2. STUDIES OF CANCER IN HUMANS

2A. Metallic medical and dental materials

2A.1 Case reports

The pathology of the cases illustrated in the reports summarized in this section was reviewed by the Working Group and the diagnoses were deemed reliable.

Compilations of the published case reports describing malignant tumours at the site of the metallic implants are presented in Tables 19 (14 cases) (static orthopaedic metallic implants) and 20 (two cases) (joint prostheses).

A total of 16 case reports of local sarcoma or lymphoma at the site of metallic implants have been found in the medical literature. The time lapse between implantation and tumour diagnosis for these cases varied from a few months to 30 years. The ranges were 1.2–30 years for static orthopaedic implants (14 cases) but the majority were less than 10 years (seven cases) and 3.5 and five years for joint endoprostheses (two cases). Almost all case reports relating to tumours at the site of static implants involved the femur. The implanted materials (where reported) were stainless steel or cobalt–chromium alloys. The number of cases appears to be small in comparison with large numbers of implanted metallic devices. Reporting of individual cases is not systematic, so the actual number of occurrences is likely to be greater.

2A.2 Analytical studies

In a case–control study of soft-tissue sarcoma by Morgan & Elcock (1995) described in the chapter on 'composite implants' (see Section 2C.2.1b), a subgroup analysis of metal implants was performed, that yielded an odds ratio of 0.8 (95% confidence interval (CI), 0.3–1.5).

A case–control study in Australia (Ryan *et al.*, 1992) studied the relationship between dental amalgam containing mercury (see IARC, 1993a), diagnostic dental X-rays (IARC, 2000) and subsequent development of brain tumours. The study included 170 cases of brain tumours (110 gliomas, 60 meningiomas) and 417 general population controls. There was a decreased odds ratio of 0.5 (95% CI, 0.3–0.9) for glioma and an odds ratio of 1.0 (95% CI, 0.4–2.5) for meningioma associated with amalgam fillings for at least one year.

Table 19. Malignant tumours at the site of static non-articulating orthopaedic metallic implants

Reference	Implant	Metal	Age at implantation/ sex	Preoperative diagnosis	Site	Histopathology	Years between implantation and diagnosis	Remarks
McDougall (1956)	Plate and screws	Plate: stainless steel, 74% Fe 18% Cr, 8% Ni screws: 88% Fe, 12% Cr	12/M	Fracture	Humerus, diaphysis	Ewing's sarcoma	30	Extensive corrosion of plate and screws (difference in potential between plate and screws of 80 mV)
Bürkle de la Camp (1958)	Medullary nail	NR	22/M	Complicated fracture	Femur, great trochanter	Alveolar sarcoma	3	
Delgado (1958)	[Egger's plate (Hughes *et al.*, 1987) and screws]	NR	37/M	Fracture	Tibia, diaphysis	Unclassified sarcoma [probably osteosarcoma (McDonald, 1981)]	3	
Dube & Fisher (1972)	Sherman (stainless steel) plate and screws	(Plate and 8 screws: stainless steel 316: 18% Cr, 10% Ni, 3% Mo 2 screws: stainless steel 304: 20% Cr, 9% Ni	58/M	Non-union of a fracture (bilateral fracture)	Tibia, diaphysis of both legs	Haemangio-endothelioma	26	Fixed with bone graft, 2 loose screws, corrosion of 2 plate screw holes (the other tibia was also fixed with bone graft, and two screws)
Monkman *et al.* (1974)	Nail plate	NR	57/M	Fracture	Proximal femur	Chondrosarcoma (grade 3)	2	

Table 19 (contd)

Reference	Implant	Metal	Age at implantation/ sex	Preoperative diagnosis	Site	Histopathology	Years between implantation and diagnosis	Remarks
Tayton (1980)	Sherman plate and six screws	CoCr (Vitallium)[a]	4/F	Congenital hip dislocation	Proximal femoral diaphysis	Ewing's sarcoma	7.5	Bilateral osteotomies and plate fixation. Removal of plates and screws one year later
McDonald (1981)	Plate and screws	CoCr (Vitallium)[a]	31/M	Fracture	Tibia, diaphysis	Histiocytic type lymphoma	17	Tumour infiltrating the bone
Dodion *et al*. (1983)	1 Strycker screw + 1 Knowles screw, 1 McLaughlin plate and 5 Phillips screws	CoCr (Vitallium)[a]	49/M	Fracture of the femoral neck	Femur (neck)	Immunoblastic lymphoma	1.2	Deep infection
Lee *et al*. (1984)	Plate and screws	NR	30/M	Open femur fracture	Femur, diaphysis	Malignant fibrous histiocytoma	14	Removal of plate and screws and bone grafting for suspected osteomyelitis 4 months before diagnosis
Hughes *et al*. (1987)	One Sherman screw	CoCr[b]	14/M	Slipped proximal femoral epiphysis	Femur, neck	Malignant fibrous histiocytoma	29	Single screw
Ward *et al*. (1990)	Smith-Petersen nail	Stainless steel (Ni, Co, Cr, Mo, Fe)	56/F	Fracture of the femoral neck	Femur, neck	Osteosarcoma	9	

Table 19 (contd)

Reference	Implant	Metal	Age at implantation/ sex	Preoperative diagnosis	Site	Histopathology	Years between implantation and diagnosis	Remarks
Khurana *et al*. (1991)	Hansen Street intramedullary nail	Stainless steel (17–19% Cr, 12–14% Ni, 2-3% Mo, 2% Mn; Fe)	25/M	Gunshot fracture	Proximal femoral diaphysis	Malignant fibrous histiocytoma	14	
Scully *et al*. (1991)	Staples	Stainless steel 316 (18% Cr, 10% Ni)	8/M	Morquio's syndrome, genu valgum	Distal femoral diaphysis	Osteosarcoma	10	Bilateral femoral osteotomies
Kumar (1996)	Two staples	NR	7/M	Post-poliomyelitic deformity	Distal femoral diaphysis (knee)	Osteosarcoma	9	

[a] Vitallium, 58.4% min. Co; 27–30% Cr; 5–7% Mo; 2.5% max. Ni; 1% max. Mn; 0.75% max. Fe
[b] CoCr = cobalt–chromium alloy, composition not stated
NR, not reported

Table 20. Malignant tumours at the site of joint endoprosthesis (metal only)

Reference	Prosthesis	Metal	Age at implantation/ sex	Preoperative diagnosis/site	Histopathology	Years between implantation and diagnosis	Remarks
Castleman & McNeely (1965)	Moore prosthesis	NR	49/M	Old fracture of the femoral neck (hip)	Giant cell sarcoma (malignant)	3.5	Nail and plate for 8 months before the prosthesis ('fatty' tumour excised from the knee 14 years before implantation)
Penman & Ring (1984)	Ring	Stem-head alloy: CoCr Cup: CoCr Fixation: Uncemented	75/F	Osteoarthritis THA	Osteosarcoma	5	

THA, total hip arthroplasty
NR, not reported

2B. Non-metallic Medical and Dental Materials

2B.1 Case reports

2B.1.1 *Cancer following silicone implants for the breast*

Published case reports describing malignant tumours at the site of plastic implants (silicone) are summarized in Tables 21–24.

Table 21 lists 15 cases of breast cancer reported following cosmetic augmentation with silicone injections. Injection of liquid silicone into breasts for cosmetic purposes was an illicit practice performed until about 1970 (Morgenstern *et al*., 1985). It was frequently followed by short- and long-term complications, including inflammation, sinusitis, contractures and deformities. Table 22 summarizes nine cases of breast cancer reported following cosmetic breast augmentation using silicone prostheses. Considering the large number of women with silicone implants (mainly in the United States), the number of case reports seems to be rather low. The reported cases are in general of younger age than the age distribution of breast cancer diagnosis observed in Western populations. This may reflect the younger age of most patients at the time of breast implantation and the relatively short time period during which this procedure has been in widespread use.

Six cases of breast cancer and four cases of Paget's disease of the nipple were reported after reconstructive operation generally following mastectomy. Few data are available on other risk factors in these cases (Table 23).

Table 24 summarizes six cases of lymphoma after implantation of silicone in the breast or fingers. Eighteen female cases of multiple myeloma were reported from a nationwide multiple myeloma registry in the United States (Rabkin *et al.*, 1996). One additional male case of multiple myeloma after penile implant was reported by Tricot *et al.* (1996). In addition, one case of desmoid tumour was reported by Schuh & Radford (1994).

2B.1.2 *Sarcomas at the site of vascular grafts*

Eight cases of sarcomas involving a graft have been reported (Table 25). Most patients were operated on for aortic aneurysms. Histopathological examination showed three cases of malignant fibrous histiocytoma, two angiosarcomas and three fibrosarcomas.

2B.2 Analytical studies

2B.2.1 *Cohort studies*

Six cohort studies of cancer among women undergoing cosmetic implants of silicone prosthesis have been reported and are summarized in Table 26.

A record-linkage cohort study in California, United States, included 3182 Caucasian women, resident in Los Angeles County, who had been treated for cosmetic breast enlargement between 1953 and 1980 (Deapen *et al*., 1986, 1997). Patients' records were

Table 21. Breast cancer after cosmetic augmentation with silicone injection in women

Reference	Age at injection	Histopathology	Interval between silicone injection and cancer diagnosis (years)	Remarks
Lewis (1980)	26	Inflammatory carcinoma	7	
Morgenstern *et al.* (1985)	48	Infiltrating ductal [adeno]carcinoma	20	Family history of breast cancer
Morgenstern *et al.* (1985)	45	Infiltrating ductal [adeno]carcinoma	14	
Morgenstern *et al.* (1985)	30	Infiltrating ductal [adeno]carcinoma	19	
Morgenstern *et al.* (1985)	19	Infiltrating ductal [adeno]carcinoma	15	
Morgenstern *et al.* (1985)	24	Infiltrating ductal [adeno]carcinoma	16	
Morgenstern *et al.* (1985)	21	Metaplastic squamous and pseudosarcomatous carcinoma	16	Family history of breast cancer
Morgenstern *et al.* (1985)	46	Infiltrating ductal [adeno]carcinoma	13	
Morgenstern *et al.* (1985)	30	Infiltrating ductal [adeno]carcinoma	17	
Morgenstern *et al.* (1985)	32	Poorly differentiated adenocarcinoma	6	
Timberlake & Looney (1986)	30	Poorly differentiated adenocarcinoma	12	
Maddox *et al.* (1993)	30	Poorly differentiated invasive ductal [adeno]carcinoma	5	
Ko *et al.* (1995)	27	Adenocarcinoma	25	Oestrogen and progesterone replacement therapy for previous 8 yrs
Ko *et al.* (1995)	39	Intraductal carcinoma	22	
Talmor *et al.* (1995)	45	Squamous cell carcinoma	25	

Table 22. Breast cancer after cosmetic augmentation with silicone prostheses in women

Reference	Prosthesis composition	Age at implan-tation	Histopathology	Interval between silicone implant and cancer diagnosis (years)	Remarks
Gottlieb *et al.* (1984)	Gel-filled	29	Invasive lobular carcinoma	3	
Gottlieb *et al.* (1984)	Gel-filled	39	Invasive ductal carcinoma	4	
Morgenstern *et al.* (1985)	Silicone	35	Infiltrating ductal [adeno]carcinoma	7	Family history of breast cancer
Morgenstern *et al.* (1985)	Silicone	36	Infiltrating ductal [adeno]carcinoma	12	
Morgenstern *et al.* (1985)	Silicone	39	Infiltrating ductal adenocarcinoma	5	
Bingham *et al.* (1988)	Silicone gel-filled	32	Ductal [adeno]-carcinoma	13	Mother had Paget's disease
Silverstein *et al.* (1990)	Silicone gel-filled	54	Ductal [adeno]-carcinoma	12	
Paletta *et al.* (1992)	240 mL style 2100 Heyer Schulte silicone gel	37	Squamous cell carcinoma originating from the posterior implant capsule	15	
Kitchen *et al.* (1994)	240 mL style 2100 Heyer Schulte silicone gel	37	Squamous cell carcinoma	15	

abstracted from 35 private practices (out of a total of about 100 in the county at that time). Subjects receiving reconstructive implants after mastectomy, either for prophylactic purposes or for cancer treatment, were excluded. Subjects moving out of the county were excluded from the time of the last contact as residents. The mean age of subjects at implantation was 37.4 years. Eighty-six per cent of the prostheses used were silicone gel or silicone/saline and the remainder (14%) were 'other' or 'unknown' types. Sixty patients received polyurethane-coated silicone implants and nine more from the 'unknown' group were believed to have received polyurethane devices also. Cohort members were followed up through record linkage with the local population-based tumour registry—the Los Angeles County Cancer Surveillance Program—from the time of surgical implantation (or 1 January 1972, whichever was later) until 31 December 1991. A total of 37 439 person–years were accumulated, with a median duration of follow-up of 14.4 years. Great effort was made to identify subjects moving

