Chapter 5
Cancer

M. Rock

5.1 Introduction

The widespread use of temporary and permanent implants in the post World War II era has had a dramatic impact on the practice of medicine and on the life of disabled and ill individuals. Nowhere has this been more obvious than in the frequent use of implants to stabilize fractures and replace diseased joints which has revolutionized orthopedic practice and afforded millions of patients levels of function that previously could not be achieved. Although the metal alloys used in these implants exhibit excellent resistance to corrosion, oxidation of these large components ultimately produce free ions, chlorides, oxides, and hydroxides which, in combination with particulate metal matter released by wear and fretting, are released into the surrounding environment. Efforts to improve these alloys have included compositional as well as processing changes. Additionally, modifications have been made to the plastic articulating components in efforts to produce a much more consistent ultrahigh molecular weight polyethylene. The perceived need to improve implant wear and corrosion resistance and alter design has been largely motivated by the excessive soft tissue staining noted by orthopedic surgeons at the time of removal or revision of clinically failed joint arthroplasty. The presence of particulate metal matter, polyethylene, and even fragments of polymethyl methacrylate in local tissue has been confirmed histologically and by direct analysis [1–4]. In spite of all of the modifications made in implant composition, implant fixation, and articulation, biomaterial degradation and release of these products persist [4–7].

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5.2 Release and Distribution of Degradation Products

The body’s response to the local presence of debris is dependent on the size, amount, and composition as well as rate of accumulation. The body attempts to neutralize these foreign particles by precipitating granulomatous foreign body reactions and/or removal through local lymphatic channels. If the local accumulation of debris exceeds the body’s ability to neutralize and/or transport, the debris migrates from the site to remote areas including the bone-implant interface, possibly contributing to if not initiating the phenomena of loosening and osteolysis (Figure 5.1).

Of equal or possibly even greater concern is the detection of metal ions, metallic debris, polyethylene, and even methylmethacrylate in areas remote from the implant including circulating serum, excreted urine, and regional draining lymph nodes. Elevated serum levels of metal ions consistent with the composition of the implanted alloy have been confirmed in animal models [8] and in human patients after total hip arthroplasty [9]; identifying serum levels of cobalt, chromium, nickel, and titanium that are two and three fold higher than preoperative determinations. These figures represent significant elevations both over means for contemporary control groups and for the individual patients before operation [9]. However, since they are within the widely accepted normal range for these metallic ions in the unimplanted human controls, it is assumed that toxic levels of these foreign materials do not materialize. However, when analyzing the serum to urine concentration in patients subjected to conventional total hip arthroplasty, it has become apparent that the urinary concentration of chromium in particular does not rise with the same magnitude and time course as the serum level [9]. This observation parallels that made in the accounts of industrial overexposure to Cr⁶⁺ and suggests that metal ions accumulate in organs and tissues remote from implantation. Such accumulation is unlike that resulting from normal systemic circulation. This was previously suggested by Steineman [10] who calculated the potential release of metallic ions of 0.15 to 0.3 micrograms per cm² per day which would translate to between 11 and 22 milligrams per year in patients with total hip replacement. This incidentally coincides with or exceeds the total body burden of such metallic ions in a 70 kilogram man [11].

![Figure 5.1](image.png)  
**Figure 5.1** Tissue Reaction to Implant Degradation Products.
Evidence for metallic debris accumulating in distant organs has also been confirmed by Langkamer et al. [12] who identified wide spread dissemination of particulate wear debris from hip prosthesis to lymph nodes, liver, and spleen. He reported increases above normal levels in these organs of 30 fold for aluminum, chromium, and iron in the lymph node, and 10 fold in the spleen and liver.

These findings suggest that concentrations of metal ions and debris at remote sites may reach such proportions as to precipitate altered cellular dynamics in organs principally of the lymphoreticular system. It would only be logical to assume that local concentrations of such debris at the site of implantation would be even higher, although attempts at quantifying the effects of local concentrations have been fraught with inaccuracies mostly due to sampling error and the need to distinguish between bioavailable and non bioavailable metal species.

What is potentially more disturbing is that these figures for serum concentrations and the identification of this debris in remote organs have come primarily from patients who have received conventional polymethyl methacrylate cemented components. With the advent of using uncemented porous coated implants, particularly in younger patients, these figures would be expected to increase, creating the distinct possibility of toxic levels in the serum, tissues and organs that will respond with altered cellular dynamics and function.

