PERGAMON

European Journal of Cancer 36 (2000) 307–313

European Journal of Cancer

www.elsevier.com/locate/ejconline

Position Paper

Evaluation of the carcinogenic risks to humans associated with surgical implants and other foreign bodies — a report of an IARC Monographs Programme Meeting

D.B. McGregor[a,*], R.A. Baan[a], C. Partensky[a], J.M. Rice[a], J.D. Wilbourn[a]

[a]*International Agency for Research on Cancer, 150, cours Albert Thomas, 69372 Lyon 08, France*

Received 23 September 1999; accepted 20 October 1999

Abstract

A meeting was held within the International Agency for Research on Cancer (IARC) Programme on the Evaluation of Carcinogenic Risks to Humans of surgical implants and other foreign bodies. This meeting report summarises the types of materials considered, their wear and degradation, their cancer epidemiology in both humans and other animals, the published experimental carcinogenicity data and selected data on their toxic, including genotoxic, effects. Evaluations resulting in a classification of Group 2B (possibly carcinogenic to humans) were reached for: (1) polymeric implants prepared as thin smooth films [with the exception of poly(glycolic acid)]; (2) metallic implants prepared as thin smooth films; and (3) implanted foreign bodies consisting of metallic cobalt, metallic nickel and a particular alloy powder consisting of 66–67% nickel, 13–16% chromium and 7% iron. Group 3 classifications (not classifiable as to their carcinogenicity to humans) were made for: (1) organic polymeric materials as a group; (2) orthopaedic implants of complex composition and cardiac pacemakers; (3) silicone breast implants; (4) dental materials; and (5) ceramic implants. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Breast implants; Cancer; Epidemiology; Foreign bodies; Prostheses and implants; Risk evaluation; Sarcoma

1. Introduction

The IARC Monographs Programme on the Evaluation of Carcinogenic Risks to Humans convened a meeting of 22 experts from 10 different countries in Lyon, France, to evaluate the evidence for Surgical Implants and other Foreign Bodies being risk factors for human cancer. Although this was the first time that such agents had been evaluated in this programme, several commonly used components (particularly metals) had been previously evaluated. With the exception of some dental materials, devices implanted in body cavities rather than in tissues were not evaluated in this meeting. In particular, intra-uterine contraceptive devices were not included. Representative referencing has been made to the human and veterinary studies; the full list of references to the very large number of experimental studies and material descriptions is provided in [1].

2. Exposure

A wide range of metals and their alloys, polymers, ceramics and composites are used in surgically implanted medical devices and prostheses and dental materials. Most implanted devices are composed of more than one kind of material (implants of complex composition). Since the early 1900s, metal alloys have been developed for these applications to provide physical and chemical properties, such as strength, durability and corrosion resistance, that are improvements over the properties of single elements. Major classes of metals used in medical devices and dental materials include stainless steels, cobalt–chromium alloys, titanium metal and titanium alloys. In addition, dental casting alloys are often based on precious metals (gold, platinum, palladium or silver), nickel and copper and may contain smaller amounts of many other elements, which may be added to improve the alloys' properties.

Orthopaedic applications of the metal alloys include arthroplasty, osteosynthesis and the implantation of spinal and maxillofacial devices. Metallic alloys may also be used for components of prosthetic heart valve

* Corresponding author. Tel.: +33-4-72-73-85-26; fax: +33-4-72-73-83-19.

E-mail address: mcgregor@iarc.fr (D.B. McGregor).

0959-8049/00/$ - see front matter © 2000 Elsevier Science Ltd. All rights reserved.
PII: S0959-8049(99)00312-3

replacements, and pacemaker casings and leads. Small metallic parts may be used in a wide range of other implants, including skin and wound staples, vascular endoprostheses, filters and occluders. Dental applications of metals and alloys include fillings, prosthetic devices (crowns, bridges, removable prostheses), dental implants and orthodontic appliances.

Polymers of many types are used in implanted medical devices and dental materials. Illustrative examples are silicones (breast prostheses, pacemaker leads), polyurethanes (pacemaker components), polymethacrylates (dental prostheses, bone cements), polyethylene terephthalate (vascular grafts, heart valve sewing rings, sutures), polypropylene (sutures), polyethylene (prosthetic joint components), polytetrafluoroethylene (vascular prostheses), polyamides (sutures) and polylactic and polyglycolic acids (bioresorbables used as sutures, pins and other items).

