Do the cobalt and chromium released from metal-on-metal hip resurfacing cause cancer?

Mark Longman
Trainee Intern
Dunedin School of Medicine
University of Otago

Mark is currently undertaking his medical school elective at the Ivo Pitanguy Institute in Rio de Janeiro, Brazil and will spend four weeks with the orthopaedic team at Tohoku University in Sendai, Japan to finish his elective. His interests outside medicine include basketball, surfing and playing the guitar. He is interested in pursuing a career in orthopaedic surgery after graduation.

ABSTRACT

This article reviews the evidence for and against an increase in the incidence of cancer after use of cobalt-chromium-molybdenum devices for treatment of arthritis of the hip. Total hip replacement devices have been in common use for several decades and their use has been tentatively and weakly linked to changes in incidence of cancer, particularly haematopoietic malignancy. The magnitude and hence clinical relevance of these changes in cancer incidence remain largely unknown. Over the last decade metal on-metal hip resurfacing devices, a new type of metal-on-metal prosthesis, have become increasingly common, particularly in younger patient groups. The new hip resurfacing devices are made of the same materials as total hip replacement prostheses but generate more metallic wear particles. These metallic wear particles have been shown to have carcinogenic effects in-vitro and have been linked to increased rates of chromosomal abnormalities in-vivo. The relevance of these links to clinical end-points such as development of malignancy remains unknown. Analysis of long term data such as national joint registries will be necessary to demonstrate any changes in incidence of cancer.

Key words

Hip, replacement, resurfacing, arthroplasty, cancer, cobalt, chromium

AIMS

This article aims to review the scientific evidence for and against any carcinogenic effects of the cobalt-chromium-molybdenum alloy used in total hip replacement and in total hip resurfacing surgery. It also aims to review any evidence for a different strength of carcinogenic effect given the different designs and wear characteristics of total hip replacement and hip resurfacing prostheses.

INTRODUCTION

Hip resurfacing with cobalt-chrome-molybdenum components has become a common operation in patients considered likely to outlast a conventional total hip replacement (THR). Chromium and cobalt are both known carcinogens - this essay reviews the evidence regarding cancer developing due to wear particles from cobalt-chromium-molybdenum hip resurfacing.

BACKGROUND

THR is an excellent treatment for hip arthritis in older patients but is much less satisfactory in younger and more active patient groups.[1] This younger patient group is likely to require revision of their joint replacement during their lifetime, a difficult operation because bone in the upper femur is lost due to the initial procedure and subsequent osteolysis. Hip resurfacing preserves the femoral head and does not cause bone loss in the upper femur.[2] Metal-on-metal hip resurfacing is accordingly targeted at younger healthy patients who have a high chance of outliving a primary THR. It is used in patients with an average age of 48-52 years and patients have been as young as seventeen years old.[3-5] These younger patients are likely to have a prosthesis in situ for decades.

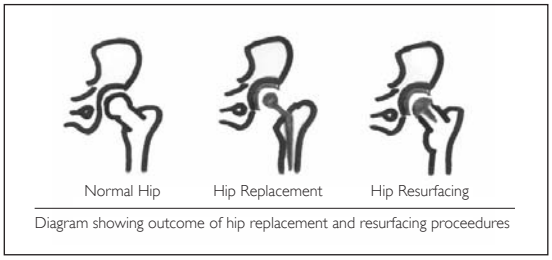


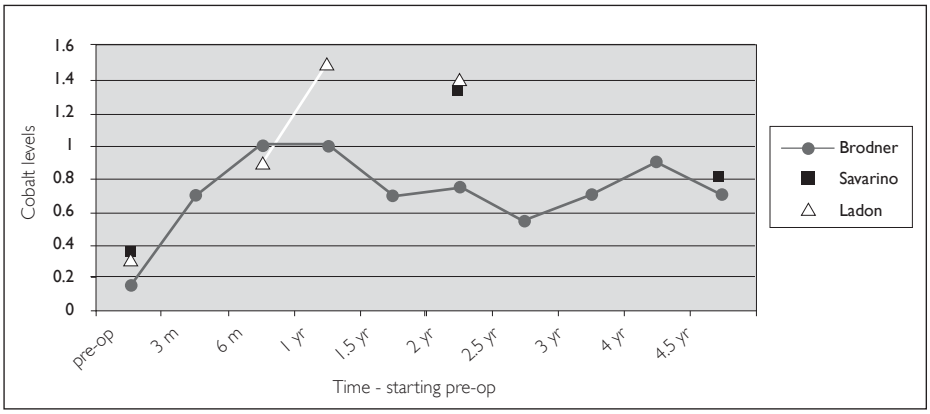
Diagram showing outcome of hip replacement and resurfacing proceedures

