Cancer and Total Hip Replacement

Cancer as a risk factor for prosthesis and prosthesis as a risk factor for cancer

Eva Hansen Dybvik

Dissertation for the degree of philosophiae doctor (PhD)

at the University of Bergen

2015

Dissertation date: 18.09.2015

Year: 2015

Title: Cancer and Total Hip Replacement

Cancer as a risk factor for prosthesis and prosthesis as a risk factor for cancer

Author: Eva Hansen Dybvik

Printed by: AIT OSLO AS / University of Bergen

Scientific environment

This thesis is based on data from the Cancer Register of Norway and the Norwegian Arthroplasty Register.

The study was initiated in 2006 while the author was working as a biostatistician at the Norwegian Arthroplasty Register. From August 2007, three-year full-time financial support was provided by the Western Norway Regional Health Authority. The last period was financed by the Norwegian Arthroplasty Register.

Supervision has been provided by staff of the Norwegian Arthroplasty Register at the Department of Orthopedic Surgery, Haukeland University Hospital, staff of the Department of Clinical Dentistry and the Department of Clinical Medicine at the University of Bergen and staff of the National Advisory Unit on Late Effects after Cancer Treatment at the Norwegian Radium Hospital, Oslo University Hospital.

As many as 19 candidates have taken PhD degrees based on data from the Norwegian Arthroplasty Register since its initiation in 1987.

This thesis is a part of the PhD programme at the Department of Clinical Medicine, University of Bergen.

Contents

1. Acknowledgements

This PhD project was carried out at the Norwegian Arthroplasty Register (NAR), Department of Orthopedic Surgery, Haukeland University Hospital in Bergen, Norway during the years 2006-2015.

There are many people who have provided important contributions and support in the process of this thesis. I would like to express my deepest gratitude to everyone who helped me realize this journey in the scientific world:

Stein Atle Lie, my main supervisor and statistician, has with great enthusiasm guided my way through formulas and statistical methods. He has shared his experiences and wide knowledge in programming and handling of large datasets. His contributions and constructive feedback have had a major impact in the progress and process of this thesis.

Ove Furnes, my co-supervisor, professor and orthopaedic surgeon, who tricked me into this project. He had faith in my academic abilities despite my own doubts. His enthusiasm and knowledge in science seem to know no boundaries.

Sophie D. Fosså, my second co-supervisor, professor and oncologist, came up with a research proposal which initiated this project. Her valuable knowledge of cancer research and data from the Cancer Registry has been crucial in this project.

Clement Trovik, professor, oncology surgeon and a member of the project group, has played an important role in planning the project and giving valuable feedback to manuscripts.

The whole supervising team has broad scientific and practical knowledge in many different fields, and all of them have contributed to the realization of this thesis!

Leif I. Havelin, professor and orthopaedic surgeon, a co-author in Paper 3, who contributed the highest level of knowledge on hip replacements.

The leaders of NAR, Leif I. Havelin (present), Lasse Engesæter and Ove Furnes, who have given me the opportunity to combine working with this thesis and working as a biostatistician at NAR.

Biostatisticians at NAR, Stein Atle Lie, Anne Marie Fenstad, Birgitte Espehaug, Christoffer Bartz-Johannessen, Valborg Baste (former) and Stein Håkon Lygre (former), who have provided an inspiring environment and valuable discussions between like-minded people.

Colleagues at NAR, including leaders and biostatisticians, Lise Kvamsdal, Ingunn Vindenes, Ruth Wasmuth, Marianne Wiese, Kari Vågstøl, Merete Husøy, Randi Furnes, Irina Kvinnesland, Håkon Langvatn, Bjørg-Tilde Fevang, Tone Nystøl, Håvard Dale, Jan Schrama, Tesfaye Leta, Målfrid Kristoffersen, Andreas Persson, Marianne Warholm, Ingvild Engesæter (former), Thomas Kadar (former), Tor Egil Sørås (former), Kjersti Steindal (former) and Inger Skar (retired), who have provided a stimulating, social and fun-filled working environment. It has been a pleasure to go to the office every day because of you!

The Cancer Registry of Norway and NAR, which have given me the opportunity to use data from these two highly rated registries. Also all doctors and health care personnel who take part in data collection for both registries need to be mentioned. Without their efforts, the registries would not have been as valuable as they are!

The Western Norway Regional Health Authority (Helse Vest) and NAR gave me financial support for the implementation of the project.

Family and friends have supported and encouraged me throughout the work on this thesis.

Anne Lise and Ole, my loving parents, have always given me the opportunities and experiences that have made me who I am. They encouraged me to get an education, and supported my choices of directions throughout the years. This journey would not have been possible without them.

My brothers *Kjell Ivar and Leif Sigurd and their families*, despite bickering early in life, have given me support and not least entertaining board games whenever we have been together.

Roy-Arild, my dear husband and best friend, has given me all the love and motivation I have needed. While studying, we explored the world of statistics together. Although our working environments now differ, elderly people are included in both our calculations: he cares about their financial situation, while I am interested in their health.

Magne and Torunn, my loving children, have given my life a new dimension.

Eva Dybvik

Bergen, June 2015

2. Abstract

Annually, 14 million new cancer cases are detected worldwide; the numbers are expected to rise by 70% over the next decades. In Norway, 30,000 new cancer cases are detected every year. Because of screenings and increased attention to cancer in the population, more cancer cases are detected at an early stage and a higher number of cancer diagnoses are detected. Results of better and earlier treatment are that patients survive and continue to live for many years after a cancer diagnosis.

In Western countries, total hip replacements have become a common treatment for hip joint disease and injury. Standards of living have risen and people are living longer, hence Western populations have an increased proportion of elderly people. Better anaesthetics, lower risks associated with surgery and better quality of prostheses enable both younger and older patients with good general health to receive total hip replacements. In Norway almost 8,000 primary total hip replacement operations are performed annually.

All papers in this thesis are based on a linkage between the Cancer Registry of Norway and the Norwegian Arthroplasty Register.

In this thesis there are two different aspects. The first aspect is the cancer patients; if they survive cancer and live on for many years, there is a risk for developing other diseases and disorders. These may be late effects related to the treatment they received for cancer. In this thesis we consider damage to bone and cartilage in the hip. Our outcome measurement is the insertion of a total hip replacement.

The second aspect is the patients who have received a total hip replacement. Could insertion of metal prosthesis with or without bone cement in the hip joint increase the patient's risk for late development of cancer?

In Paper 1 we selected cancer patients who were 16-90 years old when their first cancer was diagnosed, had no hip replacement prior to the cancer diagnosis and were alive when the Norwegian Arthroplasty Register started registration (September

1987). We compared the observed hip replacement patients with incidence in the general population. Cancer patients were divided in groups according to the location of the cancer and compared. We found an increased risk for hip replacement for patients with lymphoma malignancies and cancer in the pelvic area.

In Paper 2 we selected two groups of cancer patients to investigate whether radiation to the pelvic area increased the risk for total hip replacement. We included women only; one group consisted of patients with gynaecological cancer and radiation to the pelvic area while the other group consisted of breast cancer patients with radiation to the breast and not to the pelvic area. The mortality differed greatly in the two groups, so we used competing risk models to estimate the risk for receiving prosthesis. We found no statistically increased risk for hip replacements for patients with gynaecological cancer compared to patients with breast cancer.

In Paper 3 we selected patients with total hip replacement. We compared their cancer risk to the general population in Norway. We also used Cox models and competing risk models with time-dependent covariates to compare different prosthesis fixations. We found an increased risk of cancer for patients with uncemented total hip replacement compared to patients with cemented total hip replacement. Patients with a combination of cemented cup and uncemented stem (reversed hybrid) had a similar risk for cancer as those with uncemented prosthesis.

The overall conclusion in this thesis is that we found a relation between cancer and total hip replacements. There seems to be an increased risk for hip replacements for some cancer types, but we could not find any increased risk due to irradiation of the hips. For patients who have had a hip replacement for more than 10 years, uncemented prosthesis seems to increase the risk of cancer.

3. Norsk sammendrag

På verdensbasis oppdages årlig 14 millioner nye krefttilfeller, antallet er også forventet å stige med opp til 70 % de neste tiårene. I Norge oppdages rundt 30 tusen nye krefttilfeller i året. På grunn av screeninger og økt fokus på kreft i befolkningen blir flere krefttilfeller oppdaget på et tidlig stadium, dette fører til en økning i antall kreftdiagnoser. Behandlingen kan starte tidlig og flere av pasientene overlever og fortsetter å leve i mange år etter en kreftdiagnose.

I den vestlige verden har totale hofteproteser blitt en vanlig behandling for sykdom og skade i hofteleddet. Levestandarden har gått opp og folk lever lengre, dermed er det en større andel eldre i befolkningen. Bedre anestesi, lavere risiko forbundet med operasjonen og ikke minst bedre kvalitet på protesene gjør at både yngre pasienter og eldre pasienter med god allmenn helsetilstand kan få satt inn hofteproteser. I Norge settes det inn i underkant av 8 tusen primære hofteproteser i året.

Alle artiklene i denne avhandlingen er basert på kobling mellom Kreftregisteret og Nasjonalt register for leddproteser.

I denne avhandlingen har vi to ulike aspekter. Først kan man se på kreftpasientene, hvis de overlever kreften og lever i mange år kan de senere utvikle andre sykdommer og lidelser. Dette kan være seneffekter relatert til behandlingen de fikk for kreft. I denne avhandlingen ser vi på skader relatert til skjelettet og brusken, nærmere bestemt i hofteleddet. Vårt endepunkt var innsetting av total hofteprotese.

På den andre siden kan man se på pasientene som har fått hofteprotese. Kan innsetting av metallprotese med eller uten bensement i hoften øke pasientens risiko for å få kreft på et senere tidspunkt?

I Artikkel 1 har vi sett på kreftpasientene. Vi inkluderte pasienter som var 16-90 år da de fikk første kreftdiagnose, de måtte ikke ha protese før kreftdiagnosen og de måtte være i live når Leddregisteret startet (september 1987). Vi sammenlignet de observerte protesetilfellene med insidenstall fra befolkningen. Kreftpasientene ble

delt inn etter lokaliseringen av kreften og disse gruppene ble sammenlignet med hverandre. Vi fant økt risiko for å få hofteprotese for pasienter med lymfekreft og kreft i bekkenregionen.

I Artikkel 2 har vi valgt ut to grupper med kreftpasienter for å undersøke om stråling mot bekkenregionen gir økt risiko for hofteprotese. Vi inkluderte kun kvinner i studien, den ene gruppen bestod av pasienter med gynekologisk kreft og stråling mot bekkenregionen mens den andre gruppen bestod av brystkreftpasienter med stråling mot brystene men ikke stråling i bekkenregionen. Det var stor forskjell i dødelighet mellom gruppene, så vi brukte en competing risk modell for å beregne risikoen for å få protese. Vi fant ingen statistisk økt risiko for hofteproteser for pasientene med gynekologisk kreft sammenlignet med pasientene med brystkreft.

I Artikkel 3 har vi sett på protesepasientene. Vi sammenlignet deres kreftrisiko med den generelle befolkningen i Norge. I tillegg brukte vi Cox modeller og competing risk modeller med tidsavhengige kovariater for å sammenligne ulike operasjonsmetoder. Vi fant en økt risiko for kreft for pasienter med usementerte hofteproteser sammenlignet med pasienter med sementerte hofteproteser. Pasienter med en kombinasjon av sementert kopp og usementert stamme (omvendt hybrid) hadde samme risiko for kreft som pasienter med usementerte hofteproteser.

Hovedfunnet i denne avhandlingen er at vi finner en sammenheng mellom kreft og hofteproteser. Det ser ut som om det er en økt risiko for hofteproteser etter enkelte krefttyper, men vi fant ingen effekt i risikoen etter strålebehandling. For pasienter som har hatt en hofteprotese i mer enn 10 år ser det ut som en usementert hofteprotese øker risikoen for kreft.

4. List of Abbreviations

CI	Confidence Interval
CIF	Cumulative Incidence Function
CRN	Cancer Registry of Norway
Gy	symbol for the gray (SI unit of ionizing radiation dose)
HRR	Hazard Rate Ratio
ICD	International Classification of Diseases
IRR	Incidence Rate Ratio
NAR	Norwegian Arthroplasty Register
RCT	Randomized Clinical Trial
RR	Relative Risk
SIR	Standardized Incidence Ratio
SHR	Sub Hazard Ratio
THA	Total Hip Arthroplasty (synonym of THR)
THR	Total Hip Replacement (used in this thesis)
TKA/TKR	Total Knee Arthroplasty/Replacement

5. List of publications

Paper 1

Long-term risk of receiving a total hip replacement in cancer patients

Eva Dybvik, Ove Furnes, Sophie D. Fosså, Clement Trovik, Stein Atle Lie

Cancer Epidemiol. 2009 Oct;33(3-4):235-41.

Paper 2

Pelvic irradiation does not increase the risk of hip replacement in patients with gynecological cancer. A cohort study based on 8,507 patients.

Eva Dybvik, Ove Furnes, Sophie D. Fosså, Clement Trovik, Stein Atle Lie

Acta Orthop. 2014 Dec; 85 (6): 652-6.

Paper 3

Increased risk of cancer for uncemented total hip replacements. A study of 90,586 patients in the Norwegian Arthroplasty Register linked to the Cancer Registry of Norway.

Eva Dybvik, Ove Furnes, Leif I. Havelin, Sophie D. Fosså, Clement Trovik, Stein Atle Lie

Submitted

Reprints were made with permission from Cancer Epidemiol and Acta Orthop.

6. Introduction and background

Epidemiology is derived from Greek epi, demos and logos. Epi means “upon, among”, demos means “people, district” and logos means “study, word, discourse”. Epidemiology then becomes “the study of what is upon the people”.

Epidemiology is the branch of medicine which deals with the incidence, distribution, and possible control of diseases and other factors relating to health and also studies the relationship between diseases and risk factors.