Ceramic materials based on metal oxides (alumina, zirconia) find use in joint replacements and dental prostheses. Other materials based on calcium phosphate are used as bone fillers and implant coatings. Pyrolytic carbon applications include heart valves and coatings for implants. Composites are used mainly in dental fillings.

Although precise numbers are not available, many millions of people worldwide have received one or more deliberately implanted devices, which may remain in place for years. In addition, foreign bodies, such as bullets and pellets from firearms and metallic fragments from explosions, as well as non-metallic materials, may penetrate and can also remain in human tissues for long periods of time. Internal exposure to their constituents, including lead (from bullets and pellets) and other metals, including depleted uranium (from shell and missile fragments), may result.

3. Human carcinogenicity

Sixteen case reports have described neoplasms originating from bone or soft connective tissue in the region of metal implants. An analytical study did not report an increased risk of developing soft-tissue sarcoma after metal implants [2], and no association with dental amalgam was found in a case–control study in Australia [3].

The 30 case reports of breast cancer (i.e. carcinomas, not sarcomas) following breast silicone implants for cosmetic augmentation appear unlikely to correspond to an excess of breast cancer. Five cohort studies involving a total of more than 18 000 women treated with surgical prostheses made of silicone (or polyurethane-coated silicone) for cosmetic breast augmentation conducted in Canada, Denmark, Sweden and the United States consistently found no evidence of increased risk of breast carcinoma [4–8]. The combined results of the four largest cohort studies show a 25% reduction in risk. Similar results were reported by a large case–control study including more than 2000 cases and 2000 controls from the United States. All cohort studies were based on subjects exposed to implanted silicone at a relatively early age, usually between 30 and 40 years, so that the number of breast cancer cases reported by each study was relatively small. Except for the case–control study, little allowance was made for potential confounding factors, although no clear evidence has emerged as to the relevance of any such factor to a possible association between implanted silicone and breast cancer risk. Three of the studies considered the issue of latency, with observation periods up to 10 years or more, but even in the group of women with follow-up of 10 years or more, there was no suggestion of increased risk. The risk of cancer following surgical implantation of silicone prostheses for breast reconstruction after breast cancer was considered in a study from France [9]. The results of this study suggest no excess risk of second primary breast or other cancer, distant metastases, local recurrence or death from breast cancer. The reduced risks of developing breast cancer found in the cohort and case–control studies are unlikely to be due to chance, and no bias that would explain these findings has been identified.

Four cohort studies of women with surgical breast implants in Denmark, Sweden and the United States reported on cancers at sites other than the breast [4,7,8]. None of these studies found an increased risk for all cancers combined. Two studies reported increased risks of developing lung cancer, but these results were based on a total of only nine cases. For no other cancer was there consistent evidence of an increased risk, although the statistical power to detect an increased risk of rare neoplasms, including soft-tissue sarcomas, was low.

Out of the large number of patients with metal implants of complex composition, a total of 35 cases have been reported of malignant neoplasms arising from bone or soft tissue in the region of the implant.

Fourteen cohort studies were performed to investigate cancer incidence on patient populations in six countries, following total knee or total hip replacement [10–18]. Two of the studies from Finland and two studies from Sweden were partially overlapping. One study included only patients with metal-on-metal implants, five studies included only patients with polyethylene-on-metal implants, whilst the remaining studies included patients with mixed or unspecified types of implant. One study showed a small increase, whilst the remaining studies showed a decrease in overall cancer incidence. Four of these studies suggested an excess risk at specific sites, including Hodgkin's disease, non-Hodgkin's lymphoma, leukaemia and kidney cancer. The other studies, however, were not consistent with these observations. In one

cohort study from Denmark that included patients with a finger or hand implant, an increased risk of lymphohaematopoietic cancer was observed. Additionally, two case–control studies, one including cases with soft tissue sarcoma, the other including lymphoma and leukaemia were carried out in the United States. The latter overlapped with one of the cohort studies. Neither of these studies showed an association of carcinogenic risk with a history of an implant of complex composition. Most of these epidemiological studies did not have information on possible confounding variables, such as immunosuppressive therapy or rheumatoid arthritis for the lymphomas and analgesic drug use for the kidney cancers. The follow-up in most of the studies may have been too short to investigate cancer occurring many years after exposure; in some studies with longer follow-up the numbers of long-time survivors were small.

