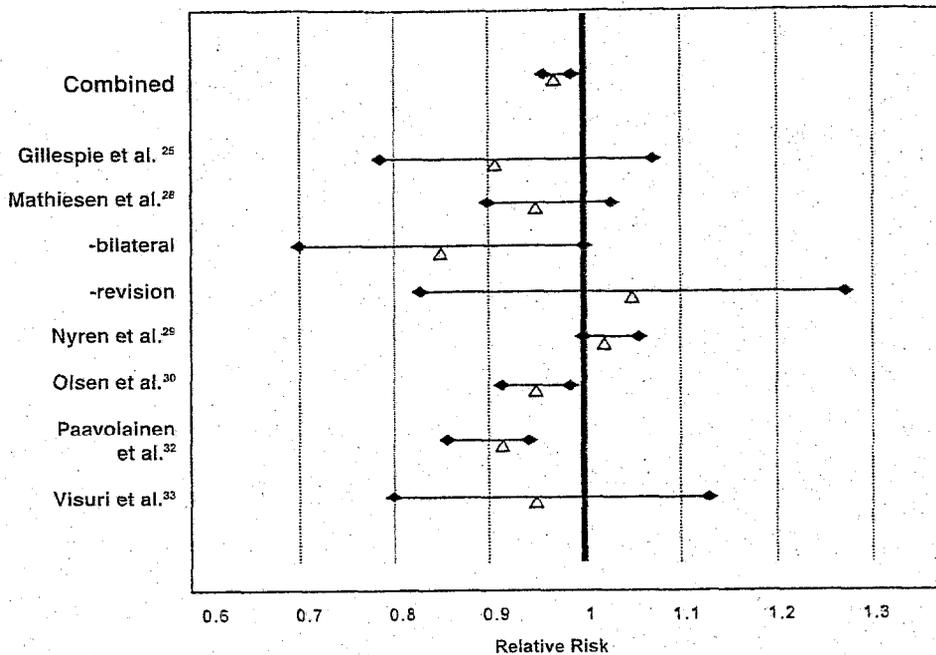


Fig. 1-A

Illustration showing the relative risks and 95% confidence intervals for all cancers associated with total hip replacement for the individual epidemiological studies and for the combined data. The combined relative risk was 0.97 (95% confidence interval, 0.95 to 0.99).

nce interval, 0.83 to 1.27).

In only three studies was the development of cancer categorized on the basis of the time to diagnosis following total joint replacement<sup>25,29,32</sup>. The relative risk tended to stay relatively constant with increasing durations of follow-up, except in one study consisting of only 1358 patients<sup>25</sup>, in which the relative risk increased to 1.60 after ten years of follow-up. However, in two larger studies<sup>29,32</sup>, encompassing a total of 70,805 total hip replacements, no substantial increase was reported over time. In one of these studies, the relative risk of cancer was <1.0, regardless of the time to diagnosis following total joint replacement<sup>32</sup>.

#### Risk of Hematopoietic Cancer

Hematopoietic cancers are identified as ICD-7 (International Classification of Disease) numbers 200 through 209 and include non-Hodgkin lymphoma, Hodgkin disease, myeloma, and leukemia. There was a combined total of 732 observed and 718.75 expected cases of hematopoietic cancer following total hip arthroplasty (relative risk, 1.02; 95% confidence interval, 0.94 to 1.08) (Fig. 1-B). Among the 2005 patients who underwent bilateral total hip replacement<sup>28</sup>,

there were five observed and 10.5 expected cases of hematopoietic cancer (relative risk, 0.48; 95% confidence interval, 0.16 to 1.12). Among the 1258 patients who underwent revision hip replacement, there were five observed and 6.7 expected cases of hematopoietic cancer (relative risk, 0.75; 95% confidence interval, 0.24 to 1.75).

In three studies<sup>25,29,32</sup>, the development of hematopoietic cancer was categorized on the basis of the time to diagnosis following total joint replacement. These studies had variable results. One study<sup>32</sup> demonstrated an increased risk in association with more than ten years of follow-up, and two<sup>25,29</sup> demonstrated a decreased risk. In one of the latter two studies, the highest relative risk occurred in the one to four-year follow-up period<sup>29</sup>.