Hip resurfacing is a surgical procedure in which a hemispherical shell is placed on the femoral head and a matching shell inserted on the acetabular surface. Resurfacing of the femoral-acetabular articulation is not a new procedure. Procedures similar to current bone resurfacing have been performed as early as 1948.[6] Metal-on-metal hip resurfacing was abandoned in the early 1970's as the results of cemented metal-on-polyethylene components were superior at that stage.[6] Hip resurfacing was performed using these cemented metal-polyethylene devices until it became clear that there was an unacceptably high level of implant failure due to excessive wear and osteolysis with loosening of the prosthesis.[7-10] Hip resurfacing was abandoned and THR became the treatment of choice.

New hip resurfacing prostheses were designed. Improvements in bearing design and surgical technique have led to improved short-term outcomes from hip resurfacing procedures.[11] The current range of resurfacing implants make use of a metal-on-metal implant design, with a cobalt, chromium and molybdenum alloy the only form currently in use.[12,13] Excellent short-term results have been reported by various authors with similar patient satisfaction to THR and few short-term complications.[4,5,14,15] Treacy et al

of Birmingham reported a 98 per cent implant survival at five years.[3] Back et al of Melbourne reported a 99.14 per cent implant survival after a mean follow-up period of three years. Ninety-seven per cent of their patients considered the outcome to be good or excellent.[5] Pollard et al reported a matched case-control study on two groups of 54 hips, one treated with hip resurfacing and the other treated with total hip arthroplasty. Both groups had similar functional scores at 5-7 years follow up and the hip resurfacing patients had higher activity levels. Long-term results, however, are not yet available. This means that the effect of long-term exposure to metallic debris is not known.

Graph 1. Time Trend in Cobalt Levels



Metal wear and ion release

A metal-on-metal articulation inevitably generates metallic debris. The patient's exposure to metal ions varies depending on implant materials, design, and implantation. Good implant design and implantation minimizes the amount of wear, but elevated serum levels of cobalt and chromium have repeatedly been demonstrated in patients with metal-on-metal bearings, in both traditional THR and in hip resurfacing.[11,16-18]

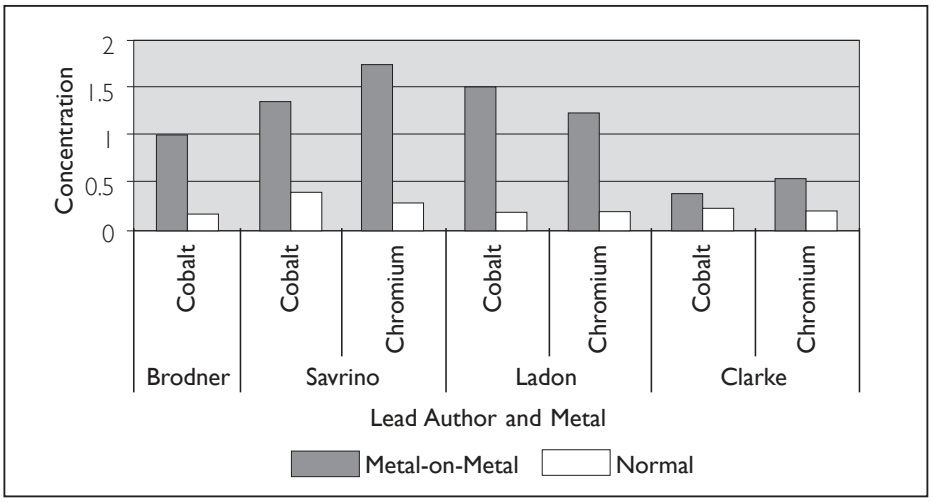
The amount of metallic debris formed is influenced by several factors. There are differences in wear rate between the initial wearing in of an implant and the steady state reached after a period of use. Linear annual wear in second generation metal-on-metal THR has been shown to be 25µm in the first year falling to 5µm after the third year.[19,20] Particle generation and wear rate are elevated by increases in activity levels.[21] Size, shape, and composition of wear particles are affected by the time a prosthesis is in situ.[13] The metal particles are released locally then circulated in the blood stream before being excreted by the kidneys. Elevated levels of these ions have been found in autopsy specimens of various organs including lymph nodes, liver and spleen.[22,23]