Finally, 32 cases of various neoplasms have been reported in patients with a variety of miscellaneous, surgical or accidentally implanted foreign bodies. Thirteen cases of breast cancer and one case of plasmacytoma have been reported in patients with cardiac pacemakers. Ten cases of different neoplasms have been reported at the site of non-metallic foreign bodies. Eight cases of sarcoma have been reported at the site of vascular grafts. No conclusions can be drawn from these case reports, in view of the very large, but unknown number of operations of this type performed and the substantial possibility of chance associations.

Twenty-three cases of sarcomas, twenty-three cases of carcinomas and seven cases of brain tumours have been reported as occurring at the site of metallic foreign bodies, mainly bullets and shrapnel fragments.

4. Veterinary studies

Despite the large number and variety of both metallic and non-metallic internal bone fixation devices used in dogs in recent decades, only about 60 cases of sarcomas, primarily of bone, in dogs have been reported. In addition, four cases of sarcomas at the site of other foreign bodies have been reported in dogs. One case–control study found no association between metallic implants used to stabilise fractures in dogs and the development of soft-tissue tumours [19].

In contrast, at least 650 cases of vaccine-associated sarcomas in cats were reported in just 6 years, with estimated annual incidences of 1–13 per 10 000 vaccinated cats [20,21]. Vaccine-associated sarcomas have been mostly associated with administration of recently introduced adjuvanted feline vaccines containing aluminium compounds. Tumours that develop at vaccination sites are morphologically different from those that develop at non-vaccination sites. A cohort study found that cats developed sarcomas in a shorter time at sites used for vaccination than at non-vaccination sites and that there was an increased risk of sarcoma development with increased numbers of vaccines at a given site.

5. Experimental carcinogenicity

A substantial amount of experimental carcinogenicity research has been directed towards an understanding of solid state carcinogenesis and the so-called Oppenheimer effect, in which the development of sarcomas in rats and mice by non-metallic materials seems to be dependent upon certain physical characteristics of the materials, rather than their chemical composition. In addition, there have been many studies on the carcinogenic effects of metals and metallic compounds.

Chromium metal powder was tested in rats by intramuscular and intrarenal administration, in mice and rats by intrapleural and intraperitoneal administration, in rats and rabbits by intra-osseous implantation and in mice, rats and rabbits by intravenous injection. No increase in tumour incidences was observed in these studies, although most studies had limitations in design, duration or reporting.

Cobalt metal powder was tested in rats by intramuscular or intrathoracic injection, producing sarcomas at the injection site. Studies in rats by intrarenal injection and in rabbits by intra-osseous injection had limitations in design, duration or reporting, making them inadequate for evaluation.

Nickel metal powder was tested by inhalation exposure in mice, rats and guinea-pigs, by intratracheal instillation in rats and Syrian hamsters, by intramuscular injection in rats and hamsters and by intrapleural, intraperitoneal, intra-osseous and intrarenal injection in rats. It was also tested by intravenous injection in mice and rats. The studies by inhalation exposure were inadequate for an evaluation of carcinogenicity. After intratracheal instillation of nickel, significant numbers of squamous-cell carcinomas and adenocarcinomas of the lung were observed in rats; one adenocarcinoma of the lung was observed in Syrian hamsters. Intrapleural injections induced sarcomas in rats. Intramuscular injection of nickel powder induced sarcomas in rats and hamsters; and intraperitoneal injections induced local carcinomas, mesotheliomas and sarcomas in rats. Subcutaneous administration of nickel metal pellets induced sarcomas in rats. No significant increase in the incidence of local kidney tumours in rats was seen following intrarenal injection. Studies by the intra-osseous and intravenous routes were inadequate for evaluation.