Table 23. Breast cancer and Paget's disease of the nipple after silicone implantation for medical indication in women

Reference	Prosthesis composition	Age at implan-tation	Preoperative diagnosis	Histopathology	Interval between silicone implant and cancer diagnosis (years)	Remarks
Hoopes *et al.* (1967)	Silastic prosthesis, (RT V 53G2, Dow Corning) then 3 yrs later Silicone liquid no. 360 injection 0.5 years before diagnosis	37	NR	Infiltrating lobular carcinoma	3	
Bowers & Radlauer (1969)	Silastic prosthesis	46	Fibrocystic disease, subcutaneous mastectomy	Ductal [adeno]-carcinoma	3	Prosthesis under pectoralis major muscle
Bowers & Radlauer (1969)	Silastic prosthesis	44	Fibrocystic disease, subcutaneous mastectomy	Scirrhous adeno-carcinoma	1.5	
Dalinka *et al.* (1969)	Silastic prosthesis	38	Fibrocystic disease, mastectomy	Carcinoma (not specified)	3	
Frantz & Herbst (1975)	Cronin silastic prosthesis	30	Postirradiation atrophy of the breast	Poorly differentiated adenocarcinoma	2.5	Irradiation of the breast at the age of 3–15 months for haemangioma

Table 23 (contd)

Reference	Prosthesis composition	Age at implantation	Preoperative diagnosis	Histopathology	Interval between silicone implant and cancer diagnosis (years)	Remarks
Mendez-Fernandez *et al.* (1980)	Silicone gel prosthesis	45	Fibrocystic disease of the breast, subcutaneous mastectomy	Paget's disease plus infiltrating duct cell adenocarcinoma	8	
Pennisi (1984)	Silicone injections	20	Pectus excavatum	Ductal adenocarcinoma	23	Family history of breast cancer
Shearman & Watts (1986)	Silicone prosthesis	4	Subcutaneous mastectomy for spheroidal cell cancer	Paget's disease	1.5	
Shearman & Watts (1986)	Silicone prosthesis	50	Subcutaneous mastectomy for intraductal carcinoma	Paget's disease	1.5	
Shearman & Watts (1986)	Silicone prosthesis	46	Subcutaneous mastectomy for adenocarcnoma	Paget's disease	4	

NR, not reported

Table 24. Lymphomas and myelomas following implantation of silicone prosthesis

Reference	Prosthesis composition	Age at implantation/ sex	Indication for implantations	Histopathology	Interval between silicone implant and cancer diagnosis (years)	Remarks
Digby (1982)	Silastic Swanson finger prostheses	47/F	Rheumatoid arthritis	Undifferentiated large cell lymphoma	9	Implant fracture. Other hand was also prosthetized.
Murakata & Rangwala (1989)	Silastic finger joints	59/F	Rheumatoid arthritis	Immunoblastic lymphoma	9	
Cook *et al.* (1995)	Replicon polyurethane-covered silicone implant	50/F	Sequel after mastectomy for ductal carcinoma	Follicular mixed lymphoma	6	
Duvic *et al.* (1995)	Même polyurethane-coated silicone	35/F	Augmentation mammoplasty	Cutaneous T-cell lymphoma	3	
Duvic *et al.* (1995)	Polyurethane-coated Dow-Corning silicone implants	24/F	Eczematous eruption	Cutaneous T-cell lymphoma	11	
Duvic *et al.* (1995)	Dow-Corning silicone implants	33/F	Augmentation mammoplasty	Cutaneous T-cell lymphoma	20	
Rabkin *et al.* (1996)	Breast silicone implant	38–75/F (at diagnosis)		18 cases of multiple myeloma	2–25	Probably reported also by Silverman *et al.* (1996) and by Tricot *et al.* (1996).
Tricot *et al.* (1996)	Penile silicone implant	67/M	Unknown	Multiple myeloma	1 month	Reports also nine female cases that are probably included in Rabkin *et al.* (1996).

Table 25. Malignant tumours at the site of vascular grafts in men[a]

Reference	Prosthesis	Site	Age at implan-tation	Preoperative diagnosis	Histopathology	Interval between operation and diagnosis (years)
Burns *et al*. (1972)	Teflon-Dacron	Thigh	21	Traumatic rupture of the superficial femoral artery after an accident	Fibrosarcoma (or angiosarcoma)	10.5
O'Connell *et al*. (1976)	Woven Dacron 19 mm	Abdominal aorta	59	Aortic aneurysm	Fibrosarcoma	0.3
Weinberg & Maini (1980)	Woven Dacron 26 mm	Thoracic, abdominal aorta	47	Thoracic-abdominal aortic aneurysm	Malignant fibrous histiocytoma	1.2
Fehrenbacher *et al*. (1981)	Woven Dacron	Abdominal aorta	55	Aortic aneurysm	Angiosarcoma	12
Paterson *et al*. (1989)	Double-velour Dacron 20 mm	Descending thoracic aorta	57	Aortic aneurysm	Malignant fibrous histiocytoma	0.5
Weiss *et al*. (1991)	Woven double-velour Dacron	Infrarenal aorta	52	Aortic aneurysm	Angiosarcoma	4
Raso *et al*. (1993)	Dacron 8 mm	Superficial femoral artery	76	Aneurysm	Fibrosarcoma	0.2
Fyfe *et al.* (1994)	Dacron	Descending thoracic aorta	66	Acute aortic dissection	Malignant fibrous histiocytoma	4

[a] The insertion of vascular grafts requires the application of sutures, an additional implanted material

Table 26. Cohort studies of cancer following implantation of silicone breast prostheses

Reference (use)	Country	Exposed cohort size	Reference population	Design	Follow-up	Cancer site	No. of cases among exposed	SIR (95% CI)
Deapen *et al*. (1997) (cosmetic)	United States	3182	Population tumour registry (Los Angeles County)	Record linkage, tumour registry	37 439 person–years; implant 1953–80; follow-up through 1991	Breast	31	0.6 (0.4–0.9)
Bryant & Brasher (1995) (cosmetic)	Canada	10 835	Population tumour registry (Alberta Province)	Record linkage, tumour registry	89 219 person–years; implant 1973–86; follow-up through 1990	Breast	45	0.8 (0.6–1.1)[a] 0.9 (0.6–1.2)[b] 0.7 (0.3–1.3)[c]
Friis *et al.* (1997) (cosmetic)	Denmark	1135	National tumour registry	Record linkage, tumour registry	[9525] person–years; implant 1977–92; follow-up through 1993	All cancers Lung Breast Ovary Melanoma Skin, other Non-Hodgkin lymphoma Sarcomas Other	27 2 8 3 1 5 1 1 6	1.1 (0.7–1.6) 1.5 (0.2–5.3) 1.0 (0.4–2.0) 2.5 (0.5–7.3) 0.7 (0.0–3.7) 1.6 (0.5–3.7) 2.2 (0.0–12.0) 2.7 (0.0–14.9) 0.7 (0.3–1.5)

Table 26 (contd)

Reference (use)	Country	Exposed cohort size	Reference population	Design	Follow-up	Cancer site	No. of cases among exposed	SIR (95% CI)
Gabriel *et al.* (1994) (mixed)	United States	534 cosmetic 125 recons-tructive 90 prophy-lactic	1498 community controls	Medical record review	5847 person–years; implant 1964–91; follow-up through 1991	Cancers other than breast	13	1.1 (0.6–2.1)
						Cosmetic	8	1.0 (0.4–2.1)
						Reconstructive	2	1.3 (0.3–4.4)
						Prophylactic	3	1.5 (0.4–4.3)
McLaughlin *et al*. (1998) (cosmetic)	Sweden	3473	National tumour registry	Record linkage, tumour registry	35 644 person–years; implant 1965–93; follow-up through 1993	All cancers	74	1.1 (0.8–1.3)
						Large bowel	3	0.7 (0.1–2.0)
						Lung	7	2.7 (1.1–5.6)
						Skin	5	0.9 (0.3–2.0)
						Breast	18	0.7 (0.4–1.1)
						Cervix	10	1.9 (0.9–3.5)
						Ovary	6	1.3 (0.5–2.8)
						Brain	4	1.1 (0.3–2.9)
						Non-Hodgkin lymphoma	1	0.6 (0.0–3.5)
						Myeloma	1	2.6 (0.1–15)
						Leukaemia	3	2.7 (0.6–7.8)
Kern *et al*. (1997) (cosmetic)	United States	680	Control cohort (n = 1022)	Record linkage, tumour registry	[Cases: 3128 Controls: 5519] person–years; implant 1980–93; follow-up through 1993	Breast	4	0.7 (0.2–2.2)[d]
						Other cancers	4	0.2 (0.1–0.6)

Table 26 (contd)

Reference (use)	Country	Exposed cohort size	Reference population	Design	Follow-up	Cancer site	No. of cases among exposed	SIR (95% CI)
Petit *et al.* (1994) (breast cancer)	France	146 women with breast cancer and silicone implant	146 women with breast cancer without silicone implant	Mortality, second primaries	Implantation 1965–83; average follow-up: 12.5 years	Second primary breast cancer	12	1.1 (0.5–2.7)
						Death from breast cancer	15	0.5 (0.3–1.0)
						Distant metastases	19	0.5 (0.3–0.8)
						Local recurrence	13	0.5 (0.3–1.1)
						Second primary cancers, other sites	5	0.8 (0.2–2.5)

SIR, standardized incidence ratio; CI, confidence interval
[a] Calculated taking into account an induction period of one year
[b] Calculated taking into account an induction period of five years
[c] Calculated taking into account an induction period of 10 years
[d] Analysis led to underestimation of the relative risk

out of the county during the study period, through extensive record linkages with the motor vehicle, voter registration, telephone, property tax and marriage files. Thirty-one patients were diagnosed with breast cancer (three *in situ* and 28 invasive) during the study period versus 49.2 expected. The standardized incidence ratio (SIR) was 0.6 (95% CI, 0.4–0.9) (Deapen *et al.*, 1997). The authors also reported on malignancies other than breast cancer (Deapen & Brody, 1995). In total, 45 cancers other than breast cancer were observed, compared with 50 expected (SIR, 0.9; 95% CI, 0.7–1.2). Among other sites, increased risk was observed for lung cancer (SIR, 2.1; 95% CI, 1.1–3.7; $n = 12$) and cancer of the vulva (SIR, 5.3; 95% CI, 1.7–12.3; $n = 5$). Furthermore, five cases of endometrial cancer (SIR, 0.7; 95% CI, 0.2–1.7) and four cases of invasive cervical cancer (SIR, 1.4; 95%, CI 0.4–3.5) were reported. [The Working Group noted that no information on potential confounding variables was available and that information on socioeconomic status was limited to a crude score based on census-tract of residence. The Working Group also noted that no allowance was made for length of induction period.]

A record-linkage cohort study in Canada identified women with breast implants from the records of the insurance payment claims of Alberta Health Care (Berkel *et al*., 1992; Bryant *et al.*, 1994; Bryant & Brasher, 1995). After excluding women treated for reconstructive breast surgery, a cohort of 11 676 women was identified who received cosmetic breast implants within the province from 1973 through 1986. Approximately 85% of the subjects were treated with silicone gel prostheses and the remainder with saline-filled prostheses. No polyurethane-covered implants were in use in Alberta during the study period. Bryant & Brasher (1995) identified 45 breast cancer cases diagnosed between 1973 and 1990 in the cohort (five *in situ*) out of a total of 10 835 women contributing 89 219 person–years at risk. The SIRs were estimated as 0.8 (95% CI, 0.6–1.0) for all breast cancers and 0.7 (95% CI, 0.5–1.0) for invasive breast cancers only. When time between first implant and cancer diagnosis (induction period) was considered, the SIRs for induction periods of one year, five years and 10 years were 0.8 (95% CI, 0.6–1.1), 0.9 (95% CI, 0.6–1.2) and 0.7 (95% CI, 0.3–1.3), respectively. These estimates did not change appreciably in analyses restricted to invasive cancers only. [The Working Group noted the absence of information on potential confounding factors.]