Normal values for cobalt and chromium levels vary depending on the method of analysis. Serum levels of cobalt and chromium are consistently elevated after metal-on-metal prostheses are implanted. A study by Clark et al found serum levels of cobalt and chromium of 38 nmol/L and 53 nmol/L respectively after metal-on-metal hip resurfacing and of 22 nmol/L and 19 nmol/L respectively after 28 mm total hip arthroplasty.[11] In a prospective randomised controlled trial of metal-on-metal THRs versus metal-on-polyethylene THRs increases in metal ion levels were significantly greater in the metal-on-metal group than in the metal-on-polyethylene group.[24]

Graph one. Serum cobalt levels following surgery and during followup. Note the initial rapid rise in cobalt levels followed by a slight fall and plateau at a level elevated above pre-operative values.

Graph two. Summary of studies comparing levels of cobalt and chromium in control groups ("normal") with levels of cobalt and chromium

Graph 2: Proportional Increase in Metal Levels
Studies comparing ion levels in metal-on-metal with normal values



in post surgical patients (metal-on-metal). This graph illustrates the elevation of ion levels above normal in post-surgical patients, and does not differentiate between THR and hip resurfacing procedures.

These results demonstrate that levels of cobalt and chromium are raised after both THR and hip resurfacing, and some suggest that levels of ions are elevated significantly higher after hip resurfacing. One recent study, however, showed no difference in systemic levels of metal ions between metal-on-metal hip replacements and hip resurfacing.[25]

Known and potential toxicity of metal ions

There are three principal sources of data on the toxicity of cobalt and chromium: (1) laboratory studies on cell cultures; (2) experimental studies on laboratory animals, and; (3) epidemiological studies in humans. Human exposure to cobalt and chromium has largely been studied from an industrial viewpoint. In the industrial setting cobalt and chromium exposure is principally by the inhalational route, with additional dermal absorption while for arthroplasty the initial exposure is localised to the area surrounding the implant, and subsequently, spreads to other organs via the blood stream.

Industrial exposure to chromium has been shown to cause lung cancer in humans and increased levels of chromium have been found in breast cancer patients.[26] Inhalation of chromium caused lung cancer in a rat model.[27] The different route of administration in arthroplasty decreases the likelihood of lung disease but the effect on other tissues is largely unknown. Chromium has been shown to be highly carcinogenic in the chromium (VI) form but to have limited, if any, carcinogenicity when administered in the chromium (III) form.[28,29] The body has several mechanisms for reducing chromium VI to chromium III. Ascorbate, glutathione, gastric juices, alveolar cell extract, and epithelial-lining fluid are able to reduce chromium VI to chromium III.[29] This reduction decreases the mutagenic ability of chromium VI as measured by the Ames reversion assay.[29] The mechanisms of toxicity and carcinogenicity are only partially understood but involve reduction of chromium (VI) to chromium (III) resulting in DNA-chromium (III) adducts.[30]

Cobalt in large quantities is known to be cardiotoxic in man and carcinogenic in animals.[26] Cobalt has been shown in laboratory studies to cause oxidative damage to DNA and interfere with DNA repair processes.[26] Localised injection of cobalt has been shown to be associated with development of musculoskeletal tumours in

animal models.[31] There is no strong evide nce that cobalt is carcinogenic in man.[32]

The effect of increased molybdenum ions is generally considered to be minimal. There is minimal information existing on human toxicity of molybdenum.[33]

Do the elevated ion levels cause cancer?