5.3 Neoplasia

Perhaps one of the greatest concerns with debris dissemination locally and within the systemic circulation is the possibility of inducing malignant neoplasia. This is thought to be possible by one of two mechanisms:

(i) A ‘solid-state’ mechanism has been proposed, whereby a large foreign object implanted in vivo possibly stimulates mutagenesis of local cells, thereby creating tumor by its mere presence. Most large foreign objects upon implantation will initiate a very marked fibrous reaction. The cells within this fibrous reaction ultimately mutate and become cancer growths.

(ii) The other possibility is that particulate metal matter or other debris have an innate capacity, upon corrosion or dissolution, to induce cancer through a more traditional chemical route.

Cancer, the end product of carcinogenesis, is the result of transformation of a normal cells to ones which grow in an uncontrolled or malignant manner. Cancer is a genetic disease, which may result from expression of genetic pre-dispositions present from birth or from later insults to cells of many different types. In particular, the phagocytosis or pinocytosis of foreign matter (in an attempt to neutralize or eliminate it) may cause or precipitate malignant conversion. Such conversion, if not lethal to the cell, may then persist through cell duplication, creating first a cluster of cells with altered DNA and eventually a clinical malignant tumor. Malignancy is characterized by rapid, uncontrolled growth, invasion in surrounding tissues and seeding to form tumors (metastases) in other anatomical locations such as the lung.
Some of the more common malignant tumors of musculoskeletal origin are osteosarcoma (OS) of bone and malignant fibrous histiocytoma (MFA) of soft tissue.

Osteosarcoma is the most common tumor of bone: it occurs in children, adolescents and, less frequently, in adults. OS may also occur as a consequence of radiation therapy or in Paget’s disease, an ostensibly benign bone embrittling disease of the elderly. It frequently appears about the knee (distal femur; proximal tibia), and in the proximal femur and proximal humerus.

MFA is the most common primary malignant tumor of soft tissues and can occur in bone in adults over the ages of 50–55. The more common soft tissue type usually involves the large muscular areas of the body, including the thigh, buttock and upper arm and shoulder.

5.4 Evidence for Carcinogenicity of Implanted Materials

Well-documented cases of carcinoma and sarcoma have developed in refinery workers who inhaled nickel and chromium and in miners who were exposed to iron or even at local injection sites of iron dextran \[13\]. Aluminum has been linked to a high rate of lung and bladder cancer in exposed individuals and titanium has been associated with experimental induction of lymphoreticular tumors and leukemia. Although the results have not been universally accepted, many animal experiments have shown a direct correlation between the initiation of sarcomas and the injection of particulate metal debris. This appears to be related to the concentration, as well as the physical nature, of the metal implanted \[14\]. Metal ions, particularly cobalt, chromium, and nickel, are known to induce infidelity of DNA synthesis by causing the pairing of non-complimentary nucleotides and thereby creating a misinterpretation of the genetic code which may lead to neoplasia.

Furthermore, it must be remembered that particulate metal matter may not be the only solid-form material that can be, and has been proven to be, carcinogenic in appropriate environments. In 1954 long before the first total hip arthroplasty was performed, Laskin \[15\] observed the carcinogenic capabilities of polymethylmethacrylate after subcutaneous introduction of this material in mice. His conclusions suggested that similar occurrences of tumor may appear in humans that were being treated at that time with methylmethacrylate for dental deficiencies and that this evolution of cancer may take up to 20 years of exposure given the proportional time exposure before tumors were seen in the mice. A similar conclusion was reached \[16\] on the use of polyethylene plastic before it was conventionally used in the management of arthritic joints. Regardless of form, whether powder or large solid segments, polyethylene plastic produced sarcomas in 25 percent and 35 percent of rats, respectively. Their conclusions also suggested a latent period, after exposure, of 20 years in humans before such an event could be expected to occur.

It is, therefore, with interest that investigators were forewarning the medical community of the carcinogenic effect of metals and polymers years before the development and introduction of joint replacement using these very same materials.
In 1961, Sir John Charnley introduced total hip arthroplasty as an alternative in the management of arthritic hips. No other orthopedic procedure has been adopted with such enthusiasm. Thirty-five years later we are still witnessing an incremental increase in the yearly utilization of this operation, attesting to the obvious success associated with it. According to some investigators, we may be coming into an era of increased tumor activity in the vicinity of or possibly remote from implantation sites of these orthopedic appliances.