#### Risk of Sarcoma

Although the studies did not specifically differentiate sarcomas of bone and connective tissue from other malignant lesions involving these tissues, an elevated risk of sarcoma would present in this group of cancers. The occurrence of bone, soft-tissue, and connective-tissue malignancy (ICD-7 numbers 196 and 197) following total

hip replacement was specifically reported in five studies involving a total of 105,166 patients<sup>28-30,32,33</sup>. Among these patients, there were sixty-six observed and 63.86 expected cases of sarcoma (relative risk of 1.03; 95% confidence interval, 0.80 to 1.31) (Fig. 1-C).

#### Total Knee Replacement

##### Risk of All Cancers

In the four studies that included data on knee replacement<sup>26,27,30,31</sup>, there was a combined total of 1978 observed and 2142.3 expected cases of cancer (relative risk, 0.92; 95% confidence interval, 0.88 to 0.96). Data on the development of cancer after bilateral or revision total knee replacement were not available, nor were data on latency.

##### Risk of Hematopoietic Cancer

In the four studies that included data on total knee replacement<sup>26,27,30,31</sup>, there were 154 observed and 139.6 expected cases of hematopoietic cancer (relative risk, 1.10; 95% confidence interval, 0.94 to 1.29). Data on the development of hematopoietic cancer after bilateral or revision total knee replacement were not available, nor were data on the time to diagnosis of cancer following total knee replacement.

**Risk of Sarcoma**

In the three studies that included data on bone, connective-tissue, and soft-tissue malignancy after total knee replacement<sup>27,30,31</sup>, there were twenty-three observed and 20.6 expected cases of sarcoma (relative risk, 1.12; 95% confidence interval, 0.71 to 1.68).

**Metal-on-Metal Compared with Metal-on-Polyethylene Total Hip Arthroplasty**

Only Visuri et al.<sup>33</sup> and Paavolainen et al.<sup>32</sup> segregated metal-on-metal prostheses from metal-on-polyethylene hip prostheses. Visuri et al. evaluated the occurrence of cancer following total hip replacement performed with the McKee-Farrar prosthesis, a metal-on-metal device made of a cast cobalt-chromium alloy. In the group of 579 patients who received this prosthesis, there were 113 observed and 118.36 expected cases of cancer (relative risk, 0.95; 95% confidence interval, 0.79 to 1.13). In the study by Paavolainen et al., which involved only metal-on-polyethylene total hip replacements, there were 2367 observed and 2626 expected cases of cancer (relative risk, 0.90; 95% confidence interval, 0.87 to 0.94).

Visuri et al. reported twelve observed and 7.56 expected cases of he-

matopoietic cancer (relative risk, 1.59; 95% confidence interval, 0.82 to 2.77) and zero observed and 0.56 expected cases of sarcoma (relative risk, 0.00; 95% confidence interval, 0.00 to 6.59) following metal-on-metal total hip replacement<sup>33</sup>. When Visuri et al. compared the occurrence of leukemia in patients who had had a metal-on-metal total hip replacement with that in patients who had had a metal-on-polyethylene replacement, they found a relative risk of 3.77 (95% confidence interval, 0.96 to 17.6), suggesting a higher risk among patients receiving a metal-on-metal implant. Paavolainen et al. reported 173 observed and 187 expected cases of hematopoietic cancer (relative risk, 0.93; 95% confidence interval, 0.69 to 1.22) and thirteen observed and seventeen expected cases of sarcoma (relative risk, 0.76; 95% confidence interval, 0.41 to 1.31) following metal-on-polyethylene total hip replacement<sup>32</sup>.

Data on the development of cancer after bilateral or revision metal-on-metal or metal-on-polyethylene total hip replacement were not available in either study. Data on the time to diagnosis of cancer following total joint replacement were available only for metal-on-polyethylene implants in the

study by Paavolainen et al.<sup>32</sup>. According to these data, the overall relative risk of all cancers remained <1.0 regardless of latency, although the relative risk of hematopoietic cancer increased after ten years.

To our knowledge, there have been no studies on the risk of cancer associated with ceramic bearings and no studies in which data were stratified on the basis of the type of fixation (use of bone cement compared with no use of bone cement). Similarly, there are insufficient data to allow comparisons of different metallic alloys (cobalt-chromium, titanium, or stainless steel) used in the implants.