A record-linkage cohort study in Denmark identified 1135 women who underwent cosmetic breast implant surgery between 1977 and 1992, through the nationwide Hospital Discharge Register (McLaughlin *et al*., 1994, 1995a; Friis *et al*., 1997). The mean age at implantation was 31 years (range, 13–64) and the average follow-up was 8.4 years (maximum, 17 years). A total of 27 cases of cancer were identified among cohort members through record linkage with the Danish population-based tumour registry. Breast cancer was the most common cancer (eight cases observed versus 7.8 expected), with an SIR of 1.0 (95% CI, 0.4–2.0). No departure from expected values was observed for any other cancer site. Four breast cancer cases developed 10 or more years after implant surgery (SIR, 1.7; 95% CI, 0.4–4.2). The authors reported that the

reproductive histories of women with implants were similar to those of the general Danish population.

A historical cohort study in the United States identified all 749 women residents in Olmstead County, Minnesota, whose medical records indicated breast augmentation performed for cosmetic reasons (534 patients) or following mastectomy, either for breast cancer (125 patients) or for prophylactic purposes among high-risk subjects (90 patients) between 1964 and 1991 (Gabriel *et al*., 1994). Exposed subjects were followed up through 1991, corresponding to 5847 person–years (mean, 7.8 years per case). Of the 1840 devices implanted in these patients, 78.3% were silicone gel, 5.2% were saline, 6.7% were combination silicone gel/saline and 9.6% were polyurethane-coated. Community controls were 1498 women who had undergone a medical evaluation within two years of the date of implantation of one of the exposed subjects (two controls per exposed subject). Eight cases of cancer (other than breast) were identified among the 534 cosmetic implant patients, corresponding to a rate ratio of 1.0 (95% CI, 0.4–2.1). Among the 125 patients with post-cancer reconstructive implants, two cases of cancer at sites other than breast were identified, corresponding to a rate ratio of 1.3 (95% CI, 0.3–4.4). Among the 90 prophylactic implant patients, there were three cases of non-breast cancer, corresponding to a rate ratio of 1.5 (95% CI, 0.4–4.3).

A nationwide systematic record-linkage cohort study in Sweden included all 3473 women listed in a national hospitalization register with surgical procedures for cosmetic breast augmentation during the period 1965 through 1993 (McLaughlin *et al*., 1995a,b, 1998). Patients with a cancer diagnosis before or up to one month after the date of implant and those who died or emigrated before the start of follow-up were excluded. Median age at implant was 30 years. Median duration of follow-up was nine years (maximum, 29 years). After accumulating 35 644 person–years at risk, 74 cases of cancer at any localization were identified versus 70.3 expected, giving an SIR of 1.1 (95% CI, 0.8–1.3). The SIR for breast cancer, the most common cancer in this population, was 0.7 (95% CI, 0.4–1.1). The second most common occurrence was cervical cancer, with an SIR of 1.9 (95% CI, 0.9–3.5). The only appreciable departure from expectation was observed in relation to lung cancer (seven cases), with an SIR of 2.7 (95% CI, 1.1–5.6). There was no significant excess for any other cancer site, including non-Hodgkin lymphomas (one case), multiple myeloma (one case) and leukaemia (three cases versus 1.1 expected). The authors reported no difference in stage of breast cancer at diagnosis, compared with the general population. [The Working Group noted the absence of information on any potential confounding factors, including tobacco smoking, and the absence of analysis by latency.]

A cohort study in the United States used the statewide hospital discharge data of the State of Connecticut to identify 680 women who received cosmetic breast augmentation silicone prostheses between October 1980 and September 1993 (Kern *et al*., 1997). The mean age at implantation was 34 years. The exposed patients thus identified were compared with a reference cohort of 1022 women with a hospital

discharge of sterilization by endoscopic tubal ligation during the period October 1981 through September 1985. Incident cases of all cancers among subjects in the exposed and control cohorts were identified by record linkage with the statewide Connecticut Tumor Registry. The mean follow-up times for the exposed and control cohorts were 4.6 and 5.4 years, respectively. Four cases of breast cancer and four cases of other malignancies (one skin, one colon and two lung cancers) were observed among the exposed patients, whereas nine cases of breast cancer and 28 cases of all other malignancies were observed among the unexposed group. The corresponding rate ratios were 0.7 (95% CI, 0.2–2.2) for breast cancer and 0.2 (95% CI, 0.1–0.6) for all other cancers combined. [The Working Group noted the absence of information on any potential confounders and that the statistical analysis that was performed led to underestimation of the relative risk.]

A study in France included 146 patients treated at the Gustave Roussy Cancer Institute between 1965 and 1983 for breast cancer with mastectomy followed by breast reconstruction with silicone gel prostheses (Petit *et al.*, 1994). These patients were compared with 146 controls with breast cancer treated at the same hospital with mastectomy without breast reconstruction. Exposed cases and cancer controls were individually matched by age and year at diagnosis, stage, histological type of cancer, grade and nodal status. The average follow-up time to identify second primaries was 12.5 years. The relative risk (RR) for second primary breast cancer was 1.1 (95% CI, 0.5–2.7), whereas the risk of second primary cancer at all other sites was 0.8 (95% CI, 0.2–2.5). There were reduced risks for death from breast cancer (RR, 0.5; 95% CI, 0.3–1.0), distant metastases (RR, 0.5; 95% CI, 0.3–0.8) and local recurrence (RR, 0.5; 95% CI, 0.3–1.1) among the women with silicone implants.

2B.2.2 *Case–control studies* (Table 27)

A case–control study reported as a research letter was performed in the State of Washington, United States (Malone *et al.*, 1992). Two groups of subjects were part of the study, one comprising 684 breast cancer cases and 816 population controls aged 21–44 years and the second 406 breast cancer cases and 339 population controls aged 50–64 years. Controls were residents of the same area as the cases and were identified through random-digit dialling. Exposure was assessed by telephone interview. In the younger group, six cases and nine controls reported a history of cosmetic breast augmentation implants, corresponding to a relative risk of 0.8 (95% CI, 0.3–2.2). In the older group, one case and six controls reported breast augmentation implants, giving a relative risk of 0.2 (95% CI, 0.1–1.3). [The Working Group noted that very limited information on study design and methods was available.]

A population-based case–control study on the role of silicone implants in breast cancer included two metropolitan areas in the United States (Atlanta, Georgia, and Seattle/Puget Sound, Washington) and five counties in central New Jersey (Brinton *et al.*, 1996). In Seattle and New Jersey, cases were restricted to women under 45 years of age at diagnosis, while in Georgia the upper age limit was 54 years. All eligible

Table 27. Case–control studies of breast cancer incidence following cosmetic surgical implantation of breast prostheses

Reference	Country	Exposure	Outcome	No. of cases	No. of controls	No. (%) of cases receiving breast prosthesis	No. (%) of controls receiving breast prosthesis	Adjustment	Odds ratio (95% CI)
Malone *et al*. (1992)	United States	Silicone	Breast cancer	1090	1155	7 (0.6%)	15 (1.2%)		0.8 (0.3–2.2) (age 20–44) 0.2 (0.1–1.3) (age 50–64)
Brinton *et al*. (1996)	United States	Silicone	Breast cancer	2174	2009	36 (1.7%)	44 (2.2%)	Study site, age, race, body size, familial risk, previous mammography	0.6 (0.4–1.0) 0.5 (0.3–1.0) (age ≥ 35 at implant) 0.5 (0.2–0.9) (≥ 10 years after implant)

CI, confidence interval

breast cancer cases diagnosed within the study area during the period from May 1990 to December 1992 were identified through a rapid ascertainment system by agreement with the local population-based tumour registries. Controls were selected through random-digit dialling (90.5% response rate) and matched to the cases on area of residence and age. Personal interviews collected a broad range of data on potential risk factors for breast cancer and detailed information on history of breast surgery, including aspirations, biopsies, lumpectomies and enlargement or reduction operations. Complete interviews were obtained from 2174 cases (85.2% of eligible) and 2009 controls (78.1% of eligible). A total of 36 cases (1.7%) and 44 controls (2.2%) reported a history of cosmetic breast augmentation, giving a relative risk of 0.6 (95% CI, 0.4–1.0), after adjustment for race, body size, family history of breast cancer and history of mammography, in addition to matching factors. The decrease in risk was seen for subjects who underwent surgery at age 35 years or older (relative risk, 0.5; 95% CI, 0.3–1.0) and in those 10 or more years after implantation (relative risk, 0.5; 95% CI, 0.2–0.9).

2C. Composite Medical and Dental Implants

2C.1 Case reports

2C.1.1 *Orthopaedic implants*

Compilations of the published case reports describing malignant tumours at the site of implants are presented in Tables 28 (three cases, joint prosthesis, metal with bone cement) and 29 (32 cases, joint prosthesis, metal and polyethylene with bone cement). Reports of metastatic tumours found at the site of a joint implant are presented in Table 30 (seven cases).

The time lapse for these cases varied from a few months to 15 years, with the majority being less than 10 years. Metastases from other sites to the proximity of a prosthesis have been discovered within lapse times of from two months to two years (seven cases, see Table 30). Almost all case reports relating to tumours at the site of static implants have involved the femur. The implanted materials (where reported) were stainless steel, cobalt–chromium alloys (rarely with alumina) or titanium, in combination with polyethylene and cements (generally poly(methyl methacrylate) (IARC, 1979b)).

The number of cases appears to be small in comparison with the estimated number of implanted devices worldwide (see Section 1C.2). Reporting of individual cases is not systematic, so that the actual number of occurrences is likely to be greater.

2C.1.2 *Cardiac pacemakers*

Thirteen cases of breast cancer and one case of plasmacytoma in the vicinity of cardiac pacemakers have been reported (Table 31). The median age at implantation was 64 (43–83) years and the median latent period four (1–18) years. A case of metastasis

Table 28. Malignant tumours at the site of joint endoprosthesis (metallic with bone cement)

Reference	Prosthesis	Composition 1) Stem-head alloy 2) Cup	Age at implan-tation/ sex	Preoperative diagnosis	Histopathology	Years between implan-tation and diagnosis	Remarks
Rushforth (1974)	McKee-Farrar THR	1) CoCr 2) CoCr (Visuri *et al*., 1996)	62/F	Radiation necrosis of the femoral head	Osteosarcoma of pelvis	0.5	3 insertions of radium (2500 rad) for carcinoma of cervix + external irradiation (mid-point dose of 2000 rad). Cancer possibly due to irradiation. Loose acetabular part
Arden & Bywaters (1978)	McKee-Farrar THR	1) CoCr 2) CoCr (Visuri *et al*., 1996)	56/M	Osteoarthritis	Fibrosarcoma, femur	2.5	
Swann (1984)	McKee-Farrar THR	1) CoCr 2) CoCr (Vitallium) cemented	63/M	Osteoarthritis	Malignant fibrous histiocytoma, femur	4	

THR, total hip replacement

Table 29. Malignant tumours at the site of joint endoprosthesis (metal/polyethylene with or without bone cement)

Reference	Prosthesis	Composition 1) Stem-head alloy 2) Cup 3) Fixation 4) Additional implants	Age at implantation/ sex	Preoperative diagnosis	Histopathology	Years between implantation and diagnosis	Remarks
Wines (1973)	Charnley THA	1–2) Not stated 3) PMMA cement	NR	Osteoarthritis	Bladder cancer, transitional cell carcinoma, WHO grade III, adjacent to extrapelvic	0.25	PMMA may have been released into the pelvis [the tumour may have preceded implantation]
Bagó-Granell *et al*. (1984)	Charnley-Müller THA	1–2) Not stated 3) PMMA cement 4) Trochanteric wires	75/F	Osteoarthritis	Malignant fibrous histiocytoma	2	Other hip, Charnley-Müller THA 2 years before
Weber (1986)	Variable axis TKA	1) CoCrMo (Vitallium) 2) Polyethylene 3) PMMA cement	76/F	Osteoarthritis	Epithelioid sarcoma (or malignant fibrous histiocytoma)	4.5	Distal femoral intramedullary enchondroma or bone infarct before operation
Ryu *et al*. (1987)	2 screws Hip	Uncemented THA (aluminium oxide acetabulum + femoral head with CoCrMo alloy)	52/M	Osteoarthritis secondary to fracture-dislocation	Soft-tissue fibrosarcoma	1.2	Ceramic prosthesis 12 years after implant of two screws
Vives *et al*. (1987)	Charnley-Müller THA	1) CoCr 2) Polyethylene 3) PMMA cement	67/M	Coxarthrosis	Malignant fibrous histiocytoma	2	