### 5.5 Case Reports of Implant Related Tumors

In 1976, Harris et al. [17] were the first to describe an aggressive granulomatous lesion around a cemented femoral stem in a total hip replacement. This was a condition of localized tumor-like bone resorption that appeared radiographically as large lytic defects within the femur, approximating the cement mantle of the implant. Initially thought to be neoplastic, these lesions were surgically biopsied and found to be consistent with well-organized connective tissue containing numerous histiocytes, monocytes, and fibroblastic reactive zones. Immunohistologic evaluation revealed multinucleated giant cells and nonspecific esterase-positive monocyte macrophages. These findings suggest a foreign-body type reaction, and with the subsequent isolation of polyethylene, polymethyl methacrylate, and metal debris, it was theorized that these constituents of the construct likely migrated down around the implant cement mantle in cemented prostheses and implant-bone interface in non-circumferentially coated ingrowth implants. Such a reaction suggests an excessive accumulation of debris at the site of articulation that surpasses the body’s ability to neutralize and/or transport the material resulting in migration of debris to sites remote from the source. This rapid appearance of bone loss radiographically which is often associated with a deteriorating clinical course has been termed type-II aseptic loosening [17].

In 1978, two years after the recognition of pseudo tumors of bone induced by the degradation products of total hip arthroplasty, Arden and Bywaters [20] (Table 5.1) reported a case of a 56-year-old patient who developed a high-grade fibrosarcoma of soft tissue 2.5 years after receiving a metal-on-metal McKee-Farrar hip prosthesis. The tumor apparently did not have a direct association with the underlying bone or any components of the total hip arthroplasty. No formal analysis of the tumor for debris products was performed. This case drew attention to the possibility of tumors being initiated in the presence of large orthopedic appliances. It was not until 1984 when this concept became fashionable in large part due to three articles that appeared simultaneously in the *Journal of Bone and Joint Surgery* recounting two malignant fibrous histiocytomas and one osteosarcoma at the site of a total hip arthroplasty [21–23].

This sudden and rather unexpected evolution prompted editorials [24, 25] in the same journal addressing the issue of sarcoma and total hip arthroplasty and encouraged the orthopedic community worldwide to report such cases to a central registry
to obtain more accurate figures on the incidence of such a problem. These tumors occurred 2, 4, and 5 years after hip replacement that was performed with various femoral and acetabular components, some with metal-on-metal articulations and others with metal on polyethylene. In two of these cases, the proximal femur was extensively involved with tumor that was in direct contact with the component. The remaining case was a soft-tissue sarcoma not in direct approximation to the prosthesis. Two of these tumors were malignant fibrous histiocytomas, one of bone and one of soft tissue. The remaining tumor was osteosarcoma. In this particular case, there was evidence of gray-brown pigmentation both intra- and extracellularly between the tumor and femoral component. No formal metal analysis was performed. Three additional cases emerged prior to 1988 at 15 months, 4.5 years, and 2.0 years after implantation [26–28].

In 1988, five cases were reported occurring at 10 [29, 30] and 11[29, 31, 32] years after implantation. The sarcomas included two osteosarcomas, two malignant fibrous histiocytomas, and one synovial sarcoma. Two of these were soft tissue in a location with no direct association with the implant, yet in the case reported by Tait et al. [32] there was evidence of nickel within tumor cells. The remaining three

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
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<th>Time interval(yrs)</th>
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<td>Austin-Moore</td>
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<td>M.F.H.*</td>
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<td>Rushforth</td>
<td>1974</td>
<td>McKee-Farrar</td>
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<td>Arden and Bywaters</td>
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<td>Bagó-Granell et al.</td>
<td>1984</td>
<td>Charnley-Muller</td>
<td>2</td>
<td>M.F.H.</td>
</tr>
<tr>
<td>Penman and Ring</td>
<td>1984</td>
<td>Ring</td>
<td>5</td>
<td>Osteosarcoma</td>
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<td>1984</td>
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<td>4</td>
<td>M.F.H.</td>
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<td>Weber [26]</td>
<td>1986</td>
<td>Cemented TKA</td>
<td>4.5</td>
<td>Epithelioid sarcoma</td>
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<tr>
<td>Ryu et al. [27]</td>
<td>1987</td>
<td>Uncemented Vitallium**</td>
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<td>Vives et al. [28]</td>
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<td>M.F.H.</td>
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<td>Van der List [29]</td>
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<td>Martin et al. [33]</td>
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<td>Haag and Adler [34]</td>
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<td>Kolstad and Högstorp</td>
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<td>Jacobs et al. [39]</td>
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<td>Solomon and Sekel [40]</td>
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<td>7</td>
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</table>