6.1 Cancer

Hippocrates, known as the ‘Father of Medicine’ (460-370 BC) used the Greek word *carcinos* (crab) and *carcinoma* to describe tumours and swellings. Most likely it was the crab-like appearance of the disease that gave rise to the name. A Roman physician, Celsus (25 BC-50 AD) translated the word into *cancer*, the Latin word for crab. A Greek physician, Galen (130-200 AD) used the word *oncos* (Greek for swelling) to describe tumours, and today this word is used as a part of the word for cancer specialists – oncologists (American Cancer Society 2015, David and Zimmerman 2010, Sudhakar 2009).

Figure 1*: Illustrated cancer cells and Brown crab (cancer pagurus).*

But even though Hippocrates came up with a name, he was not the first to discover the disease. Cancer had already been described in an ancient Egyptian textbook on trauma surgery, dating back to about 3000 BC. Cancer has been identified in skeletons from Egypt from the period between 3200 and 500 BC (Nerlich et al. 2006, Sudhakar 2009). Hence, cancer is not a modern disease.

Cancer is a group of diseases characterized by uncontrolled growth of abnormal cells in the body. When the body's normal control mechanism stops working, cancer can develop. Old cells do not die and cells grow out of control, forming new abnormal cells. These cells have the ability to form a mass of tissue, called tumour. The cells can invade the surrounding organs, and also have the ability to provide secondary tumours elsewhere in the body. Benign tumours consisting of normal cells are not considered cancer; they are often limited by normal tissue and usually stop growing after a while, in contrast to malignant tumours that will continue to grow and may eventually do serious damage to nearby tissues and organs (American Cancer Society 2015, Sudhakar 2009).

Cancer can occur anywhere in the body. In men, prostate cancer is the most common cancer, while for women breast cancer is the most common. Colorectal cancer and lung cancer affect both genders in high numbers (Bray et al. 2013, Cancer Registry of Norway 2015).

The public health care system in Norway provides cancer treatment and follow-up, free of charge, for all citizens irrespective of social and economic status (Molven and Ferkis 2011). The three main treatments are surgery, chemotherapy and radiation therapy. In surgery the tumours are directly removed, while in chemotherapy chemicals are used to kill the cancer cells. In radiation therapy X-ray beams are used to radiate and to kill cancer cells. Treatment of a patient may consist of a combination of these three methods.

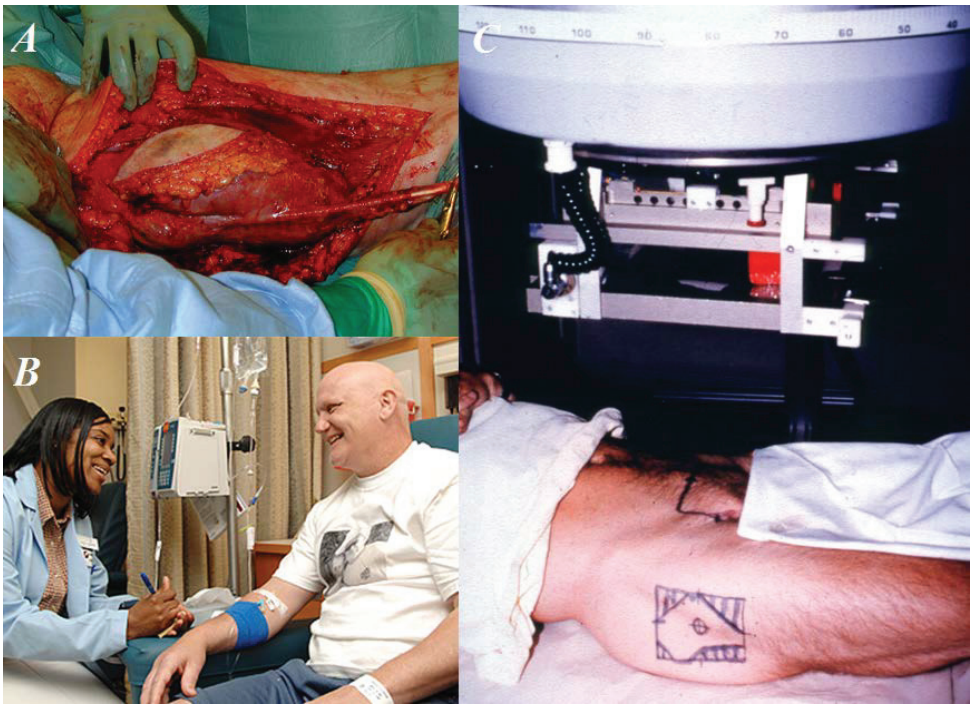

Figure 2: ***A*** *– Surgery: removing a sarcoma from the upper thigh,* ***B*** *- chemotherapy drugs,* ***C*** *– radiation to the pelvic area.*

Lifetime risk of cancer reflects the probability of being diagnosed with cancer in the course of one's lifespan. Lifetime risk is widely used as a scale of how widespread cancer is in a specific population. In Norway the lifetime risk is 35.9% for men and 28.8% for women (Cancer Registry of Norway 2015). The United States has a lifetime risk for men of 43.2% and for women 37.8% (Howlader et al. 2014). In Great Britain they have estimated the future risks and calculated the lifetime risk of cancer for people born since 1960 to be higher than 50% (Ahmad et al. 2015, Tanday 2015).

Worldwide, cancer is one of the leading causes of mortality and morbidity and the incidence has increased from 12.7 million new cases in 2008 to 14.1 million new cases in 2012 (World Health Organization 2014). Cancer caused 8.2 million deaths in 2012, which was 14.6% of all deaths worldwide. It is expected that annual cancer cases will rise from 14 million in 2012 to 22 million within the next two decades. In

Norway, 30,401 new cases of cancer and 10,699 deaths from cancer were recorded in 2013 (Cancer Registry of Norway 2015).

The reason for the increased number of cancers may be an increase in diagnosed patients due to screening, increased attention to cancer in the population and among health care providers, reduced mortality for competing diseases (e.g. coronary heart diseases) and increased life expectancy. The reduced mortality of cancer can furthermore be related to improved treatment. Some authors claim that there are other mechanisms for the increase of cancer and reduced mortalities (Zahl et al. 2013, Zahl and Maehlen 2012).

The cause of cancer has been discussed; a recent report showed that two out of three cancer cases are the result of biological bad luck (Tomasetti and Vogelstein 2015). This was based on a strong correlation between lifetime risk for different cancer types and numbers of divisions of stem cells in different organs. Hence, environmental factors or inherited predispositions are associated with only one-third of cancer episodes. Several researchers have questioned those analyses and the results (Andreassen et al. 2015, Couzin-Frankel 2015, Potter and Prentice 2015, Wodarz and Zauber 2015). A group from the Cancer Registry of Norway pointed out that cancer types used by Tomasetti and Vogelstein only covered about 50% of all cancer cases in Norway, and the most common types like breast and prostate cancer were not included (Andreassen et al. 2015).

Not all cancers can be prevented, but a large part of current cancer cases could be avoided with appropriate precautions. Tobacco, overweight and obesity, physical inactivity and diet are the modifiable causes of cancer that generate the most disease (Colditz et al. 2012, Parkin et al. 2011). Both society and individuals could contribute to lowering individuals' cancer risk.

The number or proportion of individuals in a population who have previously received a diagnosis of cancer and who are still alive at a given point in time is defined as the cancer prevalence. Worldwide, at the end of 2012, almost 32.5 million people diagnosed with cancer had survived more than five years (World Health

Organization 2014). When patients survive for many years after a cancer diagnosis, the risk for other diseases increases. These diseases could be late effects related to the treatment the patients received for the cancer. After five years, approximately two-thirds of cancer patients are still alive (Sant et al. 2009). Research on late adverse effects in cancer survivors has gained increasing interest over the last decade. However, the main interest has been on secondary cancer events (Curtis et al. 2006), cardiovascular complications and emotional problems (Meyerowitz et al. 2008). Skeletal adverse effects of irradiation include cell death, cellular injury and abnormal bone repair, although the underlying mechanisms are not fully understood (Yurut-Caloglu et al. 2010).

Radiation and chemotherapy for cancer may negatively influence the normal bone formation and thereby give rise to structural and functional alterations of the skeleton and joints. Radiation therapy directed at the pelvic region may damage bone structures or bone repair in the hip (Fu et al. 1994), through an imbalance of – or reduced activity in – osteoclasts and osteoblasts. Based on bone scan images, osteoblast activity within a radiation field is reduced for several years after radiation (Fosså and Winderen 1993). Also long-term treatment with corticosteroids, as used in childhood cancer and Hodgkin's lymphoma, will reduce osteoblast activity and thus increase the risk of osteoporotic fractures (van der Sluis and van den Heuvel-Eibrink 2008). Premature menopause in patients with gynaecological cancers or breast cancer, chemotherapy and aromatase inhibitors are associated with an increased risk of osteoporosis (Molina et al. 2005, Yamamoto and Iwase 2008) as is androgen deprivation therapy in men with prostate cancer (Israeli et al. 2008). It has been shown that high-dose pelvic irradiation is followed by micro-fractures in the sacrum (Herman et al. 2009). Similar bone alterations may occur in the hips, which are irradiated using the box technique of pelvic malignancies. In addition to the primary alterations of irradiated bone, radiotherapy of soft tissues around major joints may result in increased fibrosis and sciatic changes, leading to abnormal functional conditions with premature development of arthrosis (Goitz et al. 2007).

Hence, a hip replacement may represent an excellent modality of palliative treatment in selected patients, with metastatic spread to the hip. All these conditions may also lead to an increased risk of hip fractures which may require hip prostheses.

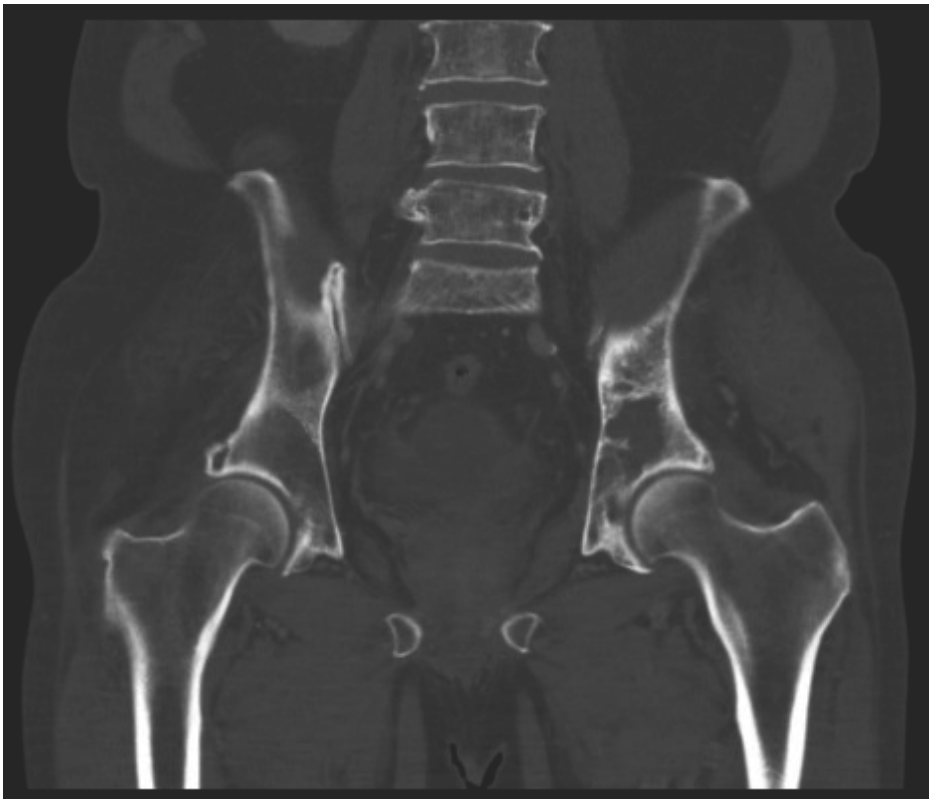

Figure 3: *X-ray showing a radiation-induced pelvic osteoporosis on the patient's left side; such osteoporosis may cause a failed hip and the need for a THR.*

6.2 Total Hip Replacement (THR)

In 1890 the first total joint replacement was performed by Gluck in Berlin; a tuberculous knee joint of a 17 year old girl was replaced by an ivory replacement (Brand et al. 2011, Eynon-Lewis et al. 1992, Gluck 1891). Gluck had remarkably successful short term results with ivory replacements in knee, wrist, elbow, shoulder, ankle and hip. But they all failed because of chronic infection. Another pioneer,

Jules-Émile Péan, designed a shoulder prosthesis made of platinum and leather in 1893. After two years the implant was removed because of chronic infection (Lugli 1978, Péan 1894). Norwegian born Marius Nygaard Smith-Petersen developed mould arthroplasty of the hip, in 1923 using glass and in 1938 using cobalt chromium, to cover the head of the femur (Smith-Petersen 1948, Smith Petersen 1939). The Smith-Petersen resurfacing hip was the usual hip replacement of the 1940s and 1950s. Other pioneers around the early 1950s were the Judet brothers from France, Haboush, Urist and McBride from the United States and McKee, Farrer and Ring from England. All of them made pioneering steps towards long-term beneficial effects of total hip arthroplasty (Toledo-Pereyra 2004). In the 1960s, Sir John Charnley introduced a new design with cemented low-friction hip arthroplasty (Charnley 1961, Charnley 1970). Charnley used a cemented polyethylene acetabular component and a cemented stainless steel monoblock component with a small stainless steel head (22mm) on the femoral side. This was the start of modern hip arthroplasty, and still this design and method is used as a reference to which new products are compared.