Titanium metal was tested in rats by intramuscular implantation of rods and by intra-osseous administration of powder, rods or wire. No local tumours occurred.

Most nickel-based alloys that have been tested for carcinogenicity in animals are not actually used in

clinical devices, and carcinogenesis data are not available for a number of alloys which are commonly used, including nickel–titanium.

Metal alloys containing a preponderance of nickel in combination with varying amounts of chromium, iron, gallium, copper, aluminium and manganese have been tested as powder or pellets by subcutaneous or intraperitoneal administration to rats and by intratracheal administration to hamsters. In these studies, local sarcomas were consistently found at the injection site in the treated animals and were absent in vehicle controls. One of the nickel-based alloys (which contained approximately 66–67% nickel, 13–16% chromium and 7% iron) was tested independently by two laboratories, using different species (hamsters and rats) and different routes of administration (intratracheal and intraperitoneal). In both studies, local tumours were seen in proportion to the dose of alloy. Local tumours were also observed in two bioassays in which rats received identification ear tags made of an alloy that contained 67% nickel, 30% copper, 2% iron and 1% manganese.

Most other nickel-containing alloys tested as powder and rods in rats by intramuscular, intraperitoneal, intrarenal and intra-osseous administration gave negative or equivocal results for induction of tumours at the injection site. One study in hamsters by intratracheal administration of an alloy powder containing approximately 27% nickel, 39% iron and 16% chromium also gave negative results.

One clinically relevant alloy, which contained 35% nickel, 35% cobalt, 20% chromium and 10% molybdenum ($MP_{35}N$ alloy), did not induce carcinogenesis when tested in two studies by intramuscular implantation in rats as rods, but produced local sarcomas in one study following intramuscular administration to rats as a powder.

Titanium-based alloys were tested in rats by intramuscular or intra-osseous implantation as rods and intra-articular administration of wear-debris. No local tumours were observed at the injection site in these experiments, except in one study by intra-osseous administration in which a titanium/aluminium/vanadium alloy implanted into the femur as hemi-cylinders produced a high incidence of local tumours, especially where there was loosening of the implant.

Cobalt-based alloys were tested in rats by intramuscular administration. Local tumours were induced by a powder (particle size, 0.1–1 μm) suspended in horse serum but not by dry powders (0.5–50 and 100–250 μm) or implanted polished rods. No local tumours were observed in guinea-pigs following intramuscular injection of cobalt as a dry powder (0.5–50 μm). A low incidence of local tumours was observed in rats following intraosseous administration of two cobalt-based alloys given as powder or wire. Local tumours did not occur following intra-osseous implantation of rods of two other cobalt-containing alloys. No local tumours occurred in rats following intra-articular administration of a cobalt alloy powder.

Stainless steels containing 13–17% chromium were tested by intratracheal administration of powder to hamsters, intrabronchial implantation of wire to rats, intramuscular implantation of rods and discs to rats and intra-osseous administration of rods and powder to rats. No local tumours were observed, except in one study with rats receiving stainless steel discs of various sizes, in which seven sarcomas were found in six rats in juxtaposition with the larger discs.

Thin foils of silver, gold, platinum, tin, steel, Vitallium® and tantalum were tested by subcutaneous implantation in rats. All of these foils produced local sarcomas.

In one study in rats, subcutaneous implantation of discs of aluminium oxide ceramic produced local sarcomas. In a few studies in mice and rats, local sarcomas were observed following subcutaneous implantation of glass sheets.

Numerous polymeric materials have been tested for carcinogenicity in mice and rats, most frequently by subcutaneous, intramuscular or intraperitoneal injection. Many materials — cellophane, ε-caprolactone–L-lactide copolymer, polyamide (Nylon), polyethylene terephthalate, polyethylene, poly-L-lactide, poly(2-hydroxyethyl methacrylate), poly(methyl methacrylate), polypropylene, polystyrene, polytetrafluoroethylene, polyurethane, poly(vinyl alcohol), poly(vinyl chloride), silicone film or polysilicone gum and vinyl chloride–vinyl acetate copolymers — produced sarcomas at the site of implantation with a variable local incidence. When tested in rats according to the same experimental protocol, sarcoma incidences ranged from 70% (polypropylene) to 7% (silicone). A low incidence of local tumours was seen with silicone in five separate experiments using rats.