* M.F.H. = malignant fibrous histiocytoma.
** Trademark, Howmedica, Inc. (Cobalt-Chromium alloy).
patients all had direct contact with either the cement or implant with the tumor originating in bone.

In 1990 there were three additional reports in the literature which included an osteosarcoma developing at the site of a Charnley total hip arthroplasty 8 years after implantation, malignant fibrous histiocytoma developing 15 years after a Charnley-Muller total hip arthroplasty, and metastatic adenocarcinoma developing at the site of a Freeman total knee arthroplasty three months after implantation. In 1992, Jacobs et al. presented a malignant fibrous histiocytoma developing one half year after implantation of a cementless AML total hip arthroplasty.

In that same journal volume, unpublished but submitted reports of five tumors occurring around implants were brought to the attention of the orthopedic community (Table 5.2). These included malignant fibrous histiocytomas around a Thompson and a Muller total hip arthroplasties, an osteosarcoma around a Charnley total hip arthroplasty, a rhabdomyosarcoma of soft tissue in the vicinity of a Christiansen total hip arthroplasty, and a chondrosarcoma developing in a patient with Maffucci syndrome having a Charnley total hip arthroplasty. The intervals from implantation to tumor detection were 9, 3, 10, 9 and 1 years respectively. To this, we add two previously unreported additional patients, neither of whom had their joint replacement done at the Mayo Clinic (Table 5.2). The first is that of a 79-year-old man who nine months previously came to total hip replacement with an uncemented Harris-Galante component who was found to have a large malignant fibrous histiocytoma engulfing the proximal femur and extending to the implant. There was, however, no evidence of any particulate debris within the tumor cells removed. The second case was that of a 56-year-old man who developed a soft tissue osteosarcoma 14 months after a left total knee arthroplasty with conventional cemented components. The tumor extended down to both the femoral and patellar components.

### 5.6 Critical Analysis of Tumors

As such, 28 tumors have been reported in direct contact or in close proximity to joint arthroplasty. The vast majority of these appeared with total hip arthroplasty with a smaller contribution from total knee arthroplasty. There have been

<table>
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<th>Author</th>
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<th>Implant</th>
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<td>Christiansen</td>
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<td>Lightowler</td>
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<td>Osteosarcoma</td>
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<td>Thompson</td>
<td>3</td>
<td>M.F.H.*</td>
</tr>
<tr>
<td>Nelson</td>
<td>1992</td>
<td>Muller</td>
<td>9</td>
<td>M.F.H.</td>
</tr>
<tr>
<td>Rock</td>
<td>1992</td>
<td>HG ingrowth</td>
<td>0.8</td>
<td>M.F.H.</td>
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<td>PCA TKA</td>
<td>1.2</td>
<td>Osteosarcoma</td>
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</table>

* M.F.H. = Malignant Fibrous Histiocytoma.
no reported cases of malignant degeneration occurring in the vicinity of total shoulder and/or total elbow arthroplasty. Of the reported 26 cases, 8 tumors were of soft tissue origin, 19 were of primary bone pathology, and 1 metastatic gastric carcinoma. The histogenesis of the soft tissue tumor included 3 malignant fibrous histiocytomas, 1 synovial sarcoma, 1 soft tissue osteogenic sarcoma, 1 fibrosarcoma, 1 epidermoid sarcoma and 1 rhabdomyosarcoma. The histogenesis of the primary bone tumors included 10 malignant fibrous histiocytomas, 6 osteosarcomas, 1 chondrosarcoma, 1 angiosarcoma, 1 fibrosarcoma. Direct contact with the underlying tumor was noted in 15 of the 19 cases in which sufficient information is known from which to make such determinations. In three of the cases, particulate metal matter was determined to be present in the tumor including one case of a soft tissue sarcoma that appeared on image and exploration to be remote from the implant but had obvious evidence of nickel present within the tumor cells.