A total hip replacement is a major surgery to replace one of the crucial joints of the body when disease or injury has caused a painful or destructed joint. More than 70 different hip diseases were found to be the cause of hip replacement in Norway (Furnes et al. 2001). THR has been known to be one of the more successful in terms of pain relief and improved functioning, and also cost-efficient operations in modern medicine (Daigle et al. 2012, Learmonth et al. 2007). Every year more than 1 million arthroplasties are performed worldwide; projections have indicated that this number will double within the next two decades (Kurtz et al. 2007, Pivec et al. 2012).

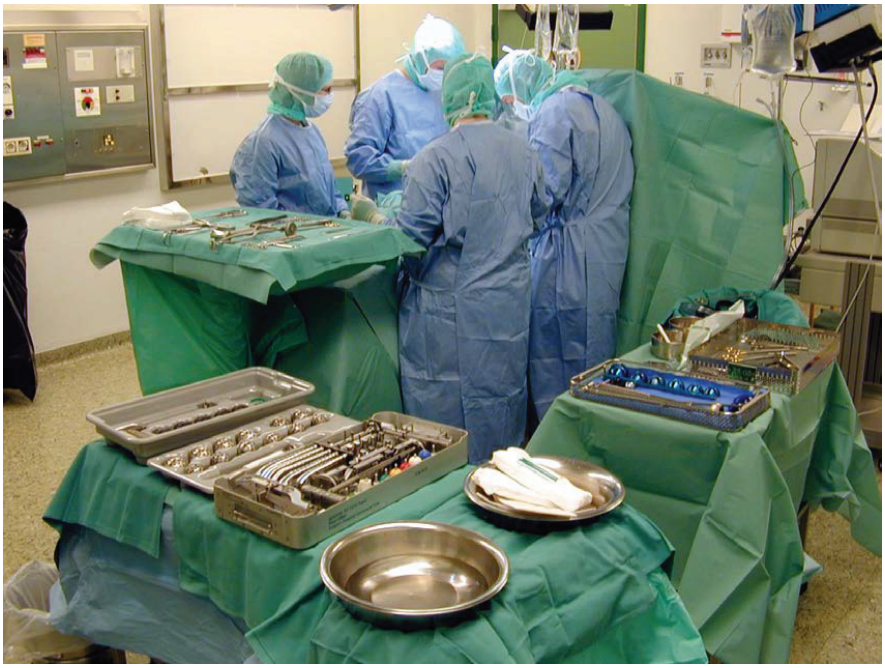

***Figure 4**: A total hip replacement operation. Photo: Yngvar Krukhaug*

Total hip replacements are common in Western countries. In populations with an increasing proportion of elderly people, there have been increases in the incidence the last decades. In Norway the frequency of primary THR has increased from 109 operations per 100,000 inhabitants in 1991-95 to 140 operations in 2006-08 (Espehaug et al. 2011). Similar increases have been documented in all the Nordic countries (Lohmander et al. 2006), Australia (Graves et al. 2004), Canada (Canadian Joint Replacement Registry 2014) and the United States (Kurtz et al. 2005).

When a THR is inserted, both the acetabular cartilage and femoral head and neck are removed and replaced by an acetabular cup and a femoral component (stem and head). Basic concepts of total hip replacements are illustrated in Figure 5. The acetabular component (cup) consists either of a single cup (in Norway polyethylene cups are mostly used) or a metal cup with inserts (liners) made of polyethylene, ceramic or metal. The femoral component could be produced with stem and head as one piece, which is called a monoblock prosthesis. The Charnley prosthesis is an

example of a historically widely used monoblock prosthesis. Today the most commonly used femoral components have separate heads and stems; these are called modular prostheses. The cup and the stem can be fixed with or without cement. If the cup and the stem components are fixed with cement, it is called a cemented THR. If both components are fixed without cement, it is called an uncemented or cementless THR. A combination of uncemented cup and cemented stem is known as hybrid THR, and a cemented cup combined with an uncemented stem is known as a reverse hybrid THR.

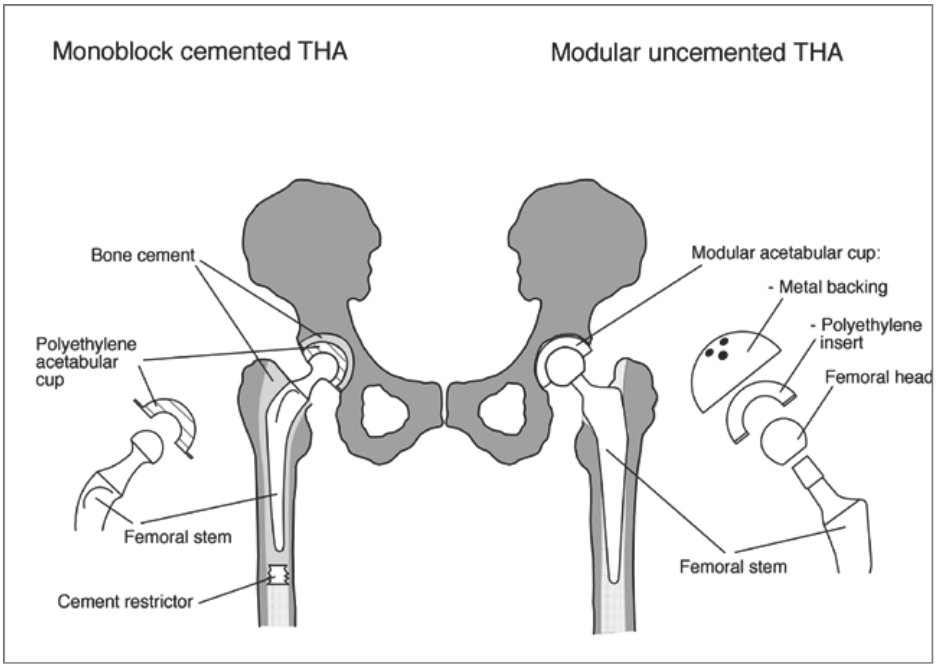

***Figure 5**: Illustration of basic concepts in total hip replacements. Courtesy of Geir Hallan.*

On the market there are many different THRs, with different brands and designs, using a variety of materials and articulations. The articulation is the sliding surface between the femoral head and the acetabular cup. The older prosthesis types generally had metal on polyethylene articulation, while newer designs can have a ceramic on polyethylene, ceramic on ceramic, ceramic on metal, or metal on metal

articulation. Also for the bone cement for fixation of the prosthesis, there exist many different brands, some with added antibiotics and some without antibiotics. In all bone cement formulations, radiopacity is provided by micron-sized particles of either zirconium dioxide (ZrO_2) or barium sulphate ($BaSO_4$) (Lewis et al. 2005). For all the mentioned components and materials, new products and procedures are being introduced continuously.

There has been a huge variety of metals and other materials, combined with a variety of sizes and bearing surfaces, used in THRs over the years. Concerns have been raised as to whether the insertion of prosthesis might lead to subsequent malignancies (Keel et al. 2001, Lidgren 2008, Mabilleau et al. 2008, Meyskens 2007). A hip replacement creates wear debris from the articulating surface and the interfaces, and in addition to local responses, debris may spread over the whole body via systemic circulation (lymph and blood). Wear particles have been identified in the macrophages of liver and spleen (Urban et al. 2000, Urban et al. 2004). However, it is not fully determined how wear debris impacts these organs. Metal ions can be generated due to crevice (Willert et al. 1996) or galvanic corrosion. These soluble metal ions (e.g. aluminium, chromium, vanadium, cobalt and titanium) may bind to proteins and disseminate into the surrounding tissues, bloodstream and remote organs. Hallab and colleagues have shown an increase of circulating metal following joint replacements (Hallab and Jacobs 2009). In a study with implant materials in rats, an increased incidence of lymphatic neoplasms was observed (Memoli et al. 1986). However, the carcinogenic potential of metallic elements used in THRs is unknown. Most studies following cancer incidence after THR have not shown an increased incidence compared to the age and gender matched population. However, it has been shown that comparison to matched population may underestimate cancer risk (Kirkeleit et al. 2013).

6.3 Personal identity number

In 1964 a system of unique 11-digit personal identity numbers was introduced in Norway (Selmer 1964). The system was in demand from trade and industry to simplify salary, taxes and social security schemes for every inhabitant of Norway.

The 11 digits are composed of six digits representing the date of birth; two digits for the day (01-31), two for the month (01-12) and two for the year (00-99), while the next three digits are individual numbers within each date of birth, and the last of them also indicates gender: an odd number for male and an even number for female. Finally, the last two digits are control digits, based on the first nine digits. These are calculated using an algorithm to avoid typographical errors when using the system.

The identity number is used for multiple purposes, such as in banking, insurance, for social benefits, police records, health, etc. In principle, information from these sources can be linked but this is regulated through strict rules. One example of a linkage of multiple sources is a publication by Moster (Moster et al. 2008).

6.4 Health registries in Norway

A health registry is a collection of health data stored systematically so that information about a single person can be retrieved.

The Norwegian parliament has established 17 mandatory national health registries to maintain national functions. These registries are regulated by law, and they have a goal of providing current, reliable and secure information about the population's health and the quality of healthcare (Folkehelseinstituttet 2015). This includes information about disease incidence, unexpected changes in incidence patterns such as during an epidemic, and knowledge about risk factors and causes of disease. Examples of mandatory national health registries are the Medical Birth Registry of Norway, Causes of Death Registry, Norwegian Patient Registry and the Cancer Registry of Norway.

There are about 200 medical health registries in Norway based on consent from the patients, 47 of which have official status as national health registries (as of August 2014). These registries are created to ensure the quality of treatment, but they are also used for research, mapping of disease incidence and treatment of patients (Nasjonalt servicemiljø for medisinske kvalitetsregistre 2015). These health registries are not regulated by law, but they are licensed by the Data Inspectorate based on the consent of the patients or linked to the mandatory health registries. Enthusiasts in the academic environments have started registers to improve the quality of treatment. Examples of such registries are the Cerebral Palsy Register of Norway, Norwegian Multiple Sclerosis Register and the Norwegian Arthroplasty Register.

There are also central health registers that treat health data in pseudonym form (Norwegian Prescription Database) or anonymized form (Register of Pregnancy Termination, NORM, NOIS) without consent.

Additionally, there are other data sources, e.g. at the health authorities, such as IPLOS which keeps a record of resources used in the healthcare sector.

7. Aims of the studies

The overall objective of this thesis was to investigate the relation between cancer and total hip replacements. In Paper 1 and Paper 2, cancer diagnosis was the starting point of the study. We wanted to determine if there was an increased risk for THR for patients with a cancer diagnosis. In Paper 3, THR was the starting point, and we wanted to determine if there was an increased risk for being diagnosed with cancer for THR patients.

The three papers had specific aims:

Paper I: To investigate whether cancer patients have an increased risk of receiving a total hip replacement compared to the general population of Norway.

A further aim was to examine whether different locations of cancer have different risks for receiving total hip replacement.

Paper 2: To examine the risk of receiving a total hip replacement for patients with cancer in the pelvic area who had been treated with radiation therapy.

Analyse patients in two cancer groups, one with pelvic irradiation and one without pelvic irradiation, and compare their risk for total hip replacements.

Paper 3: To investigate whether patients with a total hip replacement have an increased risk for being diagnosed with cancer compared to the general population of Norway.

To examine whether there are differences in cancer risk according to types of prosthesis fixations: cemented, uncemented, hybrid and reversed hybrid.

8. Data sources

8.1 Cancer Registry of Norway (CRN)

The Cancer Registry of Norway (CRN), Institute of Population-based Cancer Research, was established in 1951 (Cancer Registry of Norway 2015). This registry is one of the oldest national cancer registries in the world. The CRN has proven to be very useful for gaining new knowledge through research and for increasing information on cancer both nationally and internationally. Combined with the unique personal identification number of Norway, the CRN has a huge potential for linkage to other data sources and registries.

The CRN is one of the mandatory national health registries in Norway, regulated by law. All hospitals, laboratories and general practitioners in the country are obliged to report new cancer cases to the registry within two months. A notification is also sent in case of suspicion of cancer, even if a cancer is not verified, and the cancer is not diagnosed before autopsy. Hence, in case of doubt, a notification is expected to be sent. There are two forms for clinical notifications to the CRN, one for reporting solid tumours and one for reporting non-solid tumours (Appendices 5 and 6). These forms contain information on primary site, symptoms, stage of disease, basis for the diagnosis and primary treatment given to the patient. In addition, hospitals and independent laboratories send pathology reports providing histological, cytological or autopsy information.

The CRN receives around 140,000 reports related to cancer illness every year from several independent sources. Due to the multiple sources for the reporting of cancer, this secures a high grade of completeness of the data in the CRN. Out of the 140,000 reports, approximately 30,000 are newly diagnosed cancers.

Competence in diagnostics and treatment within the cancer registry has steadily increased since the start of the registry (Larsen et al. 2009). During the last 20 years, the cancer registry has started several clinical quality registries for different cancer types (e.g. colorectal, prostate, and lung cancer). This has been done in close

cooperation with the clinical milieus in Norway. Many of these have been approved as national health registries (Nasjonalt servicemiljø for medisinske kvalitetsregistre 2015).

More than 232,000 Norwegians with at least one cancer diagnosis at an earlier point in life were alive at the end of 2013. For almost all cancer patients, survival has improved during the last five decades; this trend is claimed to be partially due to improved treatment over time, but also to screening programmes for breast and prostate cancer. Furthermore, health care providers and the population in general have an increased awareness of cancer, which may lead to higher numbers of diagnosed cancers. The CRN is administered as part of the South-Eastern Norway Regional Health Authority and is organized as an independent institution under Oslo University Hospital Trust.