**Duration of Follow-up**

Six of the nine epidemiological studies included an analysis of the data with regard to the mean duration and range of follow-up<sup>25,28,33</sup>. The mean duration of follow-up for the six studies was 7.5 years (range, six months to seventeen years). In only three of these studies were data on person-years at risk stratified according to the duration of follow-up<sup>25,28,33</sup>. In the study by Visuri et al.<sup>33</sup>, 36% of the person-years at risk were associated with patients who had undergone surgery zero to four years prior to examination; 53%, with those who had

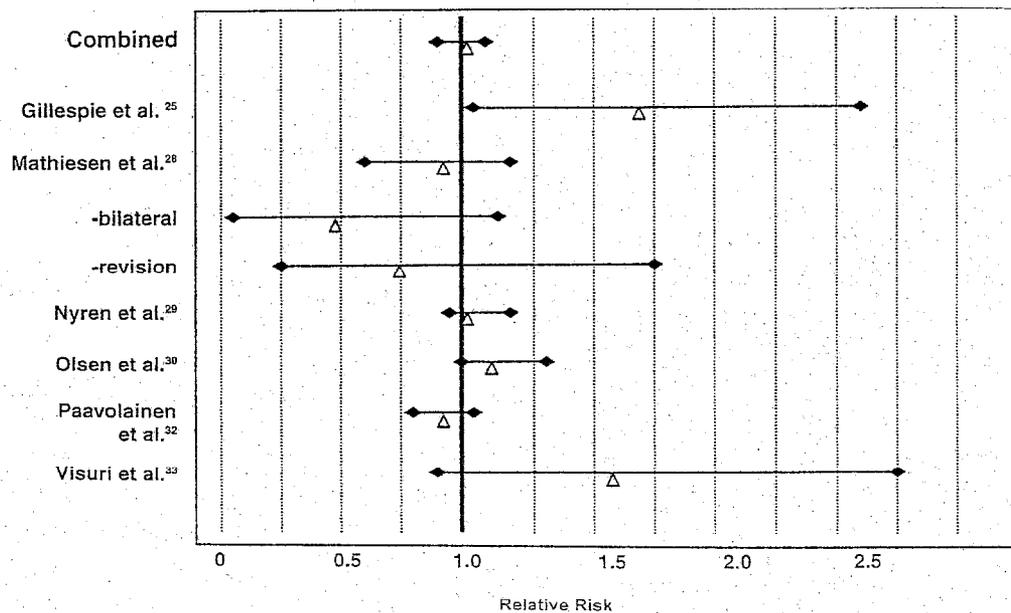


Fig. 1-B  
Illustration showing the relative risks and 95% confidence intervals for hematopoietic cancer associated with total hip replacement for the individual epidemiological studies and for the combined data. The combined relative risk was 1.02 (95% confidence interval, 0.94 to 1.08).

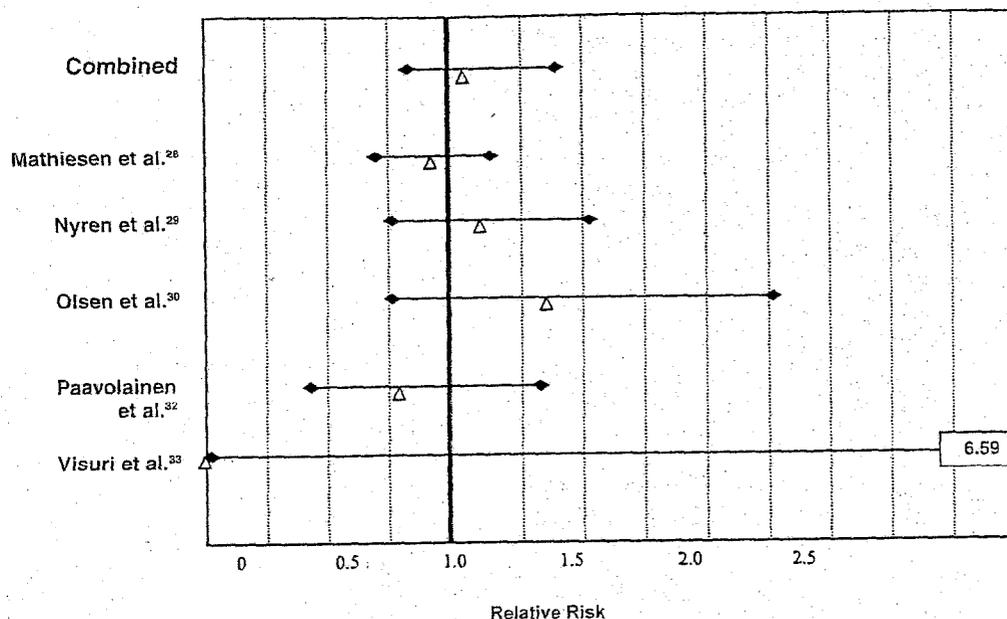


Fig. 1-C  
Illustration showing the relative risks and 95% confidence intervals for sarcoma associated with total hip replacement for the individual epidemiological studies and for the combined data. The combined relative risk was 1.03 (95% confidence interval, 0.80 to 1.31).

d surgery five to fourteen years prior examination; and only 11%, with those who had had surgery at least fifteen years prior to examination. Only four studies included a follow-up period of at least ten years<sup>25,29,32,33</sup>.