The evidence above shows that excessive chromium and cobalt are both toxic and carcinogenic. Laboratory analysis has demonstrated elevation of chromium and cobalt levels but it is not known how the elevated levels of chromium and cobalt will affect hip resurfacing patients in the long term. There have been contrasting studies showing changing rates of haematological malignancies in THR patients.[34,35]

The increased levels of cobalt and chromium are associated with various abnormalities of the blood. In vitro testing of wear particles was unable to show any toxic or mutagenic effects of cobalt-chromium-molybdenum wear particles in bacterial or mammalian cell lines at tested concentrations.[28] Increased rates of chromosomal aberrations and aneuploidy in lymphocytes have been found within two years of metal on metal hip arthroplasty.[18] This research demonstrated a fifty per cent increase in chromosomal translocations and a 2-4 fold increase in aneuploidy within two years of metal-on-metal hip resurfacing. Similar findings have been shown in vitro.[36] A correlation has been shown between levels of molybdenum in the blood and chromosome translocations.[18] This molybdenum-mutation correlation appears to be unique in the literature as most studies on this topic have only examined cobalt and/or chromium.

Immune dysfunction has been noted by various research groups but the clinical relevance of their findings is unknown. A recent study compared CD8+ T-cell counts between metal-on-metal hip resurfacing patients and metal-on-polyethylene hip replacement patients. Patients with metal-on metal joints were found to have significantly reduced total lymphocyte and CD8+ T-cell counts. Beyond a threshold of 5 ng/mL of total metal (cobalt+chromium) no patients had a CD8+ count above 0.5 x 109/L[37] This study showed a change in the bodies levels of white bloods cells which correlated with levels of metal ions. Though not evidence of a direct link with cancer it shows a deleterious effect of chromium and cobalt wear particles on haematological function. Additionally, raised levels of cobalt and chromium have been shown to lead to increased lymphocyte reactivity to these metals.[38] These changes have not been proven to cause clinically significant increases in risk to patients.

Cobalt has been shown to cause sarcomas in laboratory animals. Despite the large numbers of arthroplasties performed worldwide only twenty-six sarcomas were reported in arthroplasty patients between 1984 and 2001.[39] Lucas et al reviewed these case reports and concluded there was no causal link between arthroplasty and tumour development. The number of sarcomas did not exceed expected numbers.

A single case report exists of a psoas mass which developed in a sixty-one year old woman within two years of resurfacing arthroplasty. Excision of the mass revealed lymphocytic aggregates, necrotic muscle, and undefined areas of necrosis. Histology of synovium and psoas tendon revealed areas of fibrous tissue with dense infiltration of lymphocytes, giant cells and histiocytes. Extremely high levels of chromium and cobalt were found in the excised tissue. This tissue was not found to be cancerous and was thought to be due to a metal hypersensitivity reaction.[40]

Cohort studies

There is evidence showing that chromium and cobalt are human carcinogens - but are the levels of these metals in hip resurfacing patients high enough to cause cancer? National joint transplant registries are able to provide information about long-term outcomes after hip surgery. Because of the relatively short history of metal-on-metal hip resurfacing, long-term studies to date have compared metal-on-metal THR and metal-on-polyethylene THR with the normal values for the populations studied. Early studies suggested a possible link between total hip joint replacement and haematological malignancy.[34,35] Gillespie et al found that the incidence of tumours of the lymphatic and haemopoietic systems was significantly greater, while incidence of cancer of the breast, colon, and rectum, was significantly reduced. They also noted prolonged life expectancy in joint recipients. The prolonged life expectancy is likely due to selection of otherwise healthy patients for joint replacement surgery.[41] Visuri et al were able to compare the standard population, metal-on-polyethylene recipients and metal-on-metal recipients. They found a decreased odds ratio for cancer (odds ratio 0.76, 95 % confidence limits 0.68-0.86) for the metal-on-polyethylene group but no decrease in odds ratio in the metal-on-metal group. The odds of leukaemia were 3.77 times higher in the metal-on-metal group compared with the metal-on-polyethylene group. Leukaemia was an uncommon outcome and this link did not reach statistical significance. There was no obvious difference between the groups other than the type of prosthesis implanted. This implies either metal-on-metal prostheses increase risk of cancer or metal-on-polyethylene prostheses protect against cancer. It also suggests a specific link between metal wear particles and haematological cancer.