8.2 The Norwegian Arthroplasty Register (NAR)

In hip replacement surgery, the use of undocumented prosthesis has been common. In the early 1970s, the Norwegian total hip replacement known as the Christiansen prosthesis became popular (Christiansen 1969). The Christiansen prosthesis was used for approximately a decade, and more than 10,000 patients in Scandinavia received the prosthesis before inferior long-term results were discovered (Sudmann et al. 1983). This incident was the main reason that members of the Norwegian Orthopaedic Association decided to establish the NAR in September 1987 (Havelin et al. 1993). From 1994, registration was extended to include arthroplasty also in knee and other joints. The Norwegian Cruciate Ligament Register started registration in 2004, the Norwegian Hip Fracture Register started in 2005, and the Paediatric Hip Register started in 2010 (Norwegian Arthroplasty Register 2015). All of these were organized under the umbrella of the NAR. The NAR is clinically governed by the Norwegian Orthopaedic Association and financed by the Western Norway Regional Health Authority and Haukeland University Hospital. In 2002, the Norwegian Ministry of Health approved the registry as a national centre of excellence for joint replacements. It was approved as a national health registry in 2009, and in 2010 the

name of the national centre was changed to the Norwegian National Advisory Unit on Arthroplasty and Hip Fractures.

The main purpose of the NAR has been to function as a surveillance tool to detect inferior results of implants as early as possible and to avoid poor performing implants from being used in large number of patients, leading to excess patient suffering and high cost for society. Data on a total hip replacement operation is reported to the registry by the operating surgeon, using a one-page standard form completed in the operation theatre, just after surgery. The form includes the patient's unique national identification number, date of the operation, diagnosis, operated side, former surgery to that particular joint, operating technique, details and stickers/labels from the components used attached to the form, use of antibiotics and thrombosis prophylaxis and more (Appendix 7). Both primary operations and reoperations defined as removing or changing of prosthesis components are registered. Reoperations can be linked to their corresponding primary operation using the unique personal identification number.

Reporting to NAR is not mandatory, but it has been estimated that at least 97% of joint replacements operated in Norway are reported (Espehaug et al. 2006), and completeness and coverage analyses show a rate of 96% reported to NAR during the years 2008-2012 (Helsedirektoratet 2014). NAR is licensed by the Data Inspectorate of Norway and patients give written informed consent to be included in the registry.

Annually approximately 8,000 primary THRs are reported to NAR, and there are about 1,300 reoperations (Norwegian Arthroplasty Register 2014).

The quality and revision rates for the prostheses have shown large variations (Espehaug et al. 2009, Hallan et al. 2010, Hallan et al. 2007, Havelin et al. 2000), in particular for the uncemented prostheses (Hailer et al. 2010, Havelin et al. 1994, Havelin et al. 1995). The quality of modern uncemented prostheses is better than for prostheses 10 to 20 years ago (Hallan et al. 2010, Hallan et al. 2007). However, surveillance of new products with respect to adverse outcomes is crucial, also in the future.

8.3 Linking of CRN and NAR

Nationwide and internationally, research based on Norwegian health registries is of high scientific value and has proven to give new and crucial knowledge (Havelin et al. 2000, Moster et al. 2008, Vikse et al. 2008). Since Norway has the unique personal identification number for each inhabitant used in most registries, linkage of two or more registries is possible, when all applications for such research have been approved by the relevant health authorities. For a scientist with a desire to enrich the world with new knowledge, the road is however long and time-consuming to obtain the necessary approvals and the linkage of data.

In 2005 Sophie D. Fosså contacted the NAR concerning a project proposal from the National Centre of Competence for Long-term Studies after Cancer. Many patients with gynaecological, urological and gastrointestinal cancer receive high-dose radiotherapy given to target volumes that include both or at least one hip. With the typical four-field box technique, each hip is irradiated with approximately 20-30 Gy, delivered to the skeletal and the soft tissue components. These radiotherapy doses may lead to reduced osteoblast activity lasting for many years (Fosså and Winderen 1993), hence one may expect increased risk of skeletal damage and arthrosis in the irradiated hip (Fu et al. 1994).

This proposal coincided with similar thoughts at the NAR. Orthopaedic surgeons and biostatisticians had the idea to study cancer as an alternative endpoint after THR as has been done by other national arthroplasty registries (Brewster et al. 2013, Goldacre et al. 2005, Makela et al. 2012, Makela et al. 2014, Nyren et al. 1995, Onega et al. 2006, Paavolainen et al. 1999, Paavolainen et al. 2002, Smith et al. 2012, Visuri et al. 1996, Visuri et al. 2003, Visuri et al. 2010, Visuri et al. 2006, Wagner et al. 2011). Since more young people now receive THR, the lifespan of THR patients has increased and long-term effects after prosthesis are important to investigate. Long-term effects such as pulmonary embolisms (PE), deep venous thrombosis and death have been in focus, but concerns have been raised as to whether insertion of an

implant might lead to subsequent malignancies (Keel et al. 2001, Lidgren 2008, Mabilleau et al. 2008, Meyskens 2007).

Based on the common idea of a linkage between the CRN and the NAR, a study group was established, the project was planned, and the necessary approvals were obtained (Appendices 1-4).

In 2007 the linking between the NAR and the CRN was performed by the CRN. Files containing information on all cancer patients from 1953 to 2005 and all patients with THR from 1987 to 2006 were created. A total of 741,901 patients with either cancer diagnosis or THR was included, and of these 17,235 patients were registered in both registries.

In 1998 the CRN started a national sub-register containing information about radiation therapy given to cancer patients. Since this information was crucial in the studies on long term effects after cancer treatment, we applied for data on radiation therapy on a subgroup of cancer patients in 2009. Information on radiation dosages given to the requested patients was obtained for the period 1998 to 2006.

A new linkage between CRN and NAR was applied for in 2011. This was done to achieve longer follow-up and add more recent years to the study. Our new file included cancer cases and THRs up to 2009. The new linkage had a total of 867,735 patients, of whom 23,515 were registered in both registries.

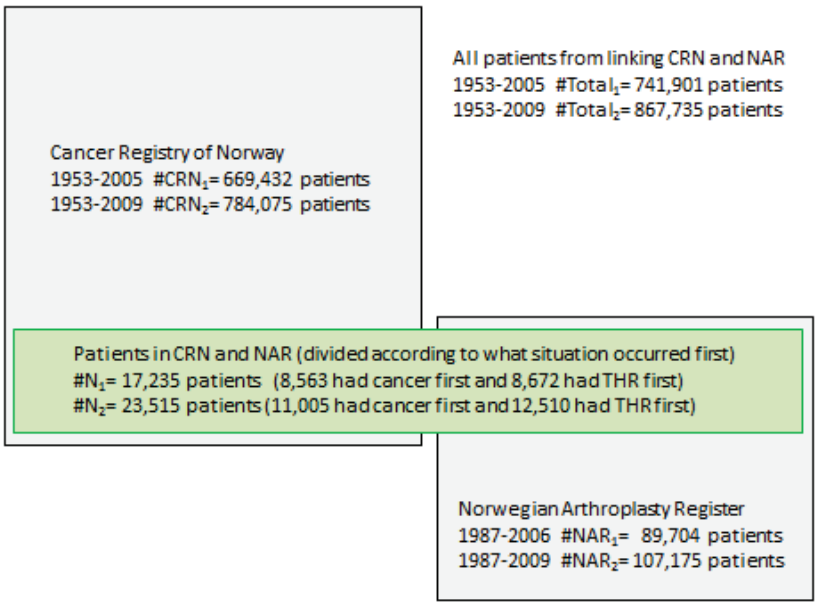

Figure 6: *Data structure from linking CRN and NAR. See text under Papers 1-3 for explanation.*

All studies in this thesis are based on these linkages between NAR and CRN.

Paper 1

In Paper 1, all patients in CRN linked to NAR from the linking in 2007 (#CRN$_1$=669,432), were used. Patients with THR prior to cancer diagnosis were excluded from the analysis (N=8,672). We included patients aged from 16 to 90 years at the time of their first cancer diagnosis and the patients had to be alive per September 1st 1987 (the starting date for registration of THRs in the NAR).

There were 403,809 patients fulfilling the inclusion criteria for the study.

Paper 2

In Paper 2 the sub-register of CRN was used to access information on radiation therapy for two patient groups. We defined an exposure group of women who had undergone pelvic curative external beam radiotherapy for gynaecological cancer and a non-exposure group of female breast cancer patients who had undergone curative

irradiation (40-60 Gy) to the chest area without routine high-dose radiotherapy to the pelvic region.

All the radiation therapy was given between the years 1998 and 2006. Only patients who started radiotherapy within six months after diagnosis were included in the study. Furthermore, we restricted the inclusion to patients with target doses of 40-60 Gy provided over at least 28 days. Patients who had received a THR prior to radiation therapy were excluded.

Included in the study were 8,507 patients, 962 with pelvic radiation exposure and 7,545 without pelvic radiation exposure.

Paper 3

In Paper 3 we used the linking from 2011, and all patients in the NAR were used as the target population (#NAR_2=107,175). Cancer cases were considered outcomes (#N_2=23,515). All THRs were inserted in the period from 1987 to 2009. Patients with cancer diagnosis prior to THR were excluded from the analysis (N=11,005). Only patients with known prosthesis fixations (cemented, uncemented, hybrid or reversed hybrid) were included in the study.

A total of 90,586 patients with a first primary THR were included in the study.

8.4 Outcome

In Paper 1 and Paper 2 the main outcome was THR after a cancer diagnosis. Cancer patients were followed from the date they had been diagnosed with cancer and until the date of a THR, death, emigration or end of study, whichever came first.

In contrast, being diagnosed with cancer after a THR was the outcome in Paper 3. THR patients were divided into groups by the prosthesis fixation technique and followed from primary operation until a cancer diagnosis, death, emigration or end of study, whichever came first.

In Paper 2 and Paper 3 death was considered a competing outcome in the statistical analyses.

In Paper 1 the outcome was 8,563 out of 403,809 patients receiving a primary total hip replacement.

In Paper 2, 26 out of 962 women with gynaecological cancer and 253 out of 7,545 women with breast cancer received a THR after the date of primary diagnosis of cancer.

For Paper 3 we observed 12,383 of 90,586 patients diagnosed with at least one cancer incident after a total hip replacement.

8.5 Approvals, ethics and conflict of interest

The linking of the Norwegian Arthroplasty Register and the Cancer Registry of Norway was approved by the Regional Committee for Medical and Health Research Ethics, Western Norway in 2006 (170.06). The project was also approved by the Norwegian Data Inspectorate (No. 14970). The Norwegian Directorate for Health and Social Affairs gave exemption from duty of confidentiality in 2006. The approvals are found in the appendices.

All co-authors declared no conflict of interest. Both registries involved had governmental funding, and the data were treated in full confidentiality and within laws and regulations.

9. Statistical analyses

The general statistical methods used in this thesis are event history analyses. When linking the Cancer Registry of Norway and the Norwegian Arthroplasty Register, we observe either time from cancer until a total hip replacement (THR) or time from a THR to cancer. Hence, the outcomes we study will in general be time from some initial event (either cancer or THR) to the outcome of interest (receiving a THR, being diagnosed with cancer, or death). Since not all individuals treated for cancer will receive a THR, and not all patients with a THR will get cancer, we have a mixture of the two outcomes time (t) and the outcome itself. In general we can define T as the minimum of two events C and Z, T=min(Z,C), where Z is time to observing an event and C is time to censoring.

A censored observation can be the time when an individual emigrates, time of death (when time to cancer is the outcome of interest), or the maximum potential time of follow-up (completed years of registration at the time of linkage).

9.1 Standardized incidence ratio (SIR)

Standardized incidence ratios (SIR) and standardized mortality ratios (SMR) have been used in epidemiology for decades (Breslow and Day 1985, Breslow and Day 1987). The general idea of the standardized ratios is to quantify the increased risk, for a disease or death, for a group of patients compared to the risk found in the general population. The numerator, O, in the calculation of the SIR (or SMR) is the total number of events observed for the patients, while the denominator, E^*, is the number of events expected to be found in the general population, when gender, age and calendar year are taken into account.

$$SIR = \frac{O}{E^*}$$

9.2 Cox regression

The Cox model was introduced in 1972 and it has been one of the most popular models in statistical analyses of event history data (Cox 1972).

The risk set at a particular point in time consists of individuals (at point t) who are at risk for experiencing the event of interest. Individuals have entered the study and have survived up to time t. Individuals leave the risk set either when they experience the event, or when they are censored.

The hazard rate h(t) has traditionally been important in regression models for survival data. The hazard can be interpreted as the instant probability of an event, within a short period of time after time t, given that the individual was at risk at time t:

$$h(t) = \lim_{dt \to 0} \frac{P(t \leq T < t + dt | \, T \geq t)}{dt}$$

Where T is a random variable of survival times, dt denotes a small interval of time and P is the conditional probability that the survival time of a subject is between t and t+dt, given that a subject has survived up to time t.

In ordinary survival analysis, with one outcome, there is a one-to-one relation between the hazard and the survival function S(t).

$$S(t) = e^{-\int_0^t h(u)du}$$

The survival function is the probability for not yet to have had an event.

$$S(t) = P(T > t)$$

F(t) is the cumulative distribution function, the risk for experiencing an event before time t:

$$F(t) = 1 - S(t)$$

At time zero no individuals will per definition have had an event (S(0)=1), while at time infinite all individuals will have experienced an event (S(∞)=0).

Hence, in single event survival analyses, the Cox proportional hazards regression model is central, since it also will be a regression model for S(t). The Cox model is semiparametric in that it has a nonparametric baseline function ($h_0(t)$). The proportionality in the Cox model is crucial since covariates (X) and regression coefficients (β) are assumed to have a constant influence on the exponential scale over time.

$$h_i(t) = h_0(t) \cdot e^{\beta^T x_i}$$

9.3 Competing risk model

When there is more than one outcome of interest, or there are important outcomes competing with the primary outcome of interest, methods from ordinary survival analyses may be inaccurate. For the competing risk model with death and receiving a total hip replacement as competing outcomes, two hazard rates have to be defined.