A substantial proportion of the cancers were observed during the first few years after joint replacement. The combined data of Gillespie et al.<sup>25</sup>, Mathiesen et al.<sup>28</sup>, and Paavolainen et al.<sup>32</sup> indicate that 34% of all cancers and 36% of hematopoietic cancers were observed during the first two postoperative years. The combined data of Mathiesen et al. and Paavolainen et al. indicate that 39% of sarcomas were observed during the first two postoperative years. The combined data of Gillespie et al.<sup>25</sup> and Nyren et al.<sup>29</sup> indicate that 32% of all cancers and 36% of hematopoietic cancers were observed at zero to four years; 47% and 43%, at five to nine years; and 21% and 20%, at ten years or more. Only Nyren et al. evaluated sarcoma in this manner; the rate was 26% at zero to four years, 62% at five to nine years, and 12% at ten years or more (Fig. 2).

#### Limitations of the Data

This analysis reveals that the available data have limitations, including an insufficient length of follow-up for pa-

tients who have undergone total joint replacement, a lack of information regarding dose-response, and the presence of confounding comorbidities. In addition, there are limited data on patients from countries outside of Scandinavia. Therefore, it is unclear if the available data are relevant to other races, cultures, or geographic regions.

The relative risks of 0.97 for total hip replacement and 0.92 for total knee replacement suggest that there is a decrease in the risk of cancer following total hip and total knee replacement compared with that in the general population. The 95% confidence intervals are also less than unity, indicating a statistically lower risk. These data could be interpreted as indicating that total joint replacement has a protective effect against cancer. It is also possible, however, that the anesthetic and surgical concerns associated with total joint arthroplasty result in the selection of a comparatively healthy patient population, in which case the general health status, and not the total joint replacement *per se*, may confer a reduced risk of cancer.

There has been concern that metal-on-metal total joint replacements may be associated with an increased risk of cancer because of an increased

exposure to metal particles or ions. The risk of cancer after metal-on-metal total hip replacement has been assessed specifically in only one epidemiological study<sup>33</sup>. In that study, the relative risk of cancer was reported to be 0.95 (95% confidence interval, 0.79 to 1.13), suggesting that there is no apparent increased risk of cancer after metal-on-metal total hip arthroplasty. In addition, the risk of sarcoma after metal-on-metal total hip replacement was found to be 0.00 (95% confidence interval, 0.00 to 6.59)<sup>33</sup>. However, those same authors found the relative risk of hematopoietic cancer to be 1.59 (95% confidence interval, 0.82 to 2.77) following metal-on-metal total hip replacement and 3.77 (95% confidence interval, 0.96 to 17.6) for leukemia when metal-on-metal implants were compared with metal-on-polyethylene implants. Again, the confidence intervals for these data are very broad and encompass unity, indicating that the risk is statistically neither increased nor decreased. From an epidemiological perspective, these data are limited because of the small number of patients (579) who underwent metal-on-metal total hip replacement. Because this number is small and the numbers of both observed and expected cases are

also small, the strength of the probability analysis is quite limited. Taken literally, the relative risk for sarcoma in this cohort (0.00) would suggest that patients with a metal-on-metal total hip replacement have a conferred immunity to sarcoma due to the surgery or the implant. This point highlights the limitations of the data and the need for cautious interpretation.

Latency is an important consideration in the determination of the cause of malignant transformation. For a carcinoma to result from exposure to an exogenous stimulus, cellular changes must occur and many cycles of division must follow. A malignant

cell would then require numerous divisions before becoming a clinically apparent cancer. Case et al., in a biochemical study of premalignant changes in bone marrow adjacent to total hip replacements, found no evidence of cellular transformation less than ten years after surgery<sup>34</sup>, suggesting that epidemiological studies should focus on patients who have had surgery more than ten years prior to evaluation.