Many of these tumors have not had an appropriate latent interval between implantation and development to be seriously considered implant induced. Given that the interval to tumor induction from bone stimulation should be at least as long as the accepted five year interval from radiation therapy to sarcoma degeneration, 15 of the 28 patients would qualify, all of whom have had tumors around total hip arthroplasties.

Apart from tumors developing at the site of prosthetic replacement, there have been ten known malignant tumors that have developed at the site of previous internal fixation (Table 5.3). To date there have been no malignancies noted around a titanium implant. The vast majority (> 80%) of malignancies both in the prosthetic and internal fixation groups have occurred in the vicinity of Vitallium™ (cobalt-chromium alloy) implants. This is not, however, to exonerate stainless steel because tumors in the proximity of the implants made of this alloy have been reported in the animal literature [52] as well as the human experience utilizing stainless steel as fixation devices for traumatology [42, 44, 50, 51]. It is interesting to note that in 1976 veterinarians were encouraged within their own literature to report similar

<table>
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<th>Author</th>
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<th>Tumor type</th>
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<td>Vitallium*</td>
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<td>Lymphoma</td>
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<td>Lee et al. [48]</td>
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<td>13</td>
<td>M.F.H.</td>
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* Trademark, Howmedica, Inc. (cobalt-chromium alloy).
** M.F.H. = malignant fibrous histiocytoma.
experiences of tumors around implants nearly eight years before such concern was voiced with the application of these same metallic alloys in humans [52].

5.7 Significance of Clinical Reports

As impressive as these cases may be, they must be put into perspective given the global use of internal fixation and prosthetic devices. Approximately 300 000 to 350 000 total hip joint replacements are performed worldwide on a yearly basis [53]. It can be assumed that approximately four million people will have had total hip arthroplasties performed by the end of 1995. To date, there have been 28 reports of malignant tumor arising in close proximity to these implants (25 total hip and three total knee arthroplasties). No direct contact was noted in four. If we assume a minimal latency of five years to suggest association between presence of implant and tumor, 15 of the 28 could have association. As such, the incidence of sarcomas in total joint replacement would be approximately 1 in 250 000. There are approximately 3000 new primary bone tumors and 5000 soft-tissue sarcomas in the United States per year. This would give an incidence of approximately 1 in 100 000 for the general population to develop a primary bone sarcoma and 1 in 40 000 to develop a soft tissue sarcoma a year. This is obviously not stratified for age given that many primary bone tumors develop in the second and third generation of life, yet it does afford the opportunity of putting this rather unusual event in perspective.

The prevalence of osteosarcoma among the osseous malignancies in this series is not entirely unexpected. Of the total osteosarcoma population 15 percent to 20 percent occur after the age of 50 years. Most of these cases are superimposed on Paget’s disease or in previously irradiated tissue, yet de novo cases of osteosarcoma do occur in this age group. Malignant fibrous histiocytoma of bone is somewhat less common. A review of the Mayo Clinic files reveals 71 cases with more than half of these occurring after age 55. Malignant fibrous histiocytoma of soft tissue is the most common soft-tissue sarcoma. It is not surprising, therefore, that two of six soft-tissue tumors in the combined series are of this histogenesis. As such, the distribution of sarcomas in the combined series could have been predicted from general population data given the age of the patients and anatomical distribution.