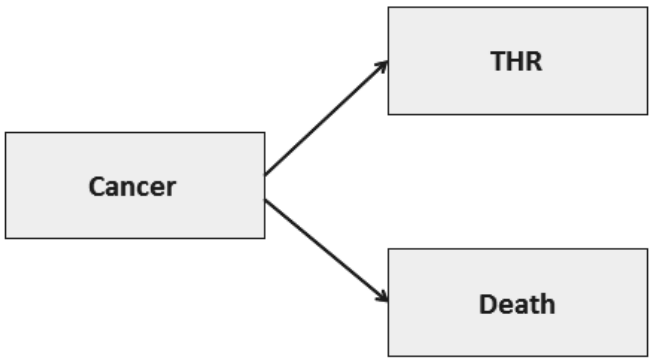

Figure 7: *A competing risk model showing time from cancer diagnosis to receiving a THR or death.*

In this model there will be one hazard for each of the two arrows. Furthermore, it is easily seen that the survival function (which is the probability of being alive with cancer and no THR) is directly related to both outcomes.

$$S(t) = 1 - (F_1(t) + F_2(t))$$

Calculating ordinary survival curves (e.g. using the Kaplan-Meier estimator) for each of the outcomes will therefore not give probabilities for each of the two outcomes. However, since the two outcomes are assumed to be mutually exclusive, the total hazard will be the sum of the two hazards for the two events.

$$h_T(u) = h_1(t) + h_2(t)$$

The overall survival (the probability of being alive with cancer and no THR) can be calculated as the product of the "survival" curves for each of the two outcomes.

$$S(t) = e^{-\int_0^t h_T(u)du} = e^{-\int_0^t h_1(u)du} \cdot e^{-\int_0^t h_2(u)du} = S_1(t) \cdot S_2(t)$$

The probability for either of the two outcomes is on the other hand

$$F_j(t) = \int_0^t S(u) \cdot h_j(u)du\,,\ \mathrm{j} = 1{,}2$$

For competing risk models, the one-to-one relation between the hazard function and the survival function (and the cumulative density function F(t)) is no longer present. As an alternative, Fine and Gray proposed a regression model yielding a sub-hazard ratio (Fine and Gray 1999). The sub-hazard is defined as

$$h_j^*(t) = \log\Big(1 - F_j(t)\Big)$$

The Fine and Gray regression model is defined using the sub-hazard, and the exponential of the coefficients in the model is interpreted as sub-hazard ratios.

$$h_i^*(t) = h_0^*(t) \cdot e^{\beta^T X_i}$$

9.4 Models with time-dependent variables

Time-dependent variables can be implemented in both the Cox regression model and the Fine and Gray model. There are two types of variables used in this thesis. The first is a time-dependent indicator, which identifies changes in the effect of covariates before and after a defined time (e.g. 10 years as in Paper 3). If we for instance introduce two indicators I(T≤10) and I(T>10), we are able to distinguish between the effect in the first 10 years and the last 10 years.

In the Cox model this would look like

$$h_i(t) = h_0(t) \cdot e^{\beta_1 \cdot I_i(T \leq 10) + \beta_2 \cdot I_i(T > 10)}$$

The Fine and Gray model would be equal, but uses sub-hazards.

Additionally, time dependent indicators, $X_i(t)$, were used to identify individuals who have a change in a variable over time (e.g. a new operation or a new cancer case) which can change the risk for the outcome of interest.

9.5 Statistical software

In Paper 1 we used S-plus 7.0 for Windows and SPSS 15.0, in Paper 2 we used R version 3.0.0 and SPSS version 21.0, and in Paper 3 we used SPSS version 22.0, R version 3.0.2, Stata version 13-IC and a custom-made Fortran programme (Lie et al. 1998).

10. Summary of Papers

10.1 Paper 1

Dybvik E, Furnes O, Fosså SD, Trovik C, Lie SA. **Long-term risk of receiving a total hip replacement in cancer patients.** *Cancer Epidemiol. 2009 Oct;33(3-4):235-41.*

Background and purpose: Approximately two thirds of cancer patients survive more than five years and we wanted to investigate whether these patients have an increased risk of receiving a total hip replacement compared to the general population in Norway.

Patients and methods: The study was based on a linkage between the Cancer Registry of Norway and the Norwegian Arthroplasty Register. To be included, patients had to fulfil three criteria; age 16-90 years at the date of their first cancer diagnosis, no hip prosthesis prior to the first cancer diagnosis and alive per September 1st 1987. 403,809 patients were included in the study, and 8,563 patients received a THR. The study ended on December 31st 2006. We used standardized incidence ratios (SIRs) as a measure of THR among cancer patients divided into gender, age groups and groups of cancer locations.

Results: Cancer patients had an overall increased risk of receiving a THR compared to the general population (SIR=1.15 (95% CI: 1.12-1.17)). When comparing to the general population, we found a statistically significant increased risk for some malignancies: malignant lymphoma (SIR=1.30 (95% CI: 1.15-1.46)), selected cancer types located within the pelvic region (SIR=1.20 (95% CI: 1.16-1.24)), leukaemia (SIR=1.17 (95% CI: 1.01-1.34)) and breast (SIR=1.13 (95% CI: 1.08-1.18)).

Conclusions: In this study we found a statistically significant increased risk for receiving a total hip replacement for cancer patients, compared to the incidences of such prostheses in the Norwegian population.

10.2 Paper 2

Dybvik E, Furnes O, Fosså SD, Trovik C, Lie SA. **Pelvic irradiation does not increase the risk of hip replacement in patients with gynecological cancer.** *Acta Orthop. 2014 Dec; 85 (6): 652-6.*

Background and purpose: After five years, about 60% of cancer patients are still alive. These patients could develop adverse effects after the treatment they received. Irradiation to the pelvic region could e.g. cause bone damage and result in an increased risk of fracture or degeneration of the hip.

Patients and methods: The study was based on a linkage between the Cancer Registry of Norway and the Norwegian Arthroplasty Register. From a sub-register of CRN, we obtained information on radiotherapy treatment. We identified an exposure group of 962 women with curative radiotherapy for gynaecological cancer and a non-exposure group of 7,545 women with curative radiotherapy for breast cancer (but without pelvic irradiation). All patients were treated between 1998 and 2006; they received 40-60 Gy for at least 28 days and radiation started within six months of diagnosis. We used Fine and Gray competing risk analysis to calculate sub-hazard ratios (SHR) and cumulative incidence functions (CIF) for receiving a THR, accounting for differences in mortality.

Results: From the exposure group, 26 out of 962 patients (3%) with gynaecological cancer received a THR. 253 out of 7,545 (3%) breast cancer patients received a THR. The eight-year CIFs for receiving a THR were 2.7% (95% CI: 2.6-2.8) and 3.0% (95% CI: 2.95-3.03) for gynaecological cancer and breast cancer respectively. From competing risk models with death as a competing outcome the SIR was 0.80 (95% CI: 0.53-1.22, p=0.30).

Conclusions: We found no statistically significantly higher risk for receiving a THR for patients with gynaecological cancer treated with pelvic radiotherapy compared to patients with breast cancer without pelvic radiotherapy.

10.3 Paper 3

Dybvik E, Furnes O, Havelin LI, Fosså SD, Trovik C, Lie SA**. Increased risk of cancer for uncemented total hip replacements. A study of 90,586 patients in the Norwegian Arthroplasty Register linked to the Cancer Registry of Norway.** *Submitted.*

Background and purpose: Concerns have been raised that implants could lead to a future increased cancer risk. Several different materials and metals are used in joint prosthesis, and different fixation techniques and types of articulation for the surface of the joint can lead to an increased escape of particles or ions into the human body. The first aim was to determine if THR patients had a higher cancer risk than the general population in Norway. The second aim was to see if there were differences between the types of fixations in the risk for late development of cancer in patients with a THR.

Patients and methods: Based on patients reported to the Norwegian Hip Arthroplasty Register in the period from 1987 to 2009, we identified 90,586 patients with one primary total hip replacement (THR). These patients were linked to the Cancer Registry of Norway and we followed them until a cancer event, emigration, death or end of the study, whichever came first. Standardized incidence ratios (SIRs) and survival curves compared the cancer risk for the patients with the general population. To account for selection mechanisms at time of primary operation we used Cox regression analyses and the Fine & Gray competing risk model with time-dependent covariates to compare the difference in cancer risk between different types of fixations after 10 years of follow-up adjusted for the difference in cancer risk in the first 10 years of follow-up.

Results: When comparing to the general population, we found a negligibly increased risk for cancer for the THR patients after 10 years of follow-up (SIR= 1.08, 95 % CI: 1.04-1.12). When comparing types of fixations, we found an increased relative risk for cancer for uncemented prostheses (SHR=1.77, 95 % CI: 1.57-2.00, $p<0.001$) and

for hybrid prostheses (SHR=1.77, 95 % CI: 1.47-2.17, p<0.001), compared to cemented prostheses.

Conclusions: Total hip replacements consisting of at least one uncemented component seem to be followed by an increased risk for late development of cancer, compared to THRs where all components are cemented.

11. General discussion

11.1 Methodological considerations

11.1.1 Study designs

In medical research it is desirable to reveal new information on health, diseases and treatments. There are in general two different types of analytical approaches: experimental studies and observational studies. In *experimental studies* the researcher has full control over the intervention given to all individuals, while in *observational studies* the researcher collects information on groups of interest, but has no influence over who receives which treatment (Altman 1991, Rothman and Greenland 1998, Röhrig et al. 2009).

When specifying study design and sample size, it is essential to collaborate with an experienced biostatistician (Altman et al. 1983, Pripp 2013, Röhrig et al. 2009). The quality and reliability of studies could be improved if all important details are considered ahead of the study in collaboration between biostatisticians and clinicians.

Studies can be classified as prospective or retrospective. In a *prospective study* exposure and covariates are recorded prior to the outcome occurrence and individuals are followed to the occurrence of the event of interest. The outcome of interest should be common, since rare outcomes will be statistically challenging. A *retrospective study* looks backward in time and examines the relations between outcomes and preceding exposures (suspected risks or factors established at the start of the study). For retrospective studies confounders and bias are more common and problematic than in prospective studies.

In a *cohort study*, the researcher defines two or more groups of disease-free people and compares them according to the extent of exposure to a potential cause of a disease, and then follows these to a disease experience. A *case-control study* explores cases with known exposure and compares these with a control group from a population to determine relative size of incidence rates of the disease. A c*ross-*

sectional study includes all persons in the population at one specific point in time, while in a *longitudinal study* individuals have repeated observations over periods in time.

Clinical trials are experimental studies and should ideally be randomized, so that the treatment is allocated to patients at random. *Blinding* is a method to avoid bias in clinical trials and *double blinded studies,* where neither the patient nor the clinician knows who receives which treatment, are considered the gold standard.

Randomized clinical trials (RCT) are considered to be on the highest level of evidence for finding causal relations between an exposure and an outcome (Figure 8) (Concato et al. 2000). Implementing a RCT to examine the effect of radiation therapy and the risk of prosthesis would not be possible, neither practically or ethically. To randomize types of treatment given to treat cancer is problematic, since every cancer case is unique. Studies of long-term effects after cancer treatment in which rare events are expected to develop after at least 10 years requires high numbers of patients.

A randomized study to examine if brands or fixations of prosthesis increase the risk for developing cancer would be difficult. Studies of hip replacements generally require long follow-up and high numbers of patients since the quality of implants is generally good. Adverse events are rare and they develop over a long time with small differences between groups. Consequently, cancer as outcome requires long follow-up and large groups of patients.

Concerns have been raised that observational studies find stronger treatment effects than RCTs. Two studies (Benson and Hartz 2000, Concato et al. 2000) have searched databases for published studies on treatments for the same conditions in RCTs and observational studies and both studies conclude that RCTs and well-designed observational studies give comparable results. A Cochrane Review from 2014 had very similar results (Anglemyer et al. 2014).

Figure 8: *Grades of evidence for the purported quality of study design (Concato et al. 2000).*

For our project, an RCT was not a feasible study design, and all studies in this thesis are therefore observational studies with a prospective cohort design.

11.1.2 Completeness and quality of data

Register studies have limitations in methodology and quality. Completeness and quality of data are amongst other things essential to draw correct conclusions. The CRN has high completeness with 99% coverage of all cancer cases in Norway (Cancer Registry of Norway 2015, Larsen et al. 2009). A study has shown that NAR contains records for 97% of all primary THRs in Norway (Espehaug et al. 2006) and a coverage analysis of primary operations and revisions gave a completeness of 94-95%. This rate was higher if only primary operations were considered (Helsedirektoratet 2014). Quality of data depends on several factors; mistakes can be made by the reporting physician (or other health care workers) or by the technical staff at the registries. Poor design of the registration forms could also lead to incorrect

reporting. The quality of registration has been validated and found reasonably accurate both in CRN (Larsen et al. 2009) and in NAR (Arthursson et al. 2005, Engesaeter et al. 2011, Hulleberg et al. 2008, Lehmann et al. 2012). With all available data on completeness and coverage, we consider the data of the registers used in this thesis to be of good quality.

The Norwegian population is a relatively stable population where emigration rates have been minor (Statistics Norway 2015). The entire population is traced by the national registries and statuses of immigration, emigration or death are also recorded accurately.

11.1.3 Outcome measures

In the CRN, researchers have studied long-term effects after cancer in numerous outcomes, e.g. hormonal dysfunction after radiotherapy to the head and neck region (Seland et al. 2015), long-term income in colorectal cancer patients (Hauglann et al. 2014), increased stomach cancer risk after radiotherapy for testicular cancer (Hauptmann et al. 2015) and arm and shoulder morbidity following surgery and radiotherapy for breast cancer (Johansen et al. 2014). Using THR as an outcome after cancer diagnosis has never been attempted in the Norwegian population before.

There could hypothetically be a selection bias in our studies, since THR is a treatment generally given to healthier patients (Lie et al. 2000). A cancer patient could have a painful and worn out hip, but the indication for a THR results from a balance between the severity of the hip disease and the general health of the patient. General health, comorbidity and mortality for different cancer types vary, and patients may be selected to receive a THR based on these factors.