Table 29 (contd)

Reference	Prosthesis	Composition 1) Stem-head alloy 2) Cup 3) Fixation 4) Additional implants	Age at implantation/ sex	Preoperative diagnosis	Histopathology	Years between implantation and diagnosis	Remarks
Lamovec *et al*. (1988)	Charnley-Müller THA	1) Stainless steel 2) Polyethylene 3) PMMA cement	50/M	Osteoarthritis secondary to congenital hip dislocation	Synovial sarcoma at THA site	12	
Lamovec *et al*. (1988)	Charnley-Müller THA	1–2) NR 3) Cemented	55/F	NR	Osteosarcoma	10	
Martin *et al*. (1988)	Charnley-Müller THA	1) CoCr 2) Polyethylene 3) PMMA cement	66/F	Osteoarthritis secondary to congenital dislocation of the hips	Telangiectatic osteosarcoma	10.5	Other hip, THA 1 month later, type not known
Tait *et al*. (1988)	Charnley-Müller THA	1) NR 2) [Polyethylene] 3) Cemented 4) Trochanter wires	45/F	Osteoarthritis	Malignant fibrous histiocytoma, gluteal region	11	
van der List *et al.* (1988)	1) Charnley-Müller 2) Revision, with bone autograft, Müller prosthesis 11 years later THA	1) CoCrMo 2) Polyethylene 3) PMMA cement	61/F	Osteoarthritis secondary to congenital hip dysplasia	Malignant epithelioid haemangioendothelioma, femur/ acetabulum	12	Other hip, Charnley-Müller THA in the same year and revised with Müller THA 3 years later

Table 29 (contd)

Reference	Prosthesis	Composition 1) Stem-head alloy 2) Cup 3) Fixation 4) Additional implants	Age at implantation/ sex	Preoperative diagnosis	Histopathology	Years between implantation and diagnosis	Remarks
Haag & Adler (1989)	Weber-Hüggler THA	1) CoCrNi (Protasul 10) 2) Polyethylene 3) PMMA cement	59/F	Osteoarthritis	Malignant fibrous histiocytoma	10	Other hip, Weber-Hüggler THA, 1 year before
Mazabraud *et al.* (1989)	McKee-Farrar THA	1) CrNiCo 2) Polyethylene 3) PMMA cement	60/M	Osteoarthritis	Epidermoid carcinoma	4.5	Previous femoral osteotomy (type of implant not reported); 1.5 years earlier, chronic sinus present at second surgery
Brien *et al.* (1990)	Charnley THA	1) Stainless steel 2) Polyethylene 3) Cemented	50/F	Osteoarthritis secondary to hip dysplasia	Osteosarcoma	8	Both hips had same treatment
Harris (1990)	Charnley THA	1–3) NR	65/F	Osteoarthritis secondary to Maffucci's syndrome	Chondrosarcoma	3	Enchondromata of the upper femur. Other hip THA 11 years earlier

Table 29 (contd)

Reference	Prosthesis	Composition 1) Stem-head alloy 2) Cup 3) Fixation 4) Additional implants	Age at implantation/ sex	Preoperative diagnosis	Histopathology	Years between implantation and diagnosis	Remarks
Troop *et al.* (1990)	1) Charnley-Müller, 2) Aufranc-Turner 3 years later, 3) Aufranc-Turner (long stem) 2 years later, 4) Sivash-Russin-Cr-Co cemented (long stem) Noiles (SRN) 3 years later, 5) Cemented titanium SRN, femoral allograft, cemented Arthropore acetabular, constraining ring 3 years later THA	1) Titanium 2) [Polyethylene] 3) Cemented	24/M	Traumatic osteoarthritis	Malignant fibrous histiocytoma	15	Deep infection, removal of wires and prosthesis in second phase – loosening

Table 29 (contd)

Reference	Prosthesis	Composition 1) Stem-head alloy 2) Cup 3) Fixation 4) Additional implants	Age at implantation/ sex	Preoperative diagnosis	Histopathology	Years between implantation and diagnosis	Remarks
Nelson & Phillips (1990)	Müller THA	1) CoCr 2) Polyethylene 3) Cemented	62/F	Post-traumatic osteoarthritis	Malignant fibrous histiocytoma	10	Revision with porous-coated femoral and bipolar acetabular component with allograft 3 months before diagnosis
Himmer *et al*. (1991)	Guepa TKA	1–2) Metal 3) Cemented	61/F	Osteoarthritis	Angiosarcoma	13	Distal femoral fracture, cerclage fixation 6 years before angio-sarcoma appearance
Eckstein *et al*. (1992)	Richards TKA	1) [CoCr] 2) [Polyethylene] 3) [Cemented] 4) Plates, screws for fixation of tibial tuberosity	76/M	Osteoarthritis	Fibrosarcoma	4	Post-operative deep infection, osteo-myelitis
Jacobs *et al*. (1992)	Cobalt alloy-UHMM polyethylene cementless THA	1) CoCrMo ASTM F-75 2) Polyethylene 3) Uncemented	65/M	Osteoarthritis	Malignant fibrous histiocytoma	0.5	

Table 29 (contd)

Reference	Prosthesis	Composition 1) Stem-head alloy 2) Cup 3) Fixation 4) Additional implants	Age at implantation/ sex	Preoperative diagnosis	Histopathology	Years between implantation and diagnosis	Remarks
Solomon & Sekel (1992)	Charnley-Müller THA	1–2) NR 3) cemented	48/F	Necrosis of the femoral head	Malignant fibrous histiocytoma	7	Preoperative histiocytic non-Hodgkin abdominal lymphoma, radio-therapy to the hip joint
Rock (1993)	Porous-coated anatomic TKA	1) [CoCr] 2) [Polyethylene] 3) [Cemented]	55/M	NR	Osteosarcoma	1.2	
Rock (1993)	Porous-coated anatomic THA	1) NR 2) [Polyethylene] 3) Uncemented	71/M	NR	Malignant fibrous histiocytoma	8	
Aboulafia *et al*. (1994)	1) Uncemented, CoCr alloy, 2) Acetabular revision 1 month later, 3) Acetabular revision 2 months later, 4) Porous coated, CoCr 7 months later THA	1) CoCr 2) Polyethylene 3) Uncemented	63/F	Rheumatoid arthritis, displaced femoral neck fracture	Malignant fibrous histiocytoma	2	Deep infection, needing removal of the prosthesis, revision and irrigation. Recurrent dislocations

Table 29 (contd)

Reference	Prosthesis	Composition 1) Stem-head alloy 2) Cup 3) Fixation 4) Additional implants	Age at implantation/ sex	Preoperative diagnosis	Histopathology	Years between implantation and diagnosis	Remarks
Iglesias *et al.* (1994)	NR TKA	1) Titanium 2) Polyethylene 3) Cemented	72/F	Rheumatoid arthritis (diabetes)	Malignant fibrous histocytoma	4	Condylar CoCrMo prosthesis of the other knee at age 67
Theegarten *et al.* (1995)	Charnley-Müller THA	1) NR 2) Polyethylene 3) Cemented	59/F	Coxarthrosis	Malignant fibrous histocytoma	15	Loose
Mathiesen *et al.* (1995)	Lord THA	1) CoCrMo ASTM F-75 2) Polyethylene 3) Uncemented	58/M	NR	Malignant fibrous histocytoma	5	
Bell *et al.* (1997)	NR Femoral prosthesis	1) CoCr 2) Polyethylene 3) PMMA cement	55/F	Osteoarthritis resulting from congenital hip dysplasia	Malignant fibrous histiocytoma	7	Loose femoral part
Cole *et al.* (1997)	1) Premier bipolar prosthesis (titanium/ uncemented) 2) Rx-90, Biomet THA, 16 months later	1) CoCr 2) Polyethylene 3) Stem cemented, cup uncemented	59/F	Fracture of the femoral neck	Malignant fibrous histocytoma	2	

Table 29 (contd)

Reference	Prosthesis	Composition 1) Stem-head alloy 2) Cup 3) Fixation 4) Additional implants	Age at implantation/ sex	Preoperative diagnosis	Histopathology	Years between implantation and diagnosis	Remarks
Langkamer *et al.* (1997)	Müller THA	1–3) NR	75/F	NR	Leiomyosarcoma	2	
Langkamer *et al.* (1997)	Müller THA	1) Stainless steel FeCrNi 2) [Polyethylene] 3) Cemented	73/M	Osteoarthritis	Malignant fibrous histocytoma	2	
Langkamer *et al.* (1997)	Charnley THA	1) NR 2) Polyethylene 3) Cemented 4) Trochanteric wires, stainless steel	77/F	NR	Leiomyosarcoma	3.5	Cemented THA 16 years earlier
Langkamer *et al.* (1997)	Charnley THA	1) Stainless steel FeCrNi 2) Polyethylene	67/F	Subcapital fracture of the femoral neck	Malignant fibrous histocytoma	2	Kinematic knee prosthesis 7 years earlier, prosthesis removed 11 months later for infection

PMMA, poly(methyl methacrylate)
CoCr, cobalt–chromium alloy
THA, total hip arthoplasty
TKA, total knee arthroplasty
NR, not reported

Table 30. Metastatic tumours in patients with joint endoprosthesis

Reference	Prosthesis	1) Alloy 2) Cup/tibial plate 3) Fixation	Age at implantation/ sex	Preoperative diagnosis	Histopathology	Interval between implantation and metastasis
Katzner & Schvingt (1983)	THA, type NR	1) NR 2) [Polyethylene] 3) Cemented	67/M	Coxarthrosis	Renal cell carcinoma	2 years
Kernohan & Hall (1985)	Stanmore THA	1) NR 2) [Polyethylene] 3) Acrylic cement	69/M	Osteoarthrosis	Lung cancer, squamous-cell carcinoma	4 months
Kim &Yun (1986)	Bipolar hip hemiarthroplasty	1) Not reported 3) Cemented	73/F	Subcapital fracture of the femoral neck	Adenocarcinoma of the lung	10 months
Kolstad & Högstorp (1990)	Freeman-Samuelsson TKA	1–3) NR	75/M	Gonarthrosis	Adenocarcinoma of the stomach	2 months
Kahn & Blazina (1993)	Staples for osteotomy TKA	1–3) NR	70/F	Gonarthrosis	Adenocarcinoma of the breast	Unknown
Jeffery & McCullough (1995)	1) Cemented THA, type NR, 2) Revision surgery 4 months later with uncemented femoral component		66/F	Osteoarthritis	Adenocarcinoma of the breast	7 months
Pellengahr *et al*. (1997)	1) Unicondylar knee prosthesis, 2) TKA, 15 months later, 3) cemented titanium prosthesis	1–3) Not reported	68/F	Gonarthrosis	Non-Hodgkin lymphoma	2 years

THA, total hip arthroplasty
TKA, total knee arthroplasty
NR, not reported

Table 31. Malignant tumours at the site of cardiac pacemakers

Reference	Type of pacemaker	Age at implantation/ sex	Pre-operative diagnosis	Histopathology	Interval (years) between implantation and cancer diagnosis	Remarks
Zafiracopoulos & Rouskas (1974)	Vitatron Pacemaker generator epicardial electrode	61/F	Complete A-V block	Scirrhous breast carcinoma	2	
Zafiracopoulos & Rouskas (1974)	Vitatron Pacemaker generator intracardiac electrode	64/F	Complete A-V block	Scirrhous breast carcinoma	4	
Hamaker *et al*. (1976)	Medtronic Model 5841 for 4 years, then titanium-covered pulse generator Medtronic Model 5942	43/M	After aortic valvuloplasty, complete A-V block	Plasmacytoma in the s.c. pocket of the pacemaker	5	
Biran *et al.* (1979)	Medtronic Model 5942	62/F	A-V block	Intraductal carcinoma of the breast	2	Operated and irradiated carcinoma of opposite breast 22 years earlier
Biran *et al.* (1979)	Medtronic Model 5942	64/F	A-V block	Breast adenocarcinoma + Paget's disease	1.5 months	
Dalal *et al*. (1980)	Vitatron MIP 43RT	71/F	NR	Breast adenocarcinoma	3	
Dalal *et al*. (1980)	Vitatron MIP 43RT	75/F	NR	Breast adenocarcinoma	2	