There have been two separate reports that have critically analyzed the cancer risk after total hip arthroplasty [54, 55]. The combined person years of exposure after operation between the two series was 20 015. The overall cancer incidence among total hip replacement procedure in both series did not appear to be any different than what was expected or anticipated. The cancer-observed/expected ratio was especially low for the first two years following surgery in both series, implying that patients undergoing this procedure are otherwise generally healthy. In both series, the observed/expected ratio of developing lymphoma or leukemia was two to three times higher in patients who had total hip arthroplasty. Additionally, there was a two fold decrease in breast carcinoma among patients who had total hip arthroplasty.
Of interest, Gillespie et al. [54] suggested a similar decrease in the incidence of rectal, colon, and lung cancer among total hip arthroplasty patients. The results suggest or are possibly compatible with the hypothesis of chronic stimulation of the immune system, thereby potentially allowing for malignancies to occur within the lymphoreticular system. We have already determined a predilection for particulate metal matter to accumulate in the reticuloendothelial system [12]. This has been further supported by studies in animals subjected to metal implants, especially those containing nickel, in which there was an increase in malignancies of the lymphoreticular systemic [52]. Additionally, due to the added immune surveillance, tumors of the breast, possibly colon, rectal, and lung may be decreased. A hyper immune state is not unexpected given the dissemination of debris locally at implantation sites as well as the well-recognized and documented capacity of this material to gain access to the systemic and possibly storage sites including the reticuloendothelial system. This trend obviously needs continued surveillance.

A recent extensive analysis of the cancer risk in a cohort of 39154 patients with at least one hip replacement operation has been performed by the Swedish Nationwide In-Patient Registry [56]. Patients were identified by means of a linkage to the Swedish Cancer Registry. The overall results, although showing a significant 3% increase in cancer, were judged by the authors not to be of clinical significance. Increases of cancer of kidney, skin and brain in women and of prostate in men were found, accompanied by a decrease in gastric cancer for women. The study showed no increase in lymphoreticular cancers as previously reported [54, 55] nor a decrease in colon, breast or rectal cancers. The authors’ judgement is that the overall cancer risk associated with total hip replacement arthroplasty is negligible and should not distract from the obvious benefits of the procedure.

A similar extensive review of the relationship between metallic implants and cancer in dogs was performed by Li et al. [57]. This case controlled study of 1857 dogs from 22 veterinary medical centers failed to reveal significant association between stainless steel fracture fixation devices and the development of bone and soft tissue sarcomas.

5.8 Summary

In summary, careful examination of the scientific and clinical literature suggests that implant materials commonly used for fixation and joint reconstruction are not entirely inert. Accumulation of particulate debris is to some extent going to occur in all patients who have large prosthetic devices. This necessarily includes the distinct possibility of systemic and remote site exposure to these foreign objects that the body attempts to neutralize and excrete. Due to the heightened immunologic surveillance and/or possible storage of particulate metal matter in sites remote from the implantation site, patients with total hip arthroplasty may be at added risk for remote malignancies, particularly of the lymphoreticular system. The incidence of primary mesenchymal tumors in close proximity to implants appears to be consistent with
the incidence in the general public. The frequency of occurrence and the associated individual and group risks of systemic and remote site malignancy remains unresolved.

**Additional Reading**


An extensive review of risk of cancer in 39 154 total hip replacement patients who appeared in the Swedish National Cancer Registry between 1965 and 1983. A review of 60 cancer-specific sites showed an overall, not clinically significant increase of 3% in incidence, slight increases noted for kidney cancer, prostate cancer (in men) and melanoma accompanied by a continuous decline in gastric cancer for both sexes. This would appear to be the definitive review of the risk for developing cancers after total hip replacement arthroplasty.


Review of possible foreign body cancer initiation in humans based upon published case reports. The authors conclude that, since the clinical use of prosthetic implants has been popular for more than twenty years and since, extrapolating from animal experience, at least 25% if not 50% of foreign body tumors should have appeared by the time of their publication, there is little risk of such non-chemically mediated tumors occurring in patients.


A New Zealand study of 1358 patients with total hip arthroplasty, for a total of 14 286 patient years. A significant increase in tumors of the hemopoetic and lymphatic systems, accompanied by a significant decrease of cancers of breast (in women), colon and bowel was observed. The authors suggest that these data are evidence for increased immune surveillance, allowing or precipitating hemopoetic and lymphatic tumors but at the same time providing better resistance to the development of soft tissue tumors. The first large scale study of this question.


A study similar to that of Gillespie *et al.* but on a Finnish patient group (433 patients; 5729 patient years) leading to the same general conclusions. Includes a historical discussion of the carcinogenic properties of various trace elements.


A review of a patient who developed a malignant fibrous histiocytoma at the site of a cementless total hip replacement five months after implantation and succumbed of diffuse metastases, as is typical for such patients, within one year of
presentation. Includes an extensive review of world literature on sarcomas in the vicinity of total hip replacement and suggest the need for an international registry of such case reports.

References