The time from the initial exposure to the diagnosis of cancer has been reported for carcinogens such as asbestos. Asbestos fibers are associated primarily with mesotheliomas and

bronchogenic carcinomas<sup>35</sup>. In theory, the carcinogenic properties of asbestos have some similarity to those of prosthetic particles. Asbestos fibers are microscopic and phagocytized, inducing chromosomal mutations (aneuploidy and aberrations) and transformations in mesothelial cells<sup>35</sup> and causing a chronic foreign-body inflammatory response similar to that induced by particles from total joint replacement. The malignant degeneration following asbestos exposure has a much longer latency period than that following total joint replacement as suggested by these epidemiological studies. In two studies, mean latency periods of twenty-two years<sup>36</sup> and thirty-seven years<sup>37</sup> were reported for development of cancer following asbestos exposure.

With regard to latency, the length of follow-up is another limitation of these epidemiological studies. Gillespie et al.<sup>25</sup> reported that the relative risk of cancer associated with total hip replacement increased to 1.60 (95% confidence interval, 1.22 to 2.09) when the duration of follow-up exceeded ten years. In that small study, there were fifty-seven cases of cancer among the 1358 patients who had undergone surgery at least ten years earlier. However, Nyren et al.<sup>29</sup> and Paavolainen et al.<sup>32</sup>, in studies based on larger sample populations, did not report such an increase after ten years. Nyren et al. reported 939 cases of cancer in 39,154 patients who had had a total hip replacement at least ten years earlier (relative risk, 1.04; 95% confidence interval, 0.98 to 1.11). Paavolainen et al. reported 236 cases of cancer in 31,651 patients who had had a total hip replacement at least ten years earlier (relative risk, 0.95; 95% confidence interval, 0.83 to 1.07).

Another argument against a causal relationship between total hip and knee arthroplasty and cancer is that bilateral arthroplasties have not been associated with a higher risk of cancer. Known carcinogens, such as asbestos and tobacco, have been shown to have a dose-dependent role in carcinogenesis<sup>38</sup>. Thus, a greater exposure to the materials used for total

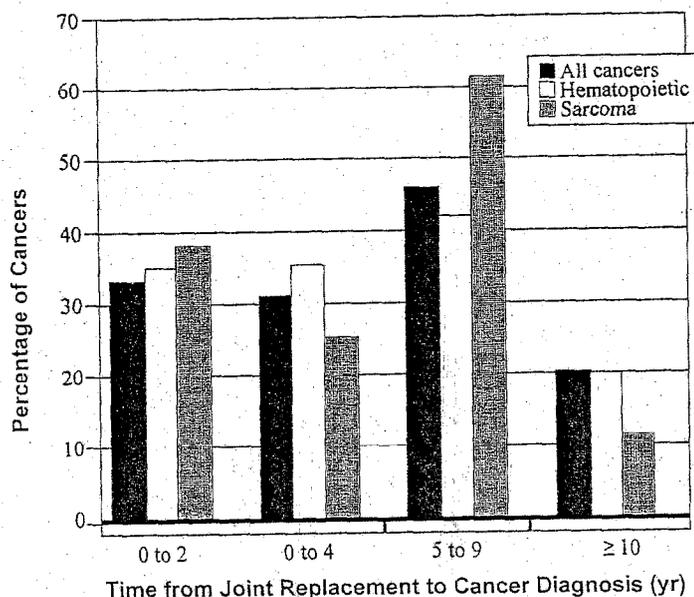


Fig. 2

Bar graph showing the percentage of all cancers in terms of the time from total joint replacement to the diagnosis of cancer. A substantial proportion of the cancers were diagnosed during the first few years after joint replacement. The first follow-up period (zero to two years) reflects the combined data from the studies by Gillespie et al.<sup>25</sup>, Mathiesen et al.<sup>28</sup>, and Paavolainen et al.<sup>32</sup>, in which 34% of all cancers and 36% of hematopoietic cancers were diagnosed during the first two postoperative years. Mathiesen et al. and Paavolainen et al. found that 39% of all sarcomas were diagnosed during the first two postoperative years. The next three follow-up periods reflect the combined data from the studies by Gillespie et al.<sup>25</sup> and Nyren et al.<sup>29</sup>, who found that 32% of all cancers and 36% of hematopoietic cancers were diagnosed at zero to four years; 47% and 43%, at five to nine years; and 21% and 20%, at ten years or more. Only Nyren et al. stratified the data on sarcoma according to time-period; the rate was 26% at zero to four years, 62% at five to nine years, and 12% at ten years or more.

joint arthroplasty, as in patients managed with bilateral replacement, would be expected to result in a greater risk of cancer. However, Mathiesen et al.<sup>28</sup> found a relative risk of 0.84 (95% confidence interval, 0.70 to 1.01) for bilateral total hip arthroplasty, which contrasts with the dose-dependent properties of established carcinogens.