Table 31 (contd)

Reference	Type of pacemaker	Age at implantation/ sex	Pre-operative diagnosis	Histopathology	Interval (years) between implantation and cancer diagnosis	Remarks
Magilligan & Isshak (1980)	1) Unknown type of generator for 6 years 2) Medtronic 5950 pacemaker	83/F	A-V dissociation	Infiltrating adenocarcinoma in the pacemaker pocket	8	Twenty-five months before pacemaker pocket cancer, a simple mastectomy was performed outside the pacemaker for infiltrating adenocarcinoma of the breast
Fraedrich *et al*. (1984)	1) Medtronic Xytron pacemaker for 3 years, then 2) Cordis Stanicor pacemaker	78/M	A-V block	Soft-tissue sarcoma in the subpectoral pocket. Metastasis of a malignant fibrous histiocytoma, situated in the lower pulmonary lobe	4	
Liczkowski & Barnbeck (1984)	NR	50/F	NR	Breast carcinoma simplex, partim medullary	6	
Liczkowski & Barnbeck (1984)	NR	54/F	NR	Breast carcinoma solidum simplex	3	
Rasmussen *et al*. (1985)	Unipolar Cordis Stanicor mercury zinc pacemaker	74/M	Bradycardia	Papillary adenocarcinoma of the breast	1	Purulent ulceration, change of battery

Table 31 (contd)

Reference	Type of pacemaker	Age at implantation/ sex	Pre-operative diagnosis	Histopathology	Interval (years) between implantation and cancer diagnosis	Remarks
Bhandarkar *et al*. (1993)	1) Cordis Omni pacemaker for 6 years, then 2) Cordis 337A VVI pacemaker	70/F	Sinus bradycardia, cardiac pauses	Breast adeno-carcinoma	13	
Bhandarkar *et al*. (1993)	1) Teletronics VVI model 120B pacemaker for 10 years, then 2) Optima MP 580 VVI generator	72/F	NR	Breast adeno-carcinoma	12	
Rothenberger-Janzen *et al*. (1998)	Leptos VVI 01-A	72/F	Sick sinus syndrome	Intraductal adeno-carcinoma of the breast	18	Replacement of the generator 3 and 14 years after insertion

A-V, auriculo-ventricular
s.c., subcutaneous
NR, not reported

of a malignant fibrous histiocytoma from the contralateral lung, next to the pacemaker pocket was described by Fraedrich *et al*. (1984).

2C.2 Analytical studies

Undifferentiated carcinomas, melanomas, and some types of lymphoma may be confused histologically with soft-tissue sarcomas. The specific diagnosis of lymphomas relies on the use of immunological markers (Fisher, 1999) in combination with flow cytometry or immunohistochemistry. These techniques were not routinely used in diagnostic pathology until 1980 to 1985.

2C.2.1 *Orthopaedic implants*

(*a*) *Cohort studies*

The incidence of malignant tumours at any site after joint replacement has been examined in 14 cohorts. The results are summarized in Table 32. For the majority of these studies, information on confounding variables was not available. Also, the exact nature of the exposure to biomaterials was unavailable in most studies, as cohorts included individuals exposed to a range of implant types. Latency data beyond 16 years of exposure were unavailable.

A cohort study performed in New Zealand included 1358 persons in five New Zealand hospitals and one private surgical practice who had had a total hip replacement implanted between 1966–73 (Gillespie *et al*., 1988). They were followed up from the date of operation until cancer diagnosis, death or end of the observation period (1983). Overall, 14 286 person–years were accumulated. Persons from surgical registers were linked manually with national death registers, electoral rolls and the cancer registry. Expected numbers of cases were calculated using national cancer data from the cancer registry. For cancers at all sites combined, the SIR was 0.9 [95% CI, not reported]. For breast cancer, a decreased SIR was observed (SIR, 0.4; 95% CI, 0.1–0.8). SIRs for other cancers were 0.9 [95% CI, not reported] for bronchus and lung, 0.6 (95% CI, 0.4–1.0) for colorectal and 1.7 (95% CI, 1.1–2.6) for lymphatic and haematopoietic cancers. No information on other cancers was given. The excess of lymphomas was largely seen in the first year after implantation.

A cohort study performed in Stockholm County, Sweden (Mathiesen *et al*., 1995) examined a population that was to a large extent included within the cohort studied by Nyrén *et al*. (1995). It included persons who had had a primary total hip replacement, hemiarthroplasty or revision hip arthroplasty implanted between 1974 and 1988. The numbers of the different types of prosthesis implanted are not known but the original Charnley stainless-steel prosthesis was most commonly used, with a substantial number of chromium–cobalt prostheses such as the Müller, CAD, HD2 and others. Less than 5% were uncemented implants. The cohort was assembled using in-patients from the care register of Stockholm County. Cases were obtained by linkage to the Swedish Cancer Registry, the Stockholm County Council Regional Cancer Registry and to the national Register of Causes-of-Death. The cohort also included persons with

Table 32. Cohort studies of cancer incidence following orthopaedic implants

Reference	Country	No. in cohort	Type of controls	Exposure	Cancer site	No. of cases	SIR (95% CI)
Gillespie *et al*. (1988)	New Zealand	1358	National register	14 286 person–years; implant 1966–73, follow-up to end of 1983. Mixed cohort, some metal on metal prosthesis (Gillespie *et al*., 1996)	All cancers	164	0.9 (NR)
					Colon/rectum	21	0.6 (0.4–1.0)
					Breast	6	0.4 (0.1–0.8)
					Bronchus/lung	26	0.9 (NR)
					Lymphoma/haematopoietic	21	1.7 (1.1–2.6)
Mathiesen *et al*. (1995) (large overlap with Nyrén *et al*., 1995)	Sweden	10 785	National register	58 437 person–years; implant 1974–88, follow-up to end of 1989. Mixed cohort THA	All cancers	881	0.96 (0.90–1.03)
					Upper gastro-intestinal tract	67	0.9 (0.7–1.1)
					Colon/rectum	117	0.95 (0.78–1.14)
					Liver/gall-bladder/pancreas	77	0.9 (0.7–1.2)
					Respiratory	12	1.0 (0.5–1.7)
					Lung	56	0.8 (0.6–1.0)
					Breast	103	0.9 (0.7–1.0)
					Female reproductive system	80	1.2 (0.9–1.5)
					Male reproductive system	112	1.2 (1.0–1.4)
					Urinary tract	63	0.8 (0.7–1.1)
					Skin + melanoma	56	1.2 (0.9–1.5)
					Brain	20	0.9 (0.5–1.4)
					Thyroid	23	1.3 (0.8–1.9)
					Bone/connective tissue	5	0.9 (0.3–2.0)
					Lymphoma/haematopoietic	62	0.9 (0.7–1.1)

Table 32 (contd)

Reference	Country	No. in cohort	Type of controls	Exposure	Cancer site	No. of cases	SIR (95% CI)
Nyrén *et al.* (1995)	Sweden	39 154	National register	327 922 person–years; implant 1965–83, follow-up to end of 1989. Mixed cohort, may have included some metal on metal prostheses during the earlier years (Gillespie *et al*., 1996) THA	All cancers	4572	1.03 (1.00–1.06)
					Stomach	189	0.8 (0.7–0.9)
					Colon	415	1.0 (0.9–1.1)
					Rectum	202	0.95 (0.82–1.09)
					Liver	188	1.1 (0.9–1.2)
					Pancreas	156	0.9 (0.8–1.0)
					Lung	303	0.98 (0.87–1.09)
					Breast (male + female)	525	1.0 (0.9–1.1)
					Cervix	40	1.0 (0.7–1.3)
					Uterus	94	0.9 (0.8–1.1)
					Ovary	120	1.1 (0.9–1.4)
					Prostate	638	1.1 (1.0–1.2)
					Kidney	191	1.3 (1.1–1.5)
					Melanoma	98	1.2 (1.0–1.5)
					Other skin	213	1.1 (1.0–1.3)
					Brain	116	1.2 (1.0–1.4)
					Thyroid	29	1.0 (0.7–1.4)
					Bone	6	1.4 (0.5–3.1)
					Connective tissue	28	1.1 (0.7–1.6)
					Lymphoma	133	0.99 (0.83–1.17)
					Myeloma	80	1.2 (0.9–1.4)
					Leukaemia	107	1.0 (0.8–1.2)

Table 32 (contd)

Reference	Country	No. in cohort	Type of controls	Exposure	Cancer site	No. of cases	SIR (95% CI)
Lewold *et al*. (1996)	Sweden	14 551: osteoarthritis, 10 120 rheumatoid arthritis, 4431	National register	66 622 person–years; implant 1975–89, follow-up to end of 1990. Polyethylene on metal only	*Osteoarthritis*		
					All cancers	483	0.86 (0.7–0.9)
					Upper gastro-intestinal tract	40	0.95 (NR)
					Colon	33	0.7 (0.5–0.9)
					Rectum	21	0.8 (0.5–1.2)
					Liver/gall-bladder/pancreas	47	1.1 (NR)
					All respiratory tract	20	0.5 (0.3–0.7)
					Breast	64	0.9 (0.7–1.1)
					Female reproductive system	45	1.0 (0.8–1.4)
					Prostate	58	1.0 (0.8–1.3)
					Urinary	38	0.8 (0.6–1.1)
					Skin	25	0.9 (0.6–1.3)
					Brain	13	0.9 (0.5–1.5)
					Thyroid	16	1.1 (0.6–1.8)
					Bone/connective tissue	4	1.0 (0.3–2.5)
					Lymphoma	14	0.8 (0.5–1.4)
					Myeloma	10	1.1 (0.5–2.0)
					Leukaemia	18	1.4 (0.9–2.2)

Table 32 (contd)

Reference	Country	No. in cohort	Type of controls	Exposure	Cancer site	No. of cases	SIR (95% CI)
Lewold *et al.* (1996) (contd)					*Rheumatoid arthritis*		
					All cancers	215	0.8 (0.7–0.9)
					Upper gastrointestinal tract	11	0.6 (NR)
					Colon	9	0.4 (0.2–0.8)
					Rectum	3	0.2 (0.1–0.7)
					Liver/gall-bladder/pancreas	15	0.9 (NR)
					All respiratory tract	15	0.8 (0.4–1.3)
					Breast	30	0.7 (0.5–0.9)
					Female reproductive system	23	0.8 (0.5–1.2)
					Prostate	14	0.7 (0.4–1.2)
					Urinary	19	0.9 (0.6–1.4)
					Skin	18	1.3 (0.8–2.1)
					Brain	15	1.8 (1.1–3.0)
					Thyroid	1	0.4 (0.0–2.4)
					Bone/connective tissue	1	0.5 (0.0–2.8)
					Lymphoma	14	1.8 (1.0–2.9)
					Myeloma	3	0.7 (0.1–2.1)
					Leukaemia	5	0.9 (0.3–2.1)

Table 32 (contd)

Reference	Country	No. in cohort	Type of controls	Exposure	Cancer site	No. of cases	SIR (95% CI)
Visuri *et al.* (1996)	Finland	579	National register	9092 person–years; implant 1967–73, follow-up to end of 1993. Metal on metal only (McKee-Farrar THA)	All cancers	113	0.95 (0.79–1.13)
					Stomach	9	0.8 (0.4–1.5)
					Colon	5	0.7 (0.2–1.6)
					Rectum	7	1.3 (0.5–2.7)
					Liver	1	0.6 (0.01–3.2)
					Gall-bladder	3	1.2 (0.2–3.4)
					Pancreas	9	1.6 (0.7–3.0)
					Larynx	1	1.2 (0.03–6.8)
					Lung	7	0.4 (0.2–0.9)
					Breast	10	0.8 (0.4–1.5)
					Uterus	7	2.0 (0.8–4.2)
					Ovary	1	0.3 (0.01–1.9)
					Prostate	15	1.5 (0.9–2.5)
					Kidney	3	0.9 (0.2–2.7)
					Urinary tract	1	0.2 (0.01–1.3)
					Melanoma	2	1.2 (0.2–4.4)
					Skin	3	0.7 (0.2–2.1)
					Brain	1	0.5 (0.01–2.6)
					Thyroid	1	0.9 (0.02–5.2)
					Non-Hodgkin lymphoma	2	0.9 (0.1–3.3)
					Hodgkin’s lymphoma	1	2.2 (0.1–12.4)
					Myeloma	2	1.1 (0.1–3.8)
					Leukaemia	7	2.3 (0.9–4.8)