Nordic countries have excellent registry systems and many studies have been published analysing long term outcomes of Nordic cohorts.[41] Again because metal-on-metal joint resurfacing has only been performed in significant numbers over the last decade much of the information available relates to metal-on-metal THRs. When joint registries for Nordic countries were analysed there was no difference in overall cancer rates between people with a McKee-Farrar metal-on-metal prosthesis and the general population. A lower rate of cancer might have been expected given the selection of patients for THR as shown by Visuri above.

These studies give information on broad trends but are lacking in statistical power when studying uncommon outcomes due to the low number of metal-on-metal arthroplasties performed in the early 1980's when registries were started. For example the latest published estimate for risk of haematopoietic cancer was 1.4 with confidence intervals of (0.7-2.5).[41] This was based on a meta-analysis of a combined cohort from Denmark and Finland. This confidence interval leaves open the possibility that risk of haematopoietic cancer is 2.5 times higher in patients with metal-on-metal prostheses. Some subgroup analyses of the same registries have shown a statistically significant increase in risk of haematopoietic cancer.[42]

If the risk of haematopoietic cancer is found to be increased slightly after metal-on-metal hip resurfacing would it change clinical practice? What would the increase in absolute risk be if the relative risk of haematopoietic cancer was shown to double after metal-on-metal hip resurfacing? Gillespie et al estimated that the incidence of lymphoreticular neoplasm is 8.67 per 1000 over ten years.[43] If their figure of 8.67 lymporeticular neoplasms per 1000 people per ten years is accurate, a doubling of relative risk would lead to an extra 8.67 patients per 1000 developing a lymporeticular neoplasm. That means a less than one percent chance of developing an avoidable lymphoreticular neoplasm within ten years for each patient.

Alternatives

Would a small increase in risk of haematological cancer be acceptable to gain the known benefits of metal-on-metal hip resurfacing? The answer to this question depends to a great extent on the patient and the alternative treatments available. If metal-on-metal hip resurfacing was shown, for example, to increase the risk of haematological cancer, as Gillespie et al suggested, the procedure might well lose its attractiveness to patients in their twenties while remaining acceptable to those in their early sixties. Alternative bearing materials for hip resurfacing might eliminate the metal wear particles while still having the bone conserving advantages of hip resurfacing. There is unfortunately no other satisfactory material for a hip resurfacing procedure currently available[44] and the alternative treatments have their own problems. A THR with a metal-on-metal articulation is likely to have similar complications to metal-on-metal hip resurfacing, as well as the problems associated with all forms of THR. The bone removal necessary in the initial THR and subsequent osteolysis makes revision surgery difficult, along with other complications such as higher dislocation rates. Alternative bearing materials for either THR or hip resurfacing could

eliminate or reduce risk of cancer and other ill effects of metal on metal hip resurfacing.

Other complications of chromium and cobalt ions

It is necessary to mention briefly other possible complications of chromium and cobalt wear particles. Chromium has nephrotoxic effects and is known to cause acute renal failure when given in extremely high doses.[45] Long-term industrial exposure to chromium has been shown to significantly increase the odds ratio of developing chronic renal failure.[46] Renal impairment is a listed contraindication to metal-on-metal orthopaedic procedures. Some patients develop a hypersensitivity reaction to the metals which can lead to revision surgery.[38,47] These issues also bear further consideration in studies of the long term outcome of metal-on-metal hip resurfacing.