A few experiments with various polymeric materials have been reported using other animal species, such as rabbits, guinea-pigs and hamsters, with generally negative findings.

Polymeric materials with a large surface area and a flat and smooth surface morphology generally induced a significantly increased incidence of sarcomas at the site of implantation. In most studies, perforated or foam materials or textiles induced lower incidences of sarcomas in comparison with flat films. Some studies suggest that surface roughening decreases local sarcoma incidence. The diameter and number of transmembrane channels (pores) per unit surface area are critical for this trend of decrease in sarcoma incidence. Segmenting or pulverising polymeric materials significantly decreases local sarcoma incidences, often to nil.

For biodegradable polymers, the degradation rate is critical for local tumour induction in rodents. Thus, no local tumours were observed with polyglycolic acid,

which is quickly degraded within 2 months, whereas local sarcomas were induced by poly-L-lactide and ε-caprolactone–L-lactide copolymer which degraded more slowly (poly-L-lactide degraded, but was dimensionally unchanged at 24 months; ε-caprolactone–L-lactide copolymer fragmented after 6 months).

6. Other data (biodegradation, migration, excretion, general and genetic toxicity)

The mutagenicity and carcinogenicity of a biomaterial are influenced by the exact composition of the biomaterial or extract(s); the composition and rates of release of leachable materials into the biological environment; degradation, which may lead to the formation of compounds with different mutagenic properties or leachability; the physical environment; and the surface properties. Much of the information available for assessment is inadequate in these respects, and methods are often not validated.

Wear and corrosion of metal implants result in the generation and release of a wide range of degradation products. The composition of the material surface or particles can vary as individual components are selectively removed or chemically modified. In the case of alloys, the release of one type of metal ion can be strongly influenced by the electrochemical properties of other metals in the alloy. Most studies provide inadequate characterisation data, however, there is potential for the release of chemical species of known mutagenicity or carcinogenicity.

Experimental studies have shown that the potential for lead intoxication as a complication of lead projectile or bullet injury appears to be related to the surface area of the bullet (the greater the surface area, the greater the absorption), the location of the bullet (muscle or joint tissues), the presence of synovial fluid and the length of time that the bullet resided in the body.

Available studies are inadequate to permit reliable and accurate estimates of long-term effects of depleted uranium in humans. Because of the low specific radioactivity of depleted uranium, the long-term toxicity is thought to be due to chemical, rather than radiation effects.

Inflammatory (fibrotic) reactions have been observed, particularly in rats and mice, with several non-metallic implant materials, including silicones and polyurethanes. Depending on the physical properties of the biomaterial, its presence can be associated with implantation-site sarcomas in rodents. There are insufficient data to conclude that a genotoxic mechanism operates in solid-state carcinogenesis. There are *in vitro* data demonstrating the inhibitory effects of polyurethane, polyethylene and poly(ethylene terephthalate) on gap-junctional intercellular communication.

Mutagenic properties of some biomaterial extracts have been demonstrated in some studies. The compounds shown or suspected to be responsible for these effects are the components of the biomaterial, unreacted monomers or products of secondary reactions.

Data characterising the local and systemic availability of particular chemical species have been reported for only a small number of biomaterials. In the case of poly(ester urethane) foam, biodegradation results in the generation of 2,4-diaminotoluene. This compound induces hepatocellular carcinomas when fed to mice and rats. There is no evidence that chemical carcinogenesis due to this compound plays a direct role in the mechanism of implant-site sarcoma development. There is no convincing evidence for the biodegradation of polydimethylsiloxanes (silicones).

Cytotoxicity of freshly cured dental composite materials and bonding agents has been demonstrated and all of the tested components of resin composites cause significant toxicity, when brought into direct contact with fibroblasts. However, the hazard for the dental pulp depends on the quantities which permeate the dentin and accumulate in the pulp.

A small number of animal studies have shown pulpal responses to acid etching and bonding agents, which indicates a possible risk of pulpal reactions in patients. Composite materials may give rise to biological effects, but microleakage and bacterial infection complicate the evaluation of pulpal effects of composites. Clinical reports on the adverse effects of composite filling materials indicate that pulpal and mucosal reactions rarely occur.