Table 32 (contd)

Reference	Country	No. in cohort	Type of controls	Exposure	Cancer site	No. of cases	SIR (95% CI)
Visuri *et al*. (1996)	Finland	1585	National register	19 846 person–years; implant 1973–85, follow-up to end of 1993. Polyethylene on metal only THA	All cancers	212	0.8 (0.7–0.9)
					Stomach	10	0.4 (0.2–0.8)
					Colon	14	0.8 (0.5–1.4)
					Rectum	11	0.9 (0.4–1.6)
					Liver	2	0.5 (0.1–1.7)
					Gall-bladder	7	1.3 (0.5–2.6)
					Pancreas	15	1.2 (0.7–1.9)
					Larynx	2	1.0 (0.1–3.6)
					Lung	18	0.5 (0.3–0.7)
					Breast	22	0.8 (0.5–1.3)
					Cervix	1	0.4 (0.0–2.2)
					Uterus	5	0.7 (0.2–1.6)
					Ovary	3	0.5 (0.1–1.4)
					Prostate	28	1.0 (0.6–1.4)
					Kidney	11	1.3 (0.6–2.3)
					Other urinary	11	0.9 (0.5–1.7)
					Melanoma	3	0.7 (0.2–2.1)
					Brain	6	1.1 (0.4–2.4)
					Thyroid	2	0.9 (0.1–3.1)
					Connective tissue	1	0.7 (0.0–3.8)
					Non-Hodgkin lymphoma	1	0.2 (0.0–1.0)
					Hodgkin’s lymphoma	1	1.1 (0.0–6.1)
					Myeloma	5	1.1 (0.4–2.7)
					Leukaemia	4	0.6 (0.2–1.6)

Table 32 (contd)

Reference	Country	No. in cohort	Type of controls	Exposure	Cancer site	No. of cases	SIR (95% CI)
Paavolainen *et al*. (1999) (partial overlap with Visuri *et al*., 1996)	Finland	31 651	National register	199 996 person–years Polyethylene on metal only THA	All sites	2367	0.90 (0.87–0.93)
					Lip	28	1.2 (0.8–1.7)
					Oral cavity and pharynx	14	0.7 (0.4–1.2)
					Oesophagus	23	0.7 (0.4–1.0)
					Stomach	132	0.8 (0.7–0.9)
					Colon	145	0.9 (0.7–1.0)
					Rectum	103	0.9 (0.7–1.1)
					Liver	35	0.9 (0.6–1.3)
					Gall-bladder	42	0.9 (0.6–1.2)
					Pancreas	93	0.8 (0.7–1.0)
					Larynx	13	0.8 (0.4–1.4)
					Lung, bronchus	222	0.7 (0.6–0.8)
					Breast	293	0.98 (0.87–1.09)
					Cervix	12	0.9 (0.5–1.6)
					Uterus	47	1.0 (0.7–1.3)
					Ovary	38	1.0 (0.7–1.3)
					Prostate	158	1.1 (0.9–1.2)
					Kidney	86	1.0 (0.8–1.2)
					Bladder, ureter	119	1.0 (0.9–1.2)
					Melanoma	51	1.1 (0.8–1.4)
					Other skin	105	1.0 (0.8–1.2)
					Brain, nervous system	59	1.0 (0.8–1.3)
					Thyroid gland	25	1.0 (0.7–1.5)
					Bone	3	1.1 (0.2–3.1)
					Soft tissue	10	0.7 (0.3–1.3)
					Non-Hodgkin lymphoma	75	0.9 (0.7–1.1)
					Hodgkin’s disease	8	1.2 (0.5–2.4)
					Multiple myeloma	40	1.0 (0.7–1.4)
					Leukaemia	50	0.9 (0.7–1.2)

Table 32 (contd)

Reference	Country	No. in cohort	Type of controls	Exposure	Cancer site	No. of cases	SIR (95% CI)
Gillespie *et al.* (1996)	USA	1034 knee replacement	Matched within same database	Implant 1972–84. Mixed cohort may contain small number of metal on metal; generally contains metal on polyethylene prosthesis	Lymphoma or leukaemia	2	0.5 (0.1–0.9)[a]
		1005 hip replacement	Matched within same database		Lymphoma or leukaemia	8	0.7 (0.3–1.4)[a]
Gillespie *et al.* (1996)	Scotland	7749 knee or hip replacement	Matched within same database	69 397 person–years; implant 1981–83. Mixed cohort may contain small number of metal on metal; generally contains metal on polyethylene prosthesis	Lymphoma or leukaemia	60	1.1 (0.8–1.5)[a]

Table 32 (contd)

Reference	Country	No. in cohort	Type of controls	Exposure	Cancer site	No. of cases	SIR (95% CI)
Fryzek *et al*. (1999) (finger/hand arthroplasty cohort)	Denmark	858	National register	7664 person–years; implant 1977–92. Follow-up to the end of 1995	All cancers	88	1.0 (0.8–1.2)
					Digestive organs	18	0.9 (0.5–1.5)
					Respiratory system	11	1.0 (0.5–1.9)
					Breast	15	1.1 (0.6–1.8)
					Female genital system	7	0.7 (0.3–1.5)
					Skin	18	1.2 (0.7–1.9)
					Lymphohaematopoietic	10	2.1 (1.0–3.8)
					Other cancers	9	0.7 (0.3–1.4)
Fryzek *et al*. (1999) (temporo-mandibular arthroplasty cohort)	Denmark	389	National register	2365 person–years implant 1977–92. Follow-up to the end of 1995	All cancers	27	1.1 (0.8–1.7)
					Digestive organs	4	0.8 (0.2–2.2)
					Respiratory system	3	1.1 (0.2–3.1)
					Breast	5	1.2 (0.4–2.9)
					Female genital system	5	2.0 (0.6–4.7)
					Skin	5	1.2 (0.4-2.7)
					Lymphohaematopoietic	0	
					Other cancers	5	2.1 (0.7–4.9)

Table 32 (contd)

Reference	Country	No. in cohort	Type of controls	Exposure	Cancer site	No. of cases	SIR (95% CI)
Olsen *et al*. (1999) (hip replacement cohort)	Denmark	22 997	National register	180 000 person–years. Follow-up to end of 1993 Mixed cohort may contain small number of metal on metal	All cancers	3304	0.94 (0.91–0.98)
					Bucccal cavity and pharynx	53	0.9 (0.7–1.2)
					Oesophagus	31	0.9 (0.6–1.2)
					Stomach	71	0.6 (0.5–0.8)
					Colon	281	0.84 (0.75–0.95)
					Rectum	153	0.9 (0.8–1.1)
					Liver	45	1.3 (0.9–1.7)
					Biliary tract	33	0.9 (0.6–1.3)
					Pancreas	105	1.0 (0.8–1.2)
					Larynx	17	0.6 (0.4–1.0)
					Lung	322	0.73 (0.66–0.82)
					Breast	289	1.0 (0.9–1.2)
					Cervix	37	1.0 (0.7–1.4)
					Uterus	84	1.2 (1.0–1.5)
					Ovary	75	1.3 (1.0–1.6)
					Prostate	280	1.0 (0.9–1.2)
					Testis	6	2.0 (0.7–4.3)
					Kidney	87	0.9 (0.7–1.1)
					Bladder	219	0.95 (0.83–1.09)
					Melanoma	80	1.5 (1.2–1.8)
					Epidermis	555	1.03 (0.95–1.12)
					Brain	55	1.0 (0.7–1.3)
					Thyroid	6	0.6 (0.2–1.4)
					Bone	4	2.0 (0.5–5.2)
					Connective tissue	10	1.2 (0.6–2.2)
					All haematopoietic	226	1.1 (1.0–1.3)
					Non-Hodgkin lymphoma	86	1.2 (1.0–1.5)
					Hodgkin’s disease	8	1.3 (0.6–2.5)
					Myeloma	38	1.0 (0.7–1.3)
					Leukaemia	94	1.1 (0.9–1.4)

Table 32 (contd)

Reference	Country	No. in cohort	Type of controls	Exposure	Cancer site	No. of cases	SIR (95% CI)
Olsen *et al.* (1999) (knee replacement cohort)	Denmark	4771	National register	31 000 person–years. Follow-up to end of 1993 [Polyethylene on metal only]	All cancers	574	0.97 (0.89–1.06)
					Bucccal cavity and pharynx	4	0.5 (0.1–1.2)
					Oesophagus	2	0.4 (0.0–1.3)
					Stomach	8	0.5 (0.2–0.9)
					Colon	59	1.0 (0.7–1.2)
					Rectum	26	0.9 (0.6–1.4)
					Liver	7	1.2 (0.5–2.5)
					Biliary tract	9	1.3 (0.6–2.5)
					Pancreas	23	1.2 (0.8–1.8)
					Larynx	1	0.3 (0.0–1.7)
					Lung	47	0.8 (0.6–1.0)
					Breast	83	1.2 (1.0–1.5)
					Cervix	10	1.2 (0.6–2.2)
					Uterus	28	1.7 (1.1–2.4)
					Ovary	9	0.7 (0.3–1.2)
					Prostate	28	1.0 (0.7–1.5)
					Testis	0	
					Kidney	10	0.7 (0.3–1.2)
					Bladder	37	1.2 (0.8–1.9)
					Melanoma	15	1.5 (0.9–2.5)
					Epidermis	90	1.0 (0.8–1.2)
					Brain	7	0.7 (0.3–1.4)
					Thyroid	3	1.6 (0.3–4.7)
					Bone	0	
					Connective tissue	2	1.4 (0.2–5.1)
					All haematopoietic	32	0.9 (0.6–1.3)
					Non-Hodgkin lymphoma	13	1.0 (0.5–1.7)
					Hodgkin's disease	2	2.0 (0.2–7.3)
					Myeloma	6	0.9 (0.3–1.9)
					Leukaemia	11	0.8 (0.4–1.4)

THA, total hip arthroplasty
NR, not reported
[a] RR

rheumatoid arthritis (8.3%). Non-Swedish citizens with no available record linkage data were excluded from the study, as well as persons with a primary total hip replacement implanted earlier than 1974 or outside Sweden and persons who had been treated for cancer before their first operation. After these exclusions, the cohort consisted of 10 785 persons, with a total follow-up of 58 437 person–years. Observed and expected numbers and SIRs (95% CIs) after one year of follow-up were reported. Expected numbers were calculated using national cancer data from the cancer registry. For cancers at all sites combined, the SIR was 0.96 (95% CI, 0.90–1.03); the SIR for lung cancer was 0.8 (95% CI, 0.6–1.0).

A cohort study undertaken in Sweden included persons recorded in the Swedish Inpatient Register with hip replacement between 1965 and 1983 (Nyrén *et al*., 1995). Persons with a discharge diagnosis of cancer during the same hospitalization or the previous six months, as well as any individual with an erroneous or incomplete national registration number, or registered in any database with invalid codes, were excluded. Record linkage to the Register of Causes-of-Death and the Swedish Cancer Registry was based on the nine-digit national registration number. A total of 14 869 men and 24 285 women were followed up from the date of entry until cancer diagnosis, death, emigration or the end of the observation period (31 December 1989). Overall, 327 922 person–years were included. Expected numbers were calculated using national cancer rates from the cancer registry. Cancers in the first year of follow-up (444 cases and [36 769 person–years]) were excluded from the analysis. For men and women combined, the SIR was 1.03 (95% CI, 1.00–1.06) for cancers at all sites combined. Increased risks were identified for cancers of the kidney (in men and women combined; SIR, 1.3; 95% CI, 1.1–1.5) and prostate (SIR, 1.1; 95% CI, 1.0–1.2) and for melanoma (in men and women combined; SIR, 1.2; 95% CI, 1.0–1.5). Decreased risks were seen for gastric cancer in men and women combined 10–25 years after exposure (SIR, 0.6; 95% CI, 0.4–0.8).