A hip fracture could be a more sensitive measure of a diseased hip (Gjertsen et al. 2008), since there is not a selection of patients treated for hip fractures similar to the selection for receiving a THR. In Norway the incidence of hip fractures is among the highest in the world (Cooper et al. 2011, Kaastad et al. 1998). The reasons for the high number of hip fractures in Norway have not been completely investigated.

However, lifestyle factors such as exercise, smoking, alcohol consumption and diet could be a reason (Pripp and Dahl 2015), and the use of medications may be another explanation (Bakken et al. 2013, Bakken et al. 2014).

Other alternative outcomes could be patient-reported measure of hip pain (Waldenstrom et al. 2012) or radiographic examination of all patients to disclose joint diseases.

Time from primary operation until failure of the implant is generally used as the primary outcome in the majority of THR studies from NAR. In Paper 3 we used time until a cancer diagnosis as outcome after THR. In recent years, increased numbers of both younger people and elderly people with good general health have received a THR. This increase may be due to an increasingly elderly population, better anaesthetics, lower risk associated with the operation and better quality of the prosthesis. Concerns have been raised as to whether insertion of metal prosthesis could lead to an increased risk for late development of cancer. Hence, cancer diagnosis from the CRN is a well-defined outcome measure after THR.

11.1.4 Validity

In scientific research, validity is to what extent a study is able to answer the questions it is intended to answer. In Modern Epidemiology (Rothman and Greenland 1998) validity is separated into two components: internal validity and external validity (Figure 9).

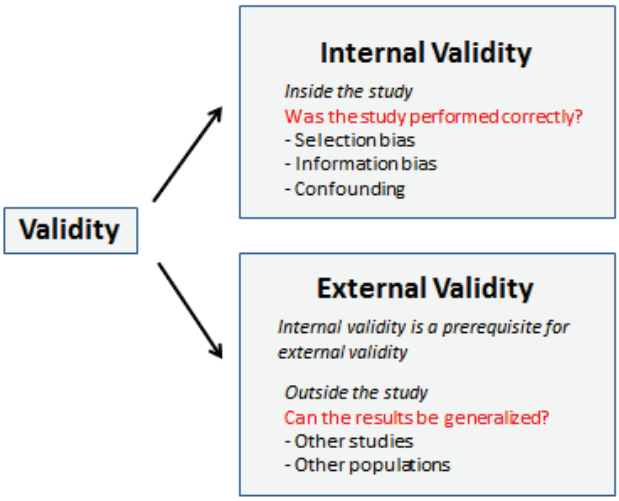

Figure 9: *Validity according to Rothman and Greenland.*

Internal Validity

Internal validity implies whether the conclusion is valid for the population in the study. Internal validity is a precondition for external validity. Systematic errors can violate the internal validity. Systematic errors can be separated into three types: selection bias, information bias and confounding.

Selection bias occurs if the sample is not representative for the study population from which it is selected. Possible causes of selection bias are individuals refusing to participate at the start of the study or dropouts during follow-up. NAR is based on written consent from all patients, and therefore it is possible to refuse to be registered there from the start. Furthermore, individuals could be lost to follow-up, e.g. due to emigration. The CRN is a mandatory register and selection bias is in general not a problem. All studies in this thesis are based on data from CRN and NAR. Both registries have demonstrated very high completeness. The data used in the present thesis can therefore be considered population-based.

Information bias occurs if information on exposure or disease is incorrectly registered. For the CRN all cancers and suspected cancers are reported. The precision of the cancer diagnosis is high, since it is often verified by biopsies. The accuracy for the insertion of a THR is very precise, since the information on this is registered at the operating theatre by the surgeon.

Confounding implies that the effect of the exposure of interest becomes mixed with the effect of other variables (Rothman and Greenland 1998). The confounding variable must be associated with both the exposure and the outcome.

Confounding could be common causes, e.g. lifestyle factors related to the risk for cancer and the risk for a damaged hip joint subsequently needing a THR.

External validity

External validity is the ability to generalize results and conclusions from the study population to individuals outside that population (Rothman and Greenland 1998). Internal validity is a prerequisite for external validity.

External validity may be problematic in experimental studies on rare subgroups of patients. For population-based observational studies, external validity is generally not the main problem, since it is the population in large which is studied.

Precision

The absence of random errors is referred to as precision (Rothman and Greenland 1998). Studies with large samples ensure high precision. In this thesis the populations are retrieved from reliable national registries leading to high precision of the estimates achieved. However, the number of cancer cases, especially in the exposure group in Paper 2, was relatively small. In order to increase the sample size of cancer individuals, collaboration with similar registries in other Nordic countries could be an option.

11.1.5 Statistical Methods

Choice of statistical methods depends on the available data and the purpose of the study.

Standardized incidence ratios (Breslow and Day 1985, Breslow and Day 1987) were used in Paper 1 and Paper 3. This method was used to describe the occurrence of THR in relation to time among cancer patients in Paper 1 and prevalence of cancer in patients with hip replacement in Paper 3 compared to the general population in Norway. Results obtained from SIR are easy to understand and can readily be compared to results from other settings.

Survival analysis, or time to an event analysis (e.g. time until death, revision of prosthesis or time until cancer), is widely used in analysis of registry data. This analytical method takes into account that not all events of interest may have occurred before the end of the whole study or before the individual patient's follow-up prematurely terminates, e.g. due to death or emigration. The most commonly used survival methods are Kaplan-Meier survival curves and Cox proportional hazards models.

The Kaplan-Meier method (Kaplan and Meier 1958) is the most common method for estimation of survival probability. According to the Web of Science citation database (Web of Science 2015) this method has been cited in 39,473 published studies. The method has been rated as one of the most frequently cited statistics papers (Ryan and Woodall 2005), and placed as number 11 in the top 100 papers of most-cited research of all time (Van Noorden et al. 2014). The Kaplan-Meier method has been widely used in cancer research and in research on hip replacements. This method estimates a survival curve indicating the proportion of subjects who have not yet experienced the event of interest at various time points.

The Cox proportional hazards (PH) model (Cox 1972) also plays an important role in analysing survival data. This method has been cited in 29,217 published studies and

is the second most cited statistical paper, ranked as number 29 in the top 100 papers (Van Noorden et al. 2014).

A Cox regression model analyses the instantaneous rate of occurrence of an event, conditional on the event having not yet occurred. The Cox PH model hence enables estimation of the effect of covariates on the hazard rate. A crucial assumption of the model is that hazard ratio is constant over time, hence the term proportional hazards. The simplest test for proportionality is a plot of the log minus log of the survival curves.

In survival analysis where the outcome is time to a single event, there is a one-to-one relation between the hazard rate and the survival function, and estimates from the Cox model can be used to directly estimate the effect of covariates on the survival probabilities.

In recent years, models for competing risks have gained popularity. These models take into account that there could be several outcomes. The occurrence of the event of interest may be precluded by another event. The method for competing risks scenarios models the direct effect of covariates on survival probabilities for the event of interest. In Paper 2, the risk of receiving a THR competes with the risk of death, and similarly in Paper 3, the risk of developing cancer competes with the risk of death. Implementation of *Fine and Grey competing risk models* (Fine and Gray 1999) in commercial statistical packages (e.g. Stata and R) has accelerated the popularity of this method. The paper has been cited in 2,037 published studies. There is an alternative method for analysing competing risks (Klein and Andersen 2005), but this method has not been nearly as popular as the Fine and Gray method.

Ignoring competing risks, or in ordinary survival probabilities treating competing events as a censored observation, would result in underestimation of survival probabilities for the event of interest.

One challenge in event history analyses is that elements may change over time. Effect can change over time and patients can change characteristics over time. In both the

Cox and Fine and Gray model, this can be handled by including time-dependent covariates. This was used in both Paper 2 and Paper 3.

11.2 Results

11.2.1 Paper 1

When comparing cancer patients to the Norwegian population in Paper 1, we found a small though statistically significant increase in the risk for receiving a total hip replacement for the cancer patients (SIR=1.15, 95% CI: 1.12-1.17). The results were consistent also when stratified by different anatomical sites of the cancers. Surprisingly, we did not find the highest risk for cancer located to the pelvic area. The highest risk was for lymphoma (SIR = 1.30, 95% CI: 1.15-1.46), followed by cancer in the pelvic area (SIR=1.20, 95% CI: 1.16-1.24), leukaemia (SIR=1.17, 95% CI: 1.01-1.34) and breast cancer (SIR=1.13, 95% CI: 1.08-1.18). The localization 'shoulders to diaphragm, without breast' had a statistically significantly lower risk for THR (SIR=0.69, 95% CI: 0.57-0.81). The categorization of cancer locations we used in this study was based on the distance from the hip.

Cox regression analysis showed that women with cancer had a significantly lower relative incidence of THR than men with cancer. When comparing cancer locations, cancer above the shoulders was set as the reference location. All locations with cancer diagnosed in 1990 or later had a higher relative incidence of THR than the reference location.

Patients with malignancies may often be treated with hemi-arthroplasties, since this is considered to be a less complicated procedure in patients with comorbidities and limited life expectancy. Hence, our endpoint of THR may not be ideal.

Furthermore, the most advanced cancer cases may have an increased risk for hip damage, but they also have the highest mortality rates. Concerning these malignancies, physicians may be reluctant to refer cancer patients to THR for some period of time due to their elevated risk of postoperative complications or expected

early death. We suspect therefore that the risk of damage to the hip joint might be higher than the observed risk for THR.

Paper 1 did not include information on radiation therapy. The group of pelvic cancers included diagnosis with other treatments than radiation therapy. In early years, surgical treatment alone has been used in many gynaecological cancers and cancer in the rectum or urinary bladder.

Survivors after malignant lymphoma and leukaemia had the highest risk of receiving THR. These two cancer types are treated with high doses of corticosteroids, in the case of leukaemia during long periods, often during childhood. It is known that corticosteroids decrease osteoblast activity (van der Sluis and van den Heuvel-Eibrink 2008) and thus bone structure modelling, which is consistent with our observation of increased risk of caput necrosis.

Increases in risk for THR found in Paper 1 could be related to treatment following cancer diagnosis. However, there may also be common causes explaining the cancer risk and the risk of receiving a THR. Life style factors related to the risk for cancer also relate to the risk for a damaged hip joint and subsequent need for a THR (Apold et al. 2011, Flugsrud et al. 2002, Parkin et al. 2011). Such factors may be obesity, smoking, alcohol abuse, occupation or genetic factors.

The increased SIR for breast cancer could indicate a higher risk for THR, or there could be a common cause increasing both the risk for breast cancer and the risk for THR. A common cause could be age at which menopause occurs, since menopause may be related to the risk for breast cancer (Grodstein et al. 1997) and could also be related to bone mineral density and fractures (Zhang et al. 1997). A study by Shapiro and colleagues found a significantly increased risk for fracture of the femoral neck after breast cancer (Shapiro et al. 2001).

We have not found any other population-based studies on the risk for receiving THR in cancer survivors. A Danish study on fracture risk in men after prostate cancer concluded with an increased risk for fracture at all ages, but most strikingly in men

aged 50-65. This increase was attributed to androgen deprivation therapy (Abrahamsen et al. 2007). A study from the US concluded an increased risk for pelvic or hip fractures in older women following pelvic irradiation (Baxter et al. 2005).

11.2.2 Paper 2

In Paper 2 we compared a group exposed to pelvic irradiation to a group without exposure to pelvic irradiation. The exposed group of gynaecological cancer was compared to the unexposed group of breast cancer. We did not find any statistically significantly higher risk for receiving total hip replacement in the exposure group compared to the unexposed group.

Radiation treatment was given during the period 1998 and 2006, our follow-up extended to the end of 2010. From studies of second cancer related to anti-neoplastic treatment, it is known that the latency from the first to the subsequent malignant tumour is 10 years or more (Solheim et al. 2014, Travis et al. 2005), so our study may have too short follow-up to reveal differences.

Even though Paper 2 was based on two large national registries, the number of available patients in the exposure group of gynaecological cancer with pelvic irradiation was limited. Our study included 962 patients, and only 26 (3%) of them received a THR.

The mortality in our two groups was different. There were 305 deaths in the group of gynaecological cancer patients (32%), while there were 1,052 deaths in the group of breast cancer patients (14%). For clinical outcomes like THR, death may be a substantial competing outcome that should be taken into consideration in the analysis, particularly for such elderly patients (Gillam et al. 2010, Gillam et al. 2011). We used the Fine and Gray method (Fine and Gray 1999) adjusted for death as a competing endpoint and THR as the endpoint of interest and breast cancer patients as the reference category, giving a sub-hazard ratio of 0.80 (95% CI: 0.53-1.22, p=0.30) for gynaecological cancer patients receiving a total hip replacement.

A THR is a clear-cut endpoint, but may not be ideal since the indication for a hip replacement results from a balance between the severity of the symptoms from the diseased hip and the general health of the patient. A total hip replacement is a major operation that is generally reserved for healthier patients (Lie et al. 2000). Patients could have diseased hips without receiving THR; these patients would thus not be included in the study. If gynaecological cancer patients have more severe comorbidity and higher mortality than breast cancer patients, this could lead to bias related to receiving a THR for the two cancer types.

Østgård and colleagues recently published a study on comorbidity in acute myeloid leukaemia patients. Data from the Danish National Registry of Patients on all hospital admissions and hospital outpatient visits and a modified Charlson's Comorbidity Index were used to categorize comorbidity (Ostgard et al. 2015). This method for categorizing comorbidity could be implemented in the Norwegian population and we could then find different groups of pelvic irradiation exposure with comparable comorbidity.

11.2.3 Paper 3

When using standardized incidence ratio (SIR), we found no overall increased risk for cancer after THR compared to the general population (SIR=0.96, 95% CI: 0.94-0.97), while we found a small increase among 10-year survivors (SIR=1.08, 95% CI: 1.04-1.12). When stratifying on fixations, the only increased risk was for uncemented THR after 10 years (SIR=1.58, 95% CI: 1.43-1.73).