With few exceptions, the amounts of individual chemicals to which professionals and patients are exposed from adhesive agents and composite dental filling materials seem to be insufficient to cause clear, systemic toxic effects. Some constituents of adhesive agents and composite materials may have genotoxic potential. For most of the compounds used in dental composites, there is little information on their toxicity. With the exception of methyl methacrylate, no relevant data are available to compare local concentrations of released compounds with levels that produce toxic effects.

Formaldehyde has been shown to be released from some dental polymers *in vitro*, but the levels appear to be low.

7. Evaluations

On the basis of the data summarised above, the Meeting reached the following conclusions regarding the risks of cancer that are associated with the various implants, prostheses and other foreign bodies. These evaluations were reached independently for the evidence coming from epidemiology and from experiments in

animals; there was then a synthesis of these evaluations to reach overall conclusions and assign classifications. This synthesis was particularly difficult on this occasion, not because of disagreements within the meeting, but because of the complexity of the human exposures in comparison with the experimental studies, which were usually confined to single components of the often extraordinarily complex implanted materials.

With regard to breast implants made of silicone, there was evidence suggesting lack of carcinogenicity in humans for female breast carcinoma and there was inadequate evidence in humans for the carcinogenicity of implanted prostheses made of silicone for neoplasms other than female breast carcinoma.

Conclusions of there being inadequate evidence in humans for carcinogenicity were reached for a number of other materials, these being: (a) non-metallic implants other than those made of silicone; (b) metallic implants and metallic foreign bodies; (c) orthopaedic implants of complex composition; and (d) cardiac pacemakers.

No epidemiological data relevant to the carcinogenicity of ceramic implants or dental alloys of precious metals were available.

In experimental animals (almost always rats and mice, but occasionally other rodents), there was sufficient evidence for the carcinogenicity of: (1) polymeric and metallic materials in the form of thin films, foils or sheets when implanted into connective tissues of rodents; and (2) implants of metallic cobalt, metallic nickel and nickel alloy powder that contains approximately 66–67% nickel, 13–16% chromium and 7% iron. There was only limited evidence for the carcinogenicity of implants of other alloys of nickel, as well as alloys of cobalt. In contrast, there was inadequate evidence in experimental animals for the carcinogenicity of: (1) implants of chromium metal, stainless steel, titanium metal, titanium-based alloys and depleted uranium; (2) polymeric materials in the form of powders when inserted into connective tissues of rodents; and (3) poly-(glycolic acid) implants.

There was limited evidence in cats for the carcinogenicity of certain feline vaccines containing adjuvants.

There was inadequate evidence in dogs for the carcinogenicity of metallic implants and metallic and non-metallic foreign bodies.

8. Overall evaluations and classifications

Overall evaluations (that are made primarily on the basis of the combined evidence from epidemiology and experimental carcinogenicity studies) resulting in a classification of Group 2B (possibly carcinogenic to humans) were reached for: (1) polymeric implants prepared as thin smooth films (with the exception of poly-(glycolic acid)); (2) metallic implants prepared as thin smooth films; and (3) implanted foreign bodies consisting of metallic cobalt, metallic nickel and a particular alloy powder consisting of 66–67% nickel, 13–16% chromium and 7% iron.

All other evaluations reached were for Group 3 (not classifiable as to their carcinogenicity to humans). Specifically, Group 3 classifications were made for: (1) organic polymeric materials as a group; (2) orthopaedic implants of complex composition and cardiac pacemakers; (3) silicone breast implants; (4) dental materials; and (5) ceramic implants.

Acknowledgements

Collaborative agreement with US National Cancer Institute (NCI), and grants from European Union, US Environmental Protection Agency (EPA) and the US National Institutes of Environmental Health Sciences (NIEHS) provided financial support for this study.