A cohort study performed in Sweden included all individuals registered in the Swedish Knee Arthroplasty Register as having undergone a total knee replacement between 1975 and 1989 (Lewold *et al*., 1996). Persons who had emigrated from Sweden were excluded. Record linkage with the Swedish Cancer Registry was performed using the national registration number. The final analysis was based on 4260 men (18 134 person–years) and 10 291 women (48 488 person–years). Results were presented separately for osteoarthritis and for rheumatoid arthritis for subgroups at 36 and 60 months latency, for all cancers combined and for 20 primary sites. For cancer at all sites combined, the SIR was 0.8 (95% CI, 0.7–0.9) for patients with rheumatoid arthritis; the corresponding SIR for osteoarthritic patients was 0.86 (0.7–0.9). Although the risk of lymphoma was not elevated in patients with osteoarthritis, an increase of risk was seen in patients with rheumatoid arthritis (relative risk, 1.8; 95% CI, 1.0–2.9). Incidence of colon cancer and rectum cancer was decreased in both patient groups (see Table 32).

A cohort study carried out in Finland included 579 persons given a McKee–Farrar total hip replacement in two hospitals of Helsinki between 1967 and 1973 (Visuri &

Koskenvuo, 1991; Visuri *et al*., 1996). Results given here are those in the second follow-up of the cohort study (Visuri *et al*., 1996). Persons with a diagnosis of operative indications other than osteoarthritis were excluded. Cases were ascertained by linkage of the surgical registers with the Central Statistical Office of Finland and the Finnish Cancer Registry. In total, 9092 person–years were accumulated. The cumulative annual incidence was calculated for 15 years of follow-up for all cancers. Expected numbers were calculated using national cancer data from the cancer registry. For cancers at all sites combined, the risk was similar to that in the general population (SIR, 0.95; 95% CI, 0.79–1.13). SIRs for cancers at specific sites were 0.8 (95% CI, 0.4–1.5) for breast, 0.4 (95% CI, 0.2–0.9) for lung, 0.7 (95% CI, 0.2–1.6) for colon, 1.3 (95% CI, 0.5–2.7) for rectum and 2.3 (95% CI, 0.9–4.8) for leukaemia.

A cohort study performed in Helsinki, Finland, included 1585 individuals with osteoarthritis of the hip who underwent primary total hip arthroplasty with polyethylene on metal between 1973 and 1985 at two hospitals in Helsinki (Visuri *et al*., 1996). Earlier results were presented by Visuri and Koskenvuo (1991). Persons with a diagnosis of hip disease other than osteoarthritis were excluded. The mean follow-up time was 12.5 years, yielding 19 846 patient–years. Observed cases were ascertained by linking the surgical registers with the Finnish Cancer Registry. Expected numbers were calculated using national cancer data from the cancer registry. For cancers at all sites combined, the SIR was 0.8 (95% CI, 0.7–0.9). SIRs for individual cancer sites were 0.8 (95% CI, 0.5–1.3) for breast, 0.5 (95% CI, 0.3–0.7) for lung, 0.8 (95% CI, 0.5–1.4) for colon, 0.9 (95% CI, 0.4–1.6) for rectum and 0.6 (95% CI, 0.2–1.6) for leukaemia.

Paavolainen *et al*. (1999) reviewed 31 651 patients who had received a metal-on-polyethylene total hip replacement between 1980 and 1995 in Finland. The study overlaps slightly with the study reported by Visuri *et al.* (1996). Patients suffering from rheumatoid arthritis were excluded. Data sources were the Finnish National Register of Arthroplasties, the Finnish Cancer Registry and the Finnish Population Register Centre. Numbers of cases observed and person–years at risk were calculated for five-year age groups, separately for three periods (1980–85, 1986–90 and 1991–95). Latency data were grouped by time since operation (0–2, 3–9, and ≥ 10 years of follow-up). Accrued follow-up was 199 996 person–years. Cancer incidence was lower than expected overall (SIR, 0.90; 95% CI, 0.87–0.93). There was no excess risk for any individual cancer site. The relative risk for non-Hodgkin lymphoma was slightly decreased (0.9; 95% CI, 0.7–1.1). Latency data were presented overall and for 12 selected cancers or cancer groups; no significant increase or reduction was identified.

A matched cohort study performed in the Seattle area of Washington state (United States) (Gillespie *et al*., 1996) included 2039 men and women who had undergone a joint replacement of the hip (n = 1005) or knee (n = 1034) between 1972 and 1984 within Group Health Cooperative. A cohort of 7599 persons without this treatment at the time of enrolment was used for comparison, matched for age and gender. Patients with a diagnosis of lymphoma, leukaemia or other cancer made before the index date

were excluded from the study. Follow-up was performed from the date of operation until development of lymphoma or leukaemia, departure from the Cooperative, or the most recent date of file updating. Results were given for lymphoma and leukaemia (ICD-9 codes 200–202.9, 204–208) only. Expected numbers were calculated from the control group. Persons with knee replacement had a relative risk of 0.5 (95% CI, 0.1–1.9; 2 cases) for lymphoma or leukaemia. The relative risk was similar for persons with a hip replacement (relative risk, 0.7; 95% CI, 0.3–1.4; 8 cases). [The Working Group noted there is overlap in this study for both cases and controls with the Group Health Cooperative case–control study reported by Gillespie *et al*. (1996) (see below).]

A matched cohort study included 2734 men (average age at operation, 65.4 years) and 5015 women (average age at operation, 67.8 years) recorded as having undergone hip or knee replacement for arthritis in Scottish hospitals between 1981 and 1983 (Gillespie *et al*., 1996). Controls were 10 936 men and 20 060 women from hospital morbidity registers who underwent surgery for reasons unrelated to arthritis or neoplasia, matched for age, gender and date of surgical procedure. Record linkage was performed with the Scottish National Cancer Registry and the Register of Deaths. Persons with a diagnosis of femoral neck fracture at the time of operation or a prior diagnosis of lymphoma or leukaemia were excluded from the study. The median follow-up time was approximately 10.5 years. Results were given for lymphoma and leukaemia (ICD-9 codes 200–202.9, 204–208). The relative risk for lymphoma or leukaemia was 1.1 (95% CI, 0.8–1.5). After controlling for a main diagnosis of rheumatoid arthritis, the relative risk remained essentially unchanged (relative risk, 1.1; 95% CI, 0.8–1.5).

A cohort study in Denmark (Fryzek *et al*., 1999) investigated the incidence of cancer after insertion of finger or hand joint (858 patients) or temporo-mandibular joint (TMJ) implants (389 patients). A range of different materials had been used for these implants (silicone, Teflon, rubber, polyethylene, ceramics and metals). Patients had been operated between 1977 and 1992 and were followed up until the end of 1995. There were no stated exclusion criteria, but patients with a hospital discharge diagnosis of rheumatoid arthritis (ICD-8 712) were identified and a separate analysis was conducted. Data sources were the Danish Hospital Discharge Register, the Danish Cancer Registry and the Danish Central Population Register. Stratification of the data by implant material was not possible. Accrued follow-up was 7664 person-years for finger/hand arthroplasty and 2365 person-years for TMJ arthroplasty. There was no overall excess of cancer in either implant cohort (finger/hand cohort, SIR, 1.0; 95% CI, 0.8–1.2; TMJ cohort, SIR, 1.1; 95% CI, 0.8–1.7). There was an excess risk for lymphohaematopoietic cancers in the finger/hand arthroplasty cohort (SIR, 2.1; 95% CI, 1.0–3.8). The risk for non-Hodgkin lymphoma was elevated in patients with a clear diagnosis of rheumatoid arthritis (SIR, 5.5; 95% CI, 1.1–16) and for the other patients (SIR 3.1, 95% CI, 0.8–7.9). No latency data were available.

A cohort study performed in Denmark (Olsen *et al*., 1999) included 22 997 osteoarthritis patients who had received a hip replacement between 1977 and 1989, and 4771

osteoarthritis patients who had received a knee replacement during the same period. Data sources were the Danish Hospital Discharge Register, the Danish Cancer Registry and the Central Population Register. Exclusions before the study included 971 patients who had died within one year of joint replacement surgery, 2168 patients with a diagnosis of rheumatoid arthritis or other connective tissue disease prior to operation (to avoid confounding by the association between these diseases and malignant lymphomas) and 964 patients who had a prior hospital admission for fracture of the hip, knee or ankle (to avoid a possible confounding effect of tobacco smoking and alcohol abuse). Accrued follow-up was 180 000 person–years for hip replacement and 31 000 person–years for knee replacement. There was no excess of cancer in either the hip replacement cohort (SIR, 0.94; 95% CI, 0.91–0.98) or the knee implant cohort (SIR, 0.97; 95% CI, 0.89–1.06). There was an elevated risk for melanoma (SIR, 1.5; 95% CI, 1.2–1.8) in the hip replacement group. Overall, there was no excess risk of lympho-haematopoietic cancers, the relative risk for the hip replacement cohort being 1.1 (95% CI, 1.0–1.3) and that for the knee replacement cohort being 0.9 (95% CI, 0.6–1.3). The role of time between implantation and diagnosis (up to 16 years) was examined for cancers of the stomach and colon; there was no pattern of risk reduction over time.

(*b*) *Case–control studies*

Morgan and Elcock (1995) performed an analysis of subjects included in a case–control study conducted by Kang *et al.* (1987) in the United States Armed Forces Institute of Pathology between 1975 and 1980. Cases were 217 men diagnosed with soft-tissue sarcoma between 1 January 1975 and 31 December 1980 identified from the records of the institute. Controls were 599 men without a record of soft-tissue sarcoma, matched for age, from the same institute. Data on orthopaedic implants were obtained by telephone interview of cases and controls or their next-of-kin. No adjustment for confounding was described, but analysis was performed controlling for respondent status (case/control or next-of-kin). The odds ratio for soft-tissue sarcoma and all implants was 0.7 (95% CI, 0.3–1.3). [The Working Group noted that the exposure data were self-reported and there was no validation with medical records].

A case–control study (Gillespie *et al.*, 1996) was performed in the Seattle area of Washington state (United States). Cases were 1177 individuals with a diagnosis of lymphoma or leukaemia (ICD-9 codes 200–202.9, 204–208) who were included in the Group Health Cooperative database. Average time between exposure and diagnosis was three years (range, 0–15 years). Controls were 4708 individuals from the same database matched for gender, date of birth and person time. Length of exposure was on average five years (range, 0–16 years in male controls). For cases and controls, information on hip or knee replacement was obtained from the Group Health Cooperative database. Adjustment was made for possible confounding by use of phenylbutazone and by rheumatoid arthritis status. Overall, no elevation in risk was observed (odds ratio, 1.1; 95% CI, 0.6–2.0). [The Working Group noted that there was overlap in this study for

both cases and controls with the Group Health Cooperative (see Gillespie *et al*., 1996, Seattle, Washington study) cohort study reported by the same authors.]

2D. Other Foreign Bodies

2D.1 Metallic foreign bodies

Compilations of the published case reports describing malignant tumours at the site of metallic foreign objects that have entered the body either accidentally or as a result of war are presented in Table 33 (sarcomas, 23 cases), Table 34 (carcinomas, 23 cases) and Table 35 (brain tumours, seven cases). Cases in which the missile was removed immediately after wounding have been excluded. There appears to have been particular attention paid to neoplasms arising after war injuries in Germany (Frey & Knauer, 1949; Dietrich, 1950; Kunze, 1965) and underreporting of cases is considered to be likely. It should be noted that the classification of sarcomas has changed and continues to change, but the older nomenclature cannot be modified reliably to take this evolution into consideration. Lead is likely to represent an important component of many of these foreign bodies. Data on human carcinogenicity of elemental lead and inorganic lead compounds have been evaluated by IARC (1980, 1987c).

The time lapse between the entry of the foreign object and the discovery of a malignant tumour ranged from four to 63 years for sarcomas arising near metallic objects (23 cases), nine of which were more than 20 years; from 5 to 48 years for carcinomas (23 cases), 21 of which were discovered after 10 or more years; from two to 40 years for malignant brain tumours (seven cases), five of which were discovered after 17 or more years.

2D.2 Non-metallic foreign bodies

Table 36 summarizes 10 case reports of cancer at the sites of various foreign objects in the body. The time lapse between the entry of the foreign object and the discovery of a malignant tumour ranged from 12 to 49 years for miscellaneous malignancies at the sites of non-metallic objects.