Several studies have been published from other national arthroplasty registries using SIR to compare cancer risk in THR or total knee replacements (TKR) with the general population (Brewster et al. 2013, Goldacre et al. 2005, Makela et al. 2012, Makela et al. 2014, Nyren et al. 1995, Onega et al. 2006, Paavolainen et al. 1999, Paavolainen et al. 2002, Smith et al. 2012, Visuri et al. 1996, Visuri et al. 2003, Visuri et al. 2010, Visuri et al. 2006). These studies conclude that there is no (or a negligible) increased risk of cancer after insertion of joint replacements, while

Wagner and colleagues report an increased risk of cancer after insertion of TKR (Wagner et al. 2011).

SIR is the common analytical approach to compare observed cancer risk for THR patients with cancer rates in the general population. The method assumes that prosthesis patients are comparable to the general population. Lie and colleagues (Lie et al. 2000) have showed that THR patients overall have a reduced mortality compared to the general population. THR patients younger than 60 years have an increased mortality and patients older than 80 years have considerably reduced mortality compared to the general population. Furnes and colleagues have shown that young patients have predominantly received uncemented prosthesis while elderly patients have received cemented prosthesis (Furnes et al. 2001). Hence, due to selections of patients, the main analyses in Paper 3 do not use the general population as a reference.

From studies on second cancer related to anti-neoplastic treatment, it is known that the latency period from the first to subsequent malignant tumour is 10 years or more (Solheim et al. 2014, Travis et al. 2005).

Since the SIR generally underestimates the risk of cancer (Kirkeleit et al. 2013), we used the Fine and Gray competing risk method for comparing patients with more than 10 years of follow-up and death as a competing event. We found an increased risk for being diagnosed with cancer for patients with uncemented THR (SHR=1.16, 95% CI: 1.02-1.31, p=0.021) compared to cemented THR.

To compare the different types of fixations for THR, we used the baseline cancer risk before 10 years as a reference. Using a competing risk model with cemented prosthesis as a reference and death as a competing outcome, both uncemented and hybrid prostheses had an increased cancer risk (SHR=1.77, 95% CI 1.57-2.00, p<0.001 and SHR=1.77, 95% CI: 1.47-2.17, p<0.001 respectively). We found increased cancer risk for patients with revision surgery (SHR=1.24, 95% CI: 1.15-1.33, p<0.001) and patients with contralateral primary prosthesis (SHR=1.15, 95% CI: 1.09-1.20, p<0.001).

One, though unlikely, interpretation could be that cemented prostheses reduce the risk for cancer. A change in life style and activity could hypothetically lead to this. Uncemented prostheses, often made of titanium, have a large surface. In animal studies an increased amount of metal ions have been found in lungs, regional lymph nodes, blood and tissues close to the implant (Frisken et al. 2002, Woodman et al. 1984). Direct contact between the uncemented prosthesis and tissue could lead to escape of ions. The structure of the surface of an uncemented prosthesis enables broad contact between the prosthesis and the bone, as the bone is intended to grow directly on the surface of the prosthesis. Furthermore, loosening of the prosthesis may induce increased debris from the prosthesis (Grosse et al. 2014).

12. Conclusions

Compared to the general population, patients diagnosed with cancer have an increased risk to receive THR (SIR=1.15, 95% CI: 1.12-1.17). However, it remains uncertain whether this increase is due to the cancer and its treatment or due to other underlying factors. For selected malignancies treatment may play a major role, as in the iatrogenic modification of a breast cancer patient's hormonal situation or high-dose pelvic radiotherapy in patients with a cancer within the pelvis region.

Overall there is no increased risk for cancer after THR compared to the general population. Only patients with an uncemented THR with more than 10-year follow-up had a greater cancer risk than the general population. Additionally, we found an increased risk for developing cancer 10 years after receiving THR if one or more components were uncemented, compared to prostheses where both components were cemented.

13. Implications and future research

The quality of cancer treatment is steadily increasing; many people survive cancer and stay alive for many years after the cancer diagnosis. In Paper 1 we found an increased risk for receiving THR for cancer patients. Therefore it is still crucial to use registries for surveillance of long term effects after cancer and cancer treatment.

New designs and materials of prostheses are continuously being developed and introduced on the market. The clinical documentation for implants is not as strict as for medication. Therefore, health registries, such as the NAR, are needed for surveillance of implants nationwide both for short and long-term effects.

Future research:

- Long-term effects after cancer, using hip fracture as the outcome, would be a natural extension of the present studies. Combined with information on type and doses of treatment, this would strengthen the study.
- An exposed group of pelvic irradiation could be compared to an unexposed group, but such a study needs to find a better group for the comparison, preferably including comorbidity data. A longer follow-up would also strengthen such a study.
- There has been increased attention to the cancer risk for different THR articulations. A linkage between the NAR and the CRN will have increasing value in the years to come.
- Co-operation with arthroplasty registries from the other Nordic countries should be initiated to enable analyses in truly large cohorts.

14. Source of data

1. Abrahamsen B, Nielsen M F, Eskildsen P, Andersen J T, Walter S, Brixen K. Fracture risk in Danish men with prostate cancer: a nationwide register study. BJU international 2007; 100 (4): 749-54.
2. Ahmad A S, Ormiston-Smith N, Sasieni P D. Trends in the lifetime risk of developing cancer in Great Britain: comparison of risk for those born from 1930 to 1960. British journal of cancer 2015; 112 (5): 943-7.
3. Altman D G. Practical statistics for medical research. Chapman & Hall 1991.
4. Altman D G, Gore S M, Gardner M J, Pocock S J. Statistical guidelines for contributors to medical journals. British medical journal (Clinical research ed) 1983; 286 (6376): 1489-93.
5. American Cancer Society, http://www.cancer.org/cancer/cancerbasics/thehistoryofcancer/the-history-of-cancer-what-is-cancer, 2015.
6. Andreassen B K, Vos L, Grimsrud T K. Kreft - ikke bare uflaks! Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke 2015; 135 (5): 416-7.
7. Anglemyer A, Horvath H T, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. The Cochrane database of systematic reviews 2014; 4: Mr000034.
8. Apold H, Meyer H E, Espehaug B, Nordsletten L, Havelin L I, Flugsrud G B. Weight gain and the risk of total hip replacement a population-based prospective cohort study of 265,725 individuals. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 2011; 19 (7): 809-15.
9. Arthursson A J, Furnes O, Espehaug B, Havelin L I, Soreide J A. Validation of data in the Norwegian Arthroplasty Register and the Norwegian Patient Register: 5,134 primary total hip arthroplasties and revisions operated at a single hospital between 1987 and 2003. Acta orthopaedica 2005; 76 (6): 823-8.
10. Bakken M S, Engeland A, Engesaeter L B, Ranhoff A H, Hunskaar S, Ruths S. Increased risk of hip fracture among older people using antidepressant drugs: data from the Norwegian Prescription Database and the Norwegian Hip Fracture Registry. Age and ageing 2013; 42 (4): 514-20.
11. Bakken M S, Engeland A, Engesaeter L B, Ranhoff A H, Hunskaar S, Ruths S. Risk of hip fracture among older people using anxiolytic and hypnotic drugs: a nationwide prospective cohort study. European journal of clinical pharmacology 2014; 70 (7): 873-80.
12. Baxter N N, Habermann E B, Tepper J E, Durham S B, Virnig B A. Risk of pelvic fractures in older women following pelvic irradiation. JAMA 2005; 294 (20): 2587-93.
13. Benson K, Hartz A J. A comparison of observational studies and randomized, controlled trials. The New England journal of medicine 2000; 342 (25): 1878-86.
14. Brand R A, Mont M A, Manring M M. Biographical sketch: Themistocles Gluck (1853-1942). Clinical orthopaedics and related research 2011; 469 (6): 1525-7.
15. Bray F, Ren J S, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. International journal of cancer Journal international du cancer 2013; 132 (5): 1133-45.

16. Breslow N E, Day N E. The standardized mortality ratio. In Biostatistics: Statistics in Biomedical Public Health and Environmental Science 1985; P.K. Sen, ed. Elsevier, New York: pp. 55-74.
17. Breslow N E, Day N E. Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. IARC scientific publications 1987; (82): 1-406.
18. Brewster D H, Stockton D L, Reekie A, Ashcroft G P, Howie C R, Porter D E, et al. Risk of cancer following primary total hip replacement or primary resurfacing arthroplasty of the hip: a retrospective cohort study in Scotland. British journal of cancer 2013; 108 (9): 1883-90.
19. Canadian Joint Replacement Registry, Hip and Knee Replacements in Canada. Annual Report, 2014
20. Cancer Registry of Norway, Cancer in Norway 2013 - Cancer incidence, mortality, survival and prevalence in Norway, Oslo, 2015
21. Cancer Registry of Norway, http://www.kreftregisteret.no, 2015.
22. Charnley J. Arthroplasty of the hip. A new operation. Lancet 1961; 1 (7187): 1129-32.
23. Charnley J. Total hip replacement by low-friction arthroplasty. Clinical orthopaedics and related research 1970; 72: 7-21.
24. Christiansen T. A new hip prosthesis with trunnion-bearing. Acta chirurgica Scandinavica 1969; 135 (1): 43-6.
25. Colditz G A, Wolin K Y, Gehlert S. Applying what we know to accelerate cancer prevention. Science translational medicine 2012; 4 (127): 127rv4.
26. Concato J, Shah N, Horwitz R I. Randomized, controlled trials, observational studies, and the hierarchy of research designs. The New England journal of medicine 2000; 342 (25): 1887-92.
27. Cooper C, Cole Z A, Holroyd C R, Earl S C, Harvey N C, Dennison E M, et al. Secular trends in the incidence of hip and other osteoporotic fractures. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2011; 22 (5): 1277-88.
28. Couzin-Frankel J. Biomedicine. The bad luck of cancer. Science (New York, NY) 2015; 347 (6217): 12.
29. Cox D R. Regression Models and Life-Tables. Journal of the Royal Statistical Society Series B (Methodological) 1972; 34 (2): 187-220.
30. Curtis R E, Freedman D M, Ron E, Ries L A G, Hacker D G, Edwards B K, et al. New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973-2000. National Cancer Institute, NIH Publ. No. 05-5302. Bethesda, MD 2006.
31. Daigle M E, Weinstein A M, Katz J N, Losina E. The cost-effectiveness of total joint arthroplasty: a systematic review of published literature. Best practice & research Clinical rheumatology 2012; 26 (5): 649-58.
32. David A R, Zimmerman M R. Cancer: an old disease, a new disease or something in between? Nature reviews Cancer 2010; 10 (10): 728-33.
33. Engesaeter I O, Lehmann T, Laborie L B, Lie S A, Rosendahl K, Engesaeter L B. Total hip replacement in young adults with hip dysplasia: age at diagnosis, previous treatment, quality of life, and validation of diagnoses reported to the Norwegian Arthroplasty Register between 1987 and 2007. Acta orthopaedica 2011; 82 (2): 149-54.

34. Espehaug B, Furnes O, Engesaeter L B, Havelin L I. 18 years of results with cemented primary hip prostheses in the Norwegian Arthroplasty Register: concerns about some newer implants. Acta orthopaedica 2009; 80 (4): 402-12.
35. Espehaug B, Furnes O, Engesaeter L B, Havelin L I. Hip arthroplasty in Norway 1989-2008. Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke 2011; 131 (16): 1543-8.
36. Espehaug B, Furnes O, Havelin L I, Engesaeter L B, Vollset S E, Kindseth O. Registration completeness in the Norwegian Arthroplasty Register. Acta Orthop 2006; 77 (1): 49-56.
37. Eynon-Lewis N J, Ferry D, Pearse M F. Themistocles Gluck: an unrecognised genius. Bmj 1992; 305 (6868): 1534-6.
38. Fine J P, Gray R J. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999; 94 (446): 496-509.
39. Flugsrud G B, Nordsletten L, Espehaug B, Havelin L I, Meyer H E. Risk factors for total hip replacement due to primary osteoarthritis: a cohort study in 50,034 persons. Arthritis and rheumatism 2002; 46 (3): 675-82.
40. Folkehelseinstituttet, http://www.fhi.no/helseregistre, 2015.
41. Fosså S D, Winderen M. Does decreased skeletal uptake of 99mTc-methylene bisphosphonate in irradiated bone indicate the absence of bone metastases? RadiotherOncol 1993; 27 (1): 63-5.
42. Frisken K W, Dandie G W, Lugowski S, Jordan G. A study of titanium release into body organs following the insertion of single threaded screw implants into the mandibles of sheep. Australian dental journal 2002; 47 (3): 214-7.
43. Fu A L, Greven K M, Maruyama Y. Radiation osteitis and insufficiency fractures after pelvic irradiation for gynecologic malignancies. AmJClinOncol 1994; 17 (3): 248-54.
44. Furnes O, Lie S A, Espehaug B, Vollset S E, Engesaeter L B, Havelin L I. Hip disease and the prognosis of total hip replacements. A review of 53,698 primary total hip replacements reported to the Norwegian Arthroplasty Register 1987-99. The Journal of bone and joint surgery British volume 2001; 83 (4): 579-86.
45. Gillam M H, Ryan P, Graves S E, Miller L N, de Steiger R N, Salter A. Competing risks survival analysis applied to data from the Australian Orthopaedic Association National Joint Replacement Registry. Acta Orthop 2010; 81 (5): 548-55.
46. Gillam M H, Salter A, Ryan P, Graves S E. Different competing risks models applied to data from the Australian Orthopaedic Association National Joint Replacement Registry. Acta Orthop 2011; 82 (5): 513-20.
47. Gjertsen J E, Engesaeter L B, Furnes O, Havelin L I, Steindal K, Vinje T, et al. The Norwegian Hip Fracture Register: experiences after the first 2 years and 15,576 reported operations. Acta Orthop 2008; 79 (5): 583-93.
48. Gluck T. Referat über die durch das moderne chirurgische Experiment gewonnenen positiven Resultate, betreffend die Naht und den Ersatz von Defecten höherer Gewebe, sowie über die Verwethung resorbirbarer und lebendiger Tampons in der Chirurgie. Arch klin chir 1891; 41: 187-239.
49. Goitz R J, Tomaino M M, Smith P, Hannallah D, Sinha R. Treatment of radiation-induced soft-tissue fibrosis and concomitant acetabular osteonecrosis: a case report. American journal of orthopedics (Belle Mead, NJ) 2007; 36 (4): E56-8.
50. Goldacre M J, Wotton C J, Seagroatt V, Yeates D. Cancer following hip and knee arthroplasty: record linkage study. British journal of cancer 2005; 92 (7): 1298-301.