Conclusion

Chromium and cobalt are released as wear particles after cobalt-chrome alloys are implanted in the body. The large surface area metal-on-metal bearings used in hip resurfacing may generate more metallic debris than the small surface area metal-on-metal bearings used in hip replacement surgery, though this point is being contended in the literature. There is a significant body of research showing these metals can cause tumours in laboratory animals, that they increase mutation rates in bacterial culture, that they are mutagenic in mammalian tissue, that they cause chromosomal abnormalities (aneuploidy and translocations) in human white blood cells, and they are linked with other tumours (lung and breast) in humans. This evidence makes an increased cancer risk after metal-on-metal resurfacing procedures a real concern. These concerns are particularly relevant given the average age of hip resurfacing patients is 48-52 and many patients are aged below thirty years old.[5] The average patient will have an implant in situ for 25-30 years and younger patients for fifty years or longer. There is data indicating a possible link with haematological malignancies. This data conversely shows a decreased rate of breast, colon, and rectum cancer in patients treated with metal-on-metal devices. Osteoarthritis patients are a selected group known to have better long-term survival than the population as a whole. This selection may account for the lowered risk of certain types of cancer.

Epidemiological studies have so far been unable to prove an increase in the risk of cancer. Any analysis looking at cancer risk in metal-on-metal patients must acknowledge this. However, it remains possible, perhaps even likely, that metal-on-metal prostheses may increase the risk of cancer. Compared to the general population, cancer risk in metal-on-polyethylene patients is lowered, but cancer risk in metal-on-metal patients is not lowered. Long-term studies have only been able to examine metal-on-metal THR, information which is not necessarily equivalent to information on metal-on-metal hip resurfacing. The information available suggests but does not prove a link with cancer. Short-term studies of metal-on-metal hip resurfacing have almost exclusively come from single centres. This approach will not provide the numbers necessary to detect small changes in cancer risk. Several countries including New Zealand operate national joint registers. Meta-analysis of large cohorts such as these registers will be the earliest way of detecting changes in the incidence of cancer after metal-on-metal hip resurfacing.

REFERENCES

1. Dorr LD, Kane IIITJ, Conaty JP.
Long-term results of cemented total hip arthroplasty in patients 45 years old or younger : A 16-year follow-up study.
The Journal of Arthroplasty. 1994;9(5):453-6.

2. Kishida Y, Sugano N, Nishii T, Miki H, Yamaguchi K, Yoshikawa H.
Preservation of the bone mineral density of the femur after surface replacement of the hip.
J Bone Joint Surg Br. 2004 March 1, 2004;86-B(2):185-9.

3. Treacy R, McBryde C, Pynsent PB.
Birmingham hip resurfacing arthroplasty: a minimum follow-up of five years.
J Bone Joint Surg [Br]. 2005;87:167-70.

4. Daniel J, Pynsent PB, D.J.W M.
Metal-on-metal resurfacing of the hip in patients under the ages of 55 years with osteoarthritis.
J Bone Joint Surg [Br]. 2004;86-B:177-84.

5. Back D, Dalziel R, Young D, Shimmin A.
Early results of primary Birmingham hip resurfacings.
J Bone Joint Surg [Br]. 2005;87:324-9.

6. Amstutz HC, Le Duff MJ.
Background of metal-on-metal resurfacing.
Proceedings of the Institution of Mechanical Engineers -- Part H -- Journal of Engineering in Medicine. 2006;220(2):85-94.

7. Ritter M, Gioe T.
Conventional versus resurfacing total hip arthroplasty. A long-term prospective study of concomitant bilateral implantation of prostheses.
J Bone Joint Surg [Am]. 1986;68(2):216-25.

8. Bell R, Schatzker J, Fornasier V, Goodman S.
A study of implant failure in the Wagner resurfacing arthroplasty.
J Bone Joint Surg [Am]. 1985;67(8):1165-75.

9. Amstutz H, Dorey F, PF OC.
THARIES resurfacing arthroplasty. Evolution and long-term results.
Clinical orthopedics and related research. 1986;213:92-114.