Table 33. Sarcomas at the site of metallic foreign bodies in war and accidental injuries in men

Reference	Foreign body/ composition	Site	Age at injury	Injury	Histopathology	Interval between injury and development of cancer (years)	Remarks
Krevet (1888)	Bullet	Thoracic wall, axilla	28	War injury, soft-tissue wound	Round-cell sarcoma	15	Chronic sinus, bullet inside tumour
Seydel (1892); Löwenthal (1895)	Bullet	Thigh	21	War injury, compound fracture	Sarcoma (not specified)	21	Chronic sinus, fragment of the bullet inside tumour
Philippsberg (1922)	Shrapnel	Back	25	War injury, soft-tissue wound	Fibrosarcoma (spindle-cell sarcoma)	6	Removal of foreign body 2 years after injury, radiotherapy 3.5 years after injury
Melzner (1927)	Bullet	Thigh	24	War injury, soft-tissue wound	Fibrosarcoma	11	Removal of foreign body 3 years after injury
Kopas (1929)	Shotgun pellets	Testicle	42	Accident, soft-tissue wound	Carcinosarcoma	4	Several pellets inside tumour
Thies (1936)	Shrapnel (numerous lead fragments)	Hand	NR	War injury, compound fracture of metacarpal bone 3	Spindle-cell sarcoma	20	Infection during 1 year after trauma
May (1937)	Shrapnel	Forearm	22	War injury, compound fracture of forearm	Spindle-cell sarcoma	18	

Table 33 (contd)

Reference	Foreign body/ composition	Site	Age at injury	Injury	Histopathology	Interval between injury and development of cancer (years)	Remarks
Keller (1938) [cited in Frey & Knauer, 1949]	Shrapnel	Back	NR	War injury. Fracture of the 3rd lumbar vertebra, paraplegia	Haemangiosarcoma	12	
Scheid (1938)	Shrapnel (numerous fragments)	Leg	20	War injury, compound fracture of left leg and right thigh	Spindle-cell sarcoma	18	
Desjacques (1939)	Shrapnel	Knee	31	War injury, soft-tissue wound	Polymorphic sarcoma	21	Multiple shrapnel injuries
Frey & Knauer (1949)	Bullet	Femur	18	War injury, infraction of the distal femur	Osteosarcoma	7	Foreign body removed 2 months after trauma
Dietrich (1950) [cited in Nolte, 1966]	Shrapnel	Thigh, proximal tibia	NR	Shrapnel injury of tibia	Polymorphic cell sarcoma	16	
Prosinger (1952)	Shrapnel	Humerus	32	War injury, soft-tissue wound	Chondromyxosarcoma	36	Chronic osteomyelitis
Dontenwill & Graf (1953)	Shotgun pellets	Femur and knee	39	Accident, soft-tissue wound	Neurosarcoma	15	
Ebert (1954)	Shrapnel, numerous metal fragments	Femur	44	War injury, soft-tissue wounds	Polymorphic spindle-cell sarcoma	8	Multiple shrapnel wounds

Table 33 (contd)

Reference	Foreign body/ composition	Site	Age at injury	Injury	Histopathology	Interval between injury and development of cancer (years)	Remarks
Blümlein (1957)	Shrapnel	Vertebra C2	35	War injury, soft-tissue wounds	Round-cell sarcoma or lymphosarcoma	8	Multiple shrapnel wounds
Kunze (1965)	Shrapnel	Pleural cavity	27	War injury, penetrating thoracic wound	Spindle-cell sarcoma	18	
Nolte (1966)	1) Explosive bullet 2) Wires	Arm	21	War injury, compound fracture of radius	Rhabdomyosarcoma	22	Infection for 6 months. Pseudoarthrosis, reconstruction with tibial graft
Nolte (1966)	Landmine fragments	Thigh	26	War injury, soft-tissue wound	Spindle-cell sarcoma	46	4 metal fragments inside tumour
Hayman & Huygens (1983)	Grenade fragment	Chest wall	21	War injury, soft-tissue wound	Angiosarcoma	63	
Jennings *et al*. (1988)	Bullet, antimonial lead	Thigh	25	War injury, soft-tissue wound	Angiosarcoma	54	
Lindeman *et al*. (1990)	Shrapnel	Humerus	21	War injury, compound fracture	Malignant fibrous histiocytoma	44	
Schneider *et al*. (1997)	Metal fragment 7 mm, lead with 2.5% antimony	Tibia	NR	War injury, compound fracture	Angiosarcoma	46	Chronic osteomyelitis, previous curettage, bone graft

NR, not reported

Table 34. Carcinomas at the site of metallic foreign bodies in war and accidental injuries

Reference	Foreign body/ composition	Site	Age at injury/sex	Injury	Histopathology	Interval between injury and development of cancer (years)	Remarks
Trampnau (1922)	Shotgun pellet, 5 mm	Frontal sinus	30/M	Accident, penetrating wound	Adenocarcinoma	25	Pellet inside tumour
Weiss & Krusen (1922)	Pin	Lung	1/F	Pulmonary abscess, foreign body	Squamous-cell carcinoma	36	Autopsy findings, pin inside tumour
Luckow (1933)	Shrapnel 1-2 cm	Lung	43/M	War injury, penetrating wound	Small-cell carcinoma	14	Autopsy findings
Blake (1943)	Metal crucifix 4×7 mm	Lung	50/M	Ingurgitation	'Anaplastic' carcinoma	6	
Haslhofer (1950)	Bullet	Lung	22/M	War injury	Squamous-cell carcinoma	34	Autopsy findings, bullet inside tumour
Leicher (1950)	Shrapnel	Parotid gland	35/M	War injury, soft-tissue wound	Adenocarcinoma of the parotid gland	5	Chronic sinus, shrapnel removed 1 year later
Dahlmann (1951)	Shrapnel, $2.6 \times 0.5 \times 1.3$ cm	Lung	32/M	War injury, penetrating thorax wound	Small-cell, undifferentiated carcinoma	32	Autopsy findings shrapnel inside tumour

Table 34 (contd)

Reference	Foreign body/ composition	Site	Age at injury/sex	Injury	Histopathology	Interval between injury and development of cancer (years)	Remarks
Fischer-Wasels (1951)	Shrapnel (numerous fragments)	Hip, amputation stump	31/M	War injury	Squamous-cell carcinoma	30	Above knee amputation after trauma, chronic ulceration
Montag & Mondry (1952)	Dum-dum bullet (numerous fragments)	Femur	26/M	War injury compound fracture	Squamous-cell carcinoma	25	Chronic osteomyelitis
Siddons & MacArthur (1952)	Bullet	Lung	23/M	War injury, penetrating thorax wound	Carcinoma (no histology)	34	
Siddons & MacArthur (1952)	Shrapnel ball	Lung	24/M	War injury, penetrating thorax wound	Squamous-cell carcinoma	32	
Birnmeyer (1963)	Shrapnel, several fragments	Frontal sinus	19/M	War injury, penetrating wound	Low differentiated large-cell carcinoma	41	Chronic suppuration
Kunze (1965)	Shrapnel 5 mm	Leg	NR/M	War injury soft-tissue wound	Squamous-cell carcinoma	48	Chronic ulceration

Table 34 (contd)

Reference	Foreign body/ composition	Site	Age at injury/sex	Injury	Histopathology	Interval between injury and develop-ment of cancer (years)	Remarks
Kunze (1965)	Shrapnel	Lung	21/M	War injury penetrating wound	Small-cell lung carcinoma	29	Autopsy findings, shrapnel outside the tumour
Peter (1966)	Shrapnel, 1.8 x 0.7 cm	Lung	38/M	War injury, penetrating wound	Squamous-cell carcinoma	20	Shrapnel inside tumour
Pomplun (1970)	Shrapnel, 97.2% Fe, 1.9% Mn, 0.6% Si, 0.3% C	Lung	39/M	War injury, penetrating wound	Squamous-cell carcinoma	21	Shrapnel inside tumour
Kurpat & Baudrexl (1971)	Shrapnel	Lung	38/M	War injury, penetrating wound	Squamous-cell carcinoma	20	Shrapnel in the vicinity of the tumour
Kurpat & Baudrexl (1971)	Bullet	Lung	33/M	War injury, penetrating wound	Squamous-cell carcinoma	25	Bullet in the vicinity of the tumour
Kurpat & Baudrexl (1971)	Shrapnel 1.2 cm	Lung	21/M	War injury, penetrating wound	Squamous-cell carcinoma	28	Shrapnel in the vicinity of the tumour
Philip (1982)	Steel bullet, lead fragments	Buttock	NR/M	War injury, penetrating pelvic wound	Well differentiated squamous-cell carcinoma	33	Persistent gluteal sinus, autopsy

Table 34 (contd)

Reference	Foreign body/ composition	Site	Age at injury/sex	Injury	Histopathology	Interval between injury and development of cancer (years)	Remarks
Stambolis *et al*. (1982)	Shrapnel 1.2 cm	Lung	28/M	War injury penetrating wound	Small-cell carcinoma with squamous cell carcinoma	36	Autopsy: siderosis around foreign body
Dubeau & Fraser (1984)	Shrapnel 1 mm	Lung	15/M	War injury penetrating wound	Well differentiated papillary adenocarcinoma and undifferentiated large-cell carcinoma	40	Autopsy
Eistert *et al.* (1989)	Shrapnel	Larynx	20/M	Shrapnel injury of the larynx	Squamous-cell carcinoma	41	Shrapnel inside tumour

NR, not reported

Table 35. Malignant brain tumours at the site of metallic foreign bodies

Reference	Foreign body/ composition	Site	Age at injury/ sex	Injury	Histopathology	Interval between injury and development of cancer (years)	Remarks
Reinhardt (1928)	Metal fragment 0.3 mm × 1 cm	Brain	36/M	Explosion penetrating wound	Meningeal sarcoma	20	Autopsy findings
Müller (1939)	Shrapnel, numerous fragments	Brain	35/M	War injury, penetrating skull wound	Astrocytoma and glioblastoma multiforme	22	Autopsy findings
Bauer & Frey (1955) [cited in Kunze, 1965]	Shrapnel	Brain	NR		Polymorphic glioblastoma	35	
Dietrich (1958)	Shrapnel	Skull	37/M	War injury, compound fracture	Malignant meningioma	13	
Schmidt & Jaquet (1963)	Darning needle, 0.786 × 24.6 mm, stainless steel	Brain	After birth/M	Murder attempt	Meningioma	40	Autopsy findings
Schäfer (1965)	Shrapnel (multiple shrapnel injuries)	Brain	31/M	War injury, penetrating skull wound	Meningioma	21	Autopsy findings
Schulze & Bingas (1968)	Silver clip	Brain	11/F	Removal of ependymoma	Meningioma	2	Clip inside tumour, recurrence of ependymoma needed 3 operations

NR, not reported

Table 36. Malignant tumours at the site of non-metallic foreign bodies

Reference	Foreign body/ composition	Site of implant	Age at implan-tation/sex	Injury	Histopathology	Interval between injury and deve-lopment of cancer (years)	Remarks
Hallervorden (1948)	Vegetable matter, bone fragments	Brain	3/F	Fall, open fracture	Oligodendroglioma	39	Autopsy findings
Leicher (1950)	Paraffin injections	Larynx	35/M	Paresis of the vocal cords	Squamous-cell carcinoma	15	
Thompson & Entin (1969)	Lucite spheres (poly(methyl methacrylate))	Pleural cavity	42/F	Pulmonary tuber-culosis	Chondrosarcoma	18	
Button (1979)	Pipette glass fragments	Thumb	19/F	Thumb wound	Epithelioid sarcoma	12	
Pennisi (1984)	Paraffin injections	Breast	27/F	Cosmetic augmentation	Intraductal [adeno]-carcinoma	41	Injection in both breasts
Jennings *et al*. (1988)	Surgical sponge	Abdominal cavity	50/F	Cholelithiasis	Malignant meso-thelioma	20	
Jennings *et al*. (1988)	Bone wax	Leg	34/F	Donor site for bone graft	Angiosarcoma	30	
Maier & Beck (1992)	Paraffin injections	Larynx	32/M	Perforating missile wound, vocal cord lesion	Squamous-cell carcinoma	49	
Ben-Izhak *et al*. (1992)	Sponge	Colon	55/F	Surgery	Angiosarcoma	25	
Harland *et al*. (1993)	Lucite spheres (poly(methyl methacrylate))	Lung	21/F	Pulmonary tuber-culosis extrapleural pneumonolysis	Squamous-cell carcinoma of the lung	42	