An additional limitation of the available data is that comorbidities that may influence the occurrence of cancer were not accounted for in most of these epidemiological studies. Some conditions that necessitate or that are associated with hip or knee replacement have themselves been associated with an increased risk of cancer.

Rheumatoid arthritis is a common condition that leads to total joint arthroplasty, and such autoimmune disorders have been associated with a predisposition to lymphoma<sup>39</sup> and leukemia<sup>40</sup>. Lewold et al.<sup>27</sup> stratified data on the development of cancer following total knee replacement according to whether the patients had rheumatoid arthritis or osteoarthritis. Figure 3 demonstrates that the risk of cancer in patients with rheumatoid arthritis remained high compared with that in patients with osteoarthritis, regardless of latency time. This suggests that the elevated risk is associated with the systemic disease (rheumatoid arthritis) and that it may not be associated with the local treatment (total knee replacement). Future studies should stratify data according to diagnosis or should exclude patients with rheumatoid arthritis in order to avoid a confounding effect on the association between cancer and total joint replacement.

Other potential comorbidities that have been independently associated with cancer include Paget disease<sup>41</sup>, osteomyelitis<sup>42</sup>, hereditary bone dysplasia<sup>43</sup>, and bone infarcts<sup>44</sup>. These conditions have been linked to malignant fibrous histiocytoma, a soft-tissue sarcoma that has been reported frequently in studies of cancer following total hip and knee arthroplasty.

Thermal necrosis can result from the use of polymethylmethacrylate

bone cement during orthopaedic procedures<sup>45</sup>. Areas of bone immediately adjacent to cement become necrotic and undergo repair in a manner similar to bone infarcts. The association between bone infarcts and malignant fibrous histiocytoma is the basis for the theory that this type of tumor may arise in bone adjacent to cement as a result of the repair process becoming malignant<sup>3</sup>. However, there have been no studies, to our knowledge, in which the risk of cancer in patients who have had total joint replacement with bone cement is compared with that in patients who have had total joint replacement without cement.

In summary, the available data do not support a causal link between total hip or knee arthroplasty and the development of cancer. Although it is biologically plausible for the materials used in total joint replacement to induce malignant degeneration, this relationship has not been demonstrated. There is ongoing concern about an association between hematopoietic cancer and total joint replacement. The most important finding of this review, however, is the identification of the limitations of the available data. In or-

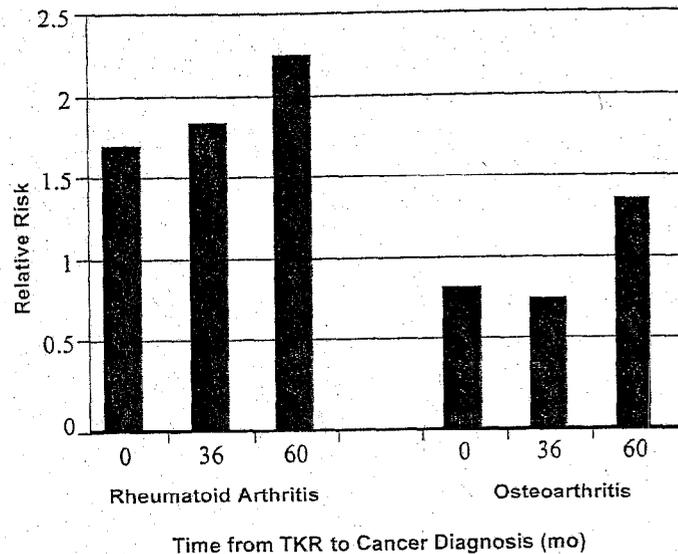


Fig. 3  
Bar graph showing the relative risk of lymphoma versus the time from total knee replacement (TKR) to the diagnosis of cancer for patients with rheumatoid arthritis and those with osteoarthritis<sup>27</sup>.

der to better define the relationship between total hip or total knee replacement and cancer, future studies must include larger patient populations with more racial and cultural diversity, adjust for comorbidities, focus on patients who had the surgery more than ten years previously, and stratify the data on the basis of the specific materials implanted and whether or not bone cement was used. ■

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