References

1. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 74, Surgical Implants and other Foreign Bodies. Lyon, IARC, 1999.
2. Morgan RW, Elcock ME. Artificial implants and soft tissue sarcomas. *J Clin Epidemiol* 1995, **48**, 545–549.
3. Ryan PC, Newcomb GM, Seymour GJ, *et al*. The pulpal response to citric acid in cats. *J Clin Periodontol* 1984, **11**, 633–643.
4. Gabriel S, O'Fallon WM, Kurland LT, Beard CM, Woods JE, Melton LJ. III. Risk of connective-tissue diseases and other disorders after breast implantation. *N Engl J Med* 1994, **330**, 1697–1702.
5. Bryant H, Brasher P. Breast implants and breast cancer — reanalysis of a linkage study. *New Engl J Med* 1995, **332**, 1535–1539.
6. Deapen DM, Bernstein L, Brody GS. Are breast implants anticarcinogenic? A 14-year follow-up of the Los Angeles study. *Plast Reconstr Surg* 1997, **99**, 1346–1353.
7. Friis S, McLaughlin JK, Mellemkjaer L, *et al*. Breast implants and cancer risk in Denmark. *Int J Cancer* 1997, **7**, 956–958.
8. McLaughlin JK, Nyrén O, Blot WJ, *et al*. Cancer risk among women with cosmetic breast implants: a population-based cohort study in Sweden. *J Natl Cancer Inst* 1998, **90**, 156–158.
9. Petit JY, Le MG, Mouriesse H, *et al*. Can breast reconstruction with gel-filled silicone implants increase the risk of death and second primary cancer in patients treated by mastectomy for breast cancer? *Plast Reconstr Surg* 1994, **94**, 115–119.
10. Gillespie WJ, Frampton CMA, Henderson RJ, Ryan PM. The incidence of cancer following total hip replacement. *J Bone Joint Surg* 1988, **70B**, 539–542.
11. Gillespie WJ, Henry DA, O'Connell DL, *et al*. Development of hematopoietic cancers after implantation of total joint replacement. *Clin Orthopaed Rel Res* 1996, **329**(Suppl.), S290–S296.
12. Mathiesen EB, Ahlbom A, Bermann G, Lindgren JU. Total hip replacement and cancer. A cohort study. *J Bone Joint Surg* 1995, **77B**, 345–350.
13. Nyrén O, McLaughlin JK, Gridley G, *et al*. Cancer risk after hip replacement with metal implants: a population based cohort study in Sweden. *J Natl Cancer Inst* 1995, **87**, 28–33.
14. Lewold S, Olsson H, Gustafson P, Rydholm A, Lidgren L. Overall cancer incidence not increased after prosthetic knee

replacement: 14,551 patients followed for 66,622 person-years. *Int J Cancer* 1996, **68**, 30–33.
15. Visuri T, Pukkala E, Paavolainen P, Pulkkinen P, Riska EB. Cancer risk after metal on metal and polyethylene on metal total hip arthroplasty. *Clin Orthop Rel Res* 1996, **329**(Suppl.), S280–S289.
16. Fryzek JP, Mellemkjaer L, McLaughlin JK, Blot WJ, Olsen JH. Cancer risk among patients with finger and hand joint and temporo-mandibular joint prostheses in Denmark. *Int J Cancer* 1999, **81**, 723–725.
17. Olsen JH, McLaughlin JK, Nyrén O, Mellemkjaer L, Lipworth L. Hip and knee implantations among patients with osteoarthritis and risk of cancer: a record-linkage study from Denmark. *Int J Cancer* 1999, **81**, 719–722.
18. Paavolainen P, Pukkala E, Pulkkinen P, Visuri T. Cancer incidence in Finnish hip replacement patients from 1980 to 1995. A nationwide cohort study involving 31,651 patients. *J Arthroplasty* 1999, **14**, 272–280.
19. Li XQ, Hom DL, Black J, Stevenson S. Relationship between metallic implants and cancer: a case–control study in a canine population. *VCOT* 1993, **6**, 70–74.
20. Lester S, Clemett TY, Burt A. Vaccine site-associated sarcomas in cats: clinical experience and a laboratory review (1982–1993). *J Am Anim Hosp Assoc* 1993, **32**, 91–95.
21. Coyne MJ, Postorini-Reeves NC, Rosen DK. Estimated prevalence of injection-site sarcomas in cats during 1992. *J Am Vet Med Assoc* 1997, **210**, 249–251.