10. Freeman M, Bradley G.
ICLH surface replacement of the hip.
J Bone Joint Surg [Br]. 1983;65(4):405-11.

11. Clarke MT, Lee P, Arora A, Villar RN.
Levels of metal ions after small- and large- diameter metal-on-metal hip arthroplasty.
J Bone Joint Surg [Br]. 2003;85-B:913-17.

12. Roberts J, Meek R, Roberts P, Grigoris P.
Metal-on-metal hip resurfacing
Scottish medical journal. 2005 50(1):10-2.

13. Catelas I, Campbell PA, Bobyn JD, Medley JB, Huk OL.
Wear particles from metal-on-metal total hip replacements: effects of implant design and implantation time.
Proceedings of the Institution of Mechanical Engineers -- Part H -- Journal of Engineering in Medicine. 2006;220(2):195-208.

14. Villar R.
Resurfacing arthroplasty of the hip.
J Bone Joint Surg [Br]. 2004;86-B:157-58.

15. Pollard T, Baker R, Eastaugh-Waring S, Bannister G.
Treatment of the young active patient with osteoarthritis of the hip.
J Bone Joint Surg [Br]. 2006;88:592-600.

16. Brodner W, Bitzan P, Meisinger V.
Serum cobalt levels after metal-on-metal total hip arthroplasty.
J Bone Joint Surg [Am]. 2003;85:2168.

17. Savarino L, Granchi D, Ciapetti G.
Ion release in stable hip arthroplasties using metal-on-metal articulating surfaces: a comparison between short- and medium- term results.
Journal of biomedical materials research. 2003;66(3):450-6.

18. Ladon D, Doherty A, Newson R, Turner J, Bhamra M, Case CP.
Changes in metal levels and chromosome aberrations in the peripheral blood of patients after metal-on-metal hip arthroplasty.
The Journal of Arthroplasty. 2004;19(8, Supplement 1):78-83.

19. Sieber H, Rieker C, Kittif P.
Analysis of 118 second-generation metal-on-metal retrieved hip implants.
J Arthroplasty. 1998;80B:46-50.

20. Rieker CB, Schöna R, Köttiga P.
Development and validation of a second-generation metal-on-metal bearing. Laboratory studies and analysis of retrievals.
The Journal of Arthroplasty. 2004;19(8):5-11.

21. Bowsher JG, Hussain A, Williams PA, Shelton JC.
Metal-on-metal hip simulator study of increased wear particle surface area due to 'severe' patient activity.
Proceedings of the Institution of Mechanical Engineers -- Part H -- Journal of Engineering in Medicine. 2006;220(2):279-87.

22. Michel R, Nolte M, Reich M, Loer F.
Systemic effects of implanted prostheses made of cobalt-chromium alloys.
Archives of Orthopaedic and Trauma Surgery. 1991;110(2):61-74.

23. Urban RM, Tomlinson MJ, Hall DJ, Jacobs JJ.
Accumulation in liver and spleen of metal particles generated at nonbearing surfaces in hip arthroplasty.
Journal of Arthroplasty. 2004;19(8):94-101.

24. MacDonald SJM, McCalden RWM, Chess DGM, Bourne RBM, Rorabeck CHM, Cleland DB, et al.
Metal-on-Metal Versus Polyethylene in Hip Arthroplasty: A Randomized Clinical Trial.
Clinical orthopedics and related research. 2003;1(406):282-96.

25. Daniel J, Ziaee H, Salama A, Pradhan C, McMinn DJW.
The effect of the diameter of metal-on-metal bearings on systemic exposure to cobalt and chromium.
J Bone Joint Surg [Br]. 2006;88(4):443-8.

26. Valko M, Rhodesb C, Moncola J, Izakovica M, Mazur M.
Free radicals, metals and antioxidants in oxidative stress-induced cancer.
Chemico-Biological Interactions. 2006;160(1):1-40.

27. Bucher JR, Hailey JR, Roycroft JR, Haseman JK, Sills RC, Grumbein SL, et al.
Inhalation toxicity and carcinogenicity studies of cobalt sulfate.
Toxicol Sci. 1999 May 1, 1999;49(1):56-67.

28. Katzer A, Hockertz S, Buchhorn GH, Loehr JF.
In vitro toxicity and mutagenicity of CoCrMo and Ti6Al wear particles.
Toxicology. 2003;190(3):145-54.

29. (USA) PHS-AfTSaDR.
Toxicological profile for chromium.
In: Services USDoHaH, editor.; 2000.

30. Zhitkovich A.
Importance of Chromium-DNA Adducts in Mutagenicity and Toxicity of Chromium(VI).
Chem Res Toxicol. 2005 January 17, 2005;18(1):3-11.

31. Heath J, GFreeman M, Swanson S.
Carcinogenic properties of wear particles from prostheses made in cobalt-chromium alloy.
The Lancet. 1971;1(7699):564-6.

32. Bradberry S, Beer S, Vale J, (UK) NPIS.
Cobalt.
UKPID Monograph. 1996.

33. Barceloux DG.
Molybdenum.
Journal of Toxicology - Clinical Toxicology. 1999; 37(2):231-7.

34. Gillespie W, Frampton C, Henderson R, Ryan P.
The incidence of cancer following total hip replacement.
J Bone Joint Surg [Br]. 1988;70:539-42.

35. Visuri T, Pukkala E, Paavolainen P, Pulkkinen P, Riska E.
Cancer risk after metal on metal and polyethylene on metal total hip arthroplasty.
Clinical orthopedics and related research. 1996;1996(329S):269-79.

36. Daley B, Doherty A, Fairman B, Case C.
Wear debris from hip or knee replacements causes chromosomal damage in human cells in tissue culture.
Journal of Bone and Joint Surgery (British volume). 2004;86(4):598-606.

37. Hart AJ, Hester T, Sinclair K, Powell JJ, Goodship AE, Pele L, et al.
The association between metal ions from hip resurfacing and reduced T-cell counts.
Journal of Bone and Joint Surgery (British volume). 2006;88(4):449-54.

38. Hallab NJ, Anderson S, Caicedo M, Skipor A, Campbell P, Jacobs JJ.
Immune responses correlate with serum-metal in metal-on-metal hip arthroplasty.
The Journal of Arthroplasty. 2004;19(8, Supplement 1):88-93.

39. Lucas DR, Miller PR, Mott MP, Kronick JL, Unni KK.
Arthroplasty-associated malignant fibrous histiocytoma: two case reports.
Histopathology. 2001;39(6):620-8.

40. Boardman DR, Middleton FR, Kavanagh TG.
A benign psoas mass following metal-on-metal resurfacing of the hip.
J Bone Joint Surg [Br]. 2006;88-B:402-04.

41. Visuri TI, Pukkala E, Pulkkinen P, Paavolainen P.
Cancer incidence and causes of death among total hip replacement patients: a review based on Nordic cohorts with a special emphasis on metal-on-metal bearings.
Proceedings of the Institution of Mechanical Engineers -- Part H -- Journal of Engineering in Medicine. 2006;220(2):399-407.

42. Visuri T, Koskenvuo M.
Cancer risk after McKee-Farrar total hip replacement.
Orthopaedics. 1991;14:137-42.

43. Gillespie WJ, Doorn P.
Incidence Of Cancer After Total Hip Replacement.
J Bone Joint Surg Br. 1996 July 1, 1996;78-B(4):680-.

44. Isaac GH, Thompson J, Williams S, Fisher J.
Metal-on-metal bearings surfaces: materials, manufacture, design, optimization, and alternatives.
Proceedings of the Institution of Mechanical Engineers -- Part H -- Journal of Engineering in Medicine. 2006;220(2):119-33.

45. Wedeen R, De Broe ME, editors.
Heavy metals and the kidney.
2nd edition ed: Oxford Universty Press; 1998.

46. Nuyts GD, Van Vlem E, Thys J, De Leersnijder D, D'Haese PC, Elseviers MM, et al.
New occupational risk factors for chronic renal failure.
Lancet. 1995;346(8966):7-11.

47. Willert HG, Buchhorn GH, Fayyazi A, Flury R, Windler M, Koster G, et al.
Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study.
J Bone Joint Surg [Am]. 2005;87(1):28-36.