51. Graves S E, Davidson D, Ingerson L, Ryan P, Griffith E C, McDermott B F, et al. The Australian Orthopaedic Association National Joint Replacement Registry. The Medical journal of Australia 2004; 180 (5 Suppl): S31-4.
52. Grodstein F, Stampfer M J, Colditz G A, Willett W C, Manson J E, Joffe M, et al. Postmenopausal hormone therapy and mortality. The New England journal of medicine 1997; 336 (25): 1769-75.
53. Grosse S, Haugland H K, Lilleng P, Ellison P, Hallan G, Hol P J. Wear particles and ions from cemented and uncemented titanium-based hip prostheses-A histological and chemical analysis of retrieval material. Journal of biomedical materials research Part B, Applied biomaterials 2014.
54. Hailer N P, Garellick G, Karrholm J. Uncemented and cemented primary total hip arthroplasty in the Swedish Hip Arthroplasty Register. Acta orthopaedica 2010; 81 (1): 34-41.
55. Hallab N J, Jacobs J J. Biologic effects of implant debris. Bulletin of the NYU hospital for joint diseases 2009; 67 (2): 182-8.
56. Hallan G, Dybvik E, Furnes O, Havelin L I. Metal-backed acetabular components with conventional polyethylene: a review of 9113 primary components with a follow-up of 20 years. The Journal of bone and joint surgery British volume 2010; 92 (2): 196-201.
57. Hallan G, Lie S A, Furnes O, Engesaeter L B, Vollset S E, Havelin L I. Medium- and long-term performance of 11,516 uncemented primary femoral stems from the Norwegian arthroplasty register. The Journal of bone and joint surgery British volume 2007; 89 (12): 1574-80.
58. Hauglann B, Benth J, Fosså S, Tveit K, Dahl A. A controlled cohort study of long-term income in colorectal cancer patients. Support Care Cancer 2014; 22 (10): 2821-30.
59. Hauptmann M, Fossa S D, Stovall M, van Leeuwen F E, Johannesen T B, Rajaraman P, et al. Increased stomach cancer risk following radiotherapy for testicular cancer. British journal of cancer 2015; 112 (1): 44-51.
60. Havelin L I, Engesaeter L B, Espehaug B, Furnes O, Lie S A, Vollset S E. The Norwegian Arthroplasty Register: 11 years and 73,000 arthroplasties. Acta orthopaedica Scandinavica 2000; 71 (4): 337-53.
61. Havelin L I, Espehaug B, Vollset S E, Engesaeter L B. Early failures among 14,009 cemented and 1,326 uncemented prostheses for primary coxarthrosis. The Norwegian Arthroplasty Register, 1987-1992. Acta orthopaedica Scandinavica 1994; 65 (1): 1-6.
62. Havelin L I, Espehaug B, Vollset S E, Engesaeter L B. Early aseptic loosening of uncemented femoral components in primary total hip replacement. A review based on the Norwegian Arthroplasty Register. The Journal of bone and joint surgery British volume 1995; 77 (1): 11-7.
63. Havelin L I, Espehaug B, Vollset S E, Engesaeter L B, Langeland N. The Norwegian arthroplasty register. A survey of 17,444 hip replacements 1987-1990. Acta orthopaedica Scandinavica 1993; 64 (3): 245-51.
64. Helsedirektoratet, Dekningsgradsanalyse for Hofteproteseregisteret, 2008-2012, 2014
65. Herman M P, Kopetz S, Bhosale P R, Eng C, Skibber J M, Rodriguez-Bigas M A, et al. Sacral insufficiency fractures after preoperative chemoradiation for rectal cancer: incidence, risk factors, and clinical course. International journal of radiation oncology, biology, physics 2009; 74 (3): 818-23.

66. Howlader N, Noone A M, Krapcho M, Garshell J, Miller D, Altekruse S F, et al., SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER web site, April 2014., 2014
67. Hulleberg G, Aamodt A, Espehaug B, Benum P. A clinical and radiographic 13-year follow-up study of 138 Charnley hip arthroplasties in patients 50-70 years old: comparison of university hospital data and registry data. Acta orthopaedica 2008; 79 (5): 609-17.
68. Israeli R S, Ryan C W, Jung L L. Managing Bone Loss in Men With Locally Advanced Prostate Cancer Receiving Androgen Deprivation Therapy. The Journal of Urology 2008; 179 (2): 414-23.
69. Johansen S, Fosså K, Nesvold I L, Malinen E, Fosså S D. Arm and shoulder morbidity following surgery and radiotherapy for breast cancer. Acta oncologica 2014; 53 (4): 521-9.
70. Kaastad T S, Meyer H E, Falch J A. Incidence of hip fracture in Oslo, Norway: differences within the city. Bone 1998; 22 (2): 175-8.
71. Kaplan E L, Meier P. Nonparametric Estimation from Incomplete Observations. Journal of the American Statistical Association 1958; 53 (282): 457-81.
72. Keel S B, Jaffe K A, Petur Nielsen G, Rosenberg A E. Orthopaedic implant-related sarcoma: a study of twelve cases. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc 2001; 14 (10): 969-77.
73. Kirkeleit J, Riise T, Bjorge T, Christiani D C. The healthy worker effect in cancer incidence studies. American journal of epidemiology 2013; 177 (11): 1218-24.
74. Klein J P, Andersen P K. Regression modeling of competing risks data based on pseudovalues of the cumulative incidence function. Biometrics 2005; 61 (1): 223-9.
75. Kurtz S, Mowat F, Ong K, Chan N, Lau E, Halpern M. Prevalence of primary and revision total hip and knee arthroplasty in the United States from 1990 through 2002. The Journal of bone and joint surgery American volume 2005; 87 (7): 1487-97.
76. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. The Journal of bone and joint surgery American volume 2007; 89 (4): 780-5.
77. Larsen I K, Smastuen M, Johannesen T B, Langmark F, Parkin D M, Bray F, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. European journal of cancer 2009; 45 (7): 1218-31.
78. Learmonth I D, Young C, Rorabeck C. The operation of the century: total hip replacement. Lancet 2007; 370 (9597): 1508-19.
79. Lehmann T G, Engesaeter I O, Laborie L B, Lie S A, Rosendahl K, Engesaeter L B. Total hip arthroplasty in young adults, with focus on Perthes' disease and slipped capital femoral epiphysis: follow-up of 540 subjects reported to the Norwegian Arthroplasty Register during 1987-2007. Acta orthopaedica 2012; 83 (2): 159-64.
80. Lewis G, van Hooy-Corstjens C S, Bhattaram A, Koole L H. Influence of the radiopacifier in an acrylic bone cement on its mechanical, thermal, and physical properties: barium sulfate-containing cement versus iodine-containing cement. Journal of biomedical materials research Part B, Applied biomaterials 2005; 73 (1): 77-87.
81. Lidgren L. Chronic inflammation, joint replacement and malignant lymphoma. The Journal of bone and joint surgery British volume 2008; 90 (1): 7-10.

82. Lie S A, Engesaeter L B, Havelin L I, Gjessing H K, Vollset S E. Mortality after total hip replacement: 0-10-year follow-up of 39,543 patients in the Norwegian Arthroplasty Register. Acta orthopaedica Scandinavica 2000; 71 (1): 19-27.
83. Lie S A, Lie R T, Svanes C. Expected survival compared with survival of peptic ulcer patients. Statistics in medicine 1998; 17 (11): 1189-99.
84. Lohmander L S, Engesaeter L B, Herberts P, Ingvarsson T, Lucht U, Puolakka T J. Standardized incidence rates of total hip replacement for primary hip osteoarthritis in the 5 Nordic countries: similarities and differences. Acta orthopaedica 2006; 77 (5): 733-40.
85. Lugli T. Artificial shoulder joint by Pean (1893): the facts of an exceptional intervention and the prosthetic method. Clinical orthopaedics and related research 1978; (133): 215-8.
86. Mabilleau G, Kwon Y M, Pandit H, Murray D W, Sabokbar A. Metal-on-metal hip resurfacing arthroplasty: a review of periprosthetic biological reactions. Acta orthopaedica 2008; 79 (6): 734-47.
87. Makela K T, Visuri T, Pulkkinen P, Eskelinen A, Remes V, Virolainen P, et al. Risk of cancer with metal-on-metal hip replacements: population based study. Bmj 2012; 345: e4646.
88. Makela K T, Visuri T, Pulkkinen P, Eskelinen A, Remes V, Virolainen P, et al. Cancer incidence and cause-specific mortality in patients with metal-on-metal hip replacements in Finland. Acta orthopaedica 2014; 85 (1): 32-8.
89. Memoli V A, Urban R M, Alroy J, Galante J O. Malignant neoplasms associated with orthopedic implant materials in rats. Journal of orthopaedic research : official publication of the Orthopaedic Research Society 1986; 4 (3): 346-55.
90. Meyerowitz B E, Kurita K, D'Orazio L M. The psychological and emotional fallout of cancer and its treatment. Cancer J 2008; 14 (6): 410-3.
91. Meyskens F, Jr. Cancer following total joint arthroplasty. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2007; 16 (2): 356.
92. Molina J, Barton D, Loprinzi C. Chemotherapy-Induced Ovarian Failure. Drug-Safety 2005; 28 (5): 401-16.
93. Molven O, Ferkis J. Healthcare, welfare and law : health legislation as a mirror of the Norwegian welfare state. Gyldendal akademisk 2011.
94. Moster D, Lie R T, Markestad T. Long-term medical and social consequences of preterm birth. The New England journal of medicine 2008; 359 (3): 262-73.
95. Nasjonalt servicemiljø for medisinske kvalitetsregistre, http://www.kvalitetsregistre.no/, 2015.
96. Nerlich A G, Rohrbach H, Bachmeier B, Zink A. Malignant tumors in two ancient populations: An approach to historical tumor epidemiology. Oncology reports 2006; 16 (1): 197-202.
97. Norwegian Arthroplasty Register, Rapport 2014, 2014
98. Norwegian Arthroplasty Register, http://nrlweb.ihelse.net, 2015.
99. Nyren O, McLaughlin J K, Gridley G, Ekbom A, Johnell O, Fraumeni J F, Jr., et al. Cancer risk after hip replacement with metal implants: a population-based cohort study in Sweden. Journal of the National Cancer Institute 1995; 87 (1): 28-33.
100. Onega T, Baron J, MacKenzie T. Cancer after total joint arthroplasty: a meta-analysis. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2006; 15 (8): 1532-7.

101. Ostgard L S, Norgaard J M, Sengelov H, Severinsen M, Friis L S, Marcher C W, et al. Comorbidity and performance status in acute myeloid leukemia patients: a nation-wide population-based cohort study. Leukemia 2015; 29 (3): 548-55.
102. Paavolainen P, Pukkala E, Pulkkinen P, Visuri T. Cancer incidence in Finnish hip replacement patients from 1980 to 1995: a nationwide cohort study involving 31,651 patients. The Journal of arthroplasty 1999; 14 (3): 272-80.
103. Paavolainen P, Pukkala E, Pulkkinen P, Visuri T. Causes of death after total hip arthroplasty: a nationwide cohort study with 24,638 patients. The Journal of arthroplasty 2002; 17 (3): 274-81.
104. Parkin D M, Boyd L, Walker L C. 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. British journal of cancer 2011; 105 Suppl 2: S77-81.
105. Péan J-E. Des moyens prosthetiques destinés a obtenir la preparation de parties ossueses. Gaz Hôp Paris 1894; 67: 291.
106. Pivec R, Johnson A J, Mears S C, Mont M A. Hip arthroplasty. Lancet 2012; 380 (9855): 1768-77.
107. Potter J D, Prentice R L. Cancer risk: tumors excluded. Science (New York, NY) 2015; 347 (6223): 727.
108. Pripp A H. [When the numbers need treatment]. Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke 2013; Oct 1 (133(18)): 1952-4.
109. Pripp A H, Dahl O E. The population attributable risk of nutrition and lifestyle on hip fractures. Hip international : the journal of clinical and experimental research on hip pathology and therapy 2015: 0.
110. Rothman K J, Greenland S. Modern Epidemiology. Part II. Study design and conduct. Second ed. Lippincott-Raven publishers 1998.
111. Ryan T, Woodall W. The most-cited statistical papers. Journal of Applied Statistics 2005; 32 (5): 461-74.
112. Röhrig B, du Prel J B, Wachtlin D, Blettner M. Types of Study in Medical Research: Part 3 of a Series on Evaluation of Scientific Publications. Deutsches Arzteblatt International 2009; 106 (15): 262-8.
113. Sant M, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R. EUROCARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary. EurJCancer 2009; 45 (6): 931-91.
114. Seland M, Bjøro T, Furre T, Schreiner T, Bollerslev J, Fosså S, et al. Hormonal dysfunction is frequent in cancer survivors treated with radiotherapy to the head and neck region. J Cancer Surviv 2015: 1-11.
115. Selmer E S. Personnummerering i Norge: Litt anvendt tallteori og psykologi. Nordisk matematisk tidsskrift 1964; 12: 36-44.
116. Shapiro C L, Manola J, Leboff M. Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2001; 19 (14): 3306-11.
117. Smith-Petersen M N. Evolution of mould arthroplasty of the hip joint. The Journal of bone and joint surgery British volume 1948; 30b (1): 59-75.
118. Smith A J, Dieppe P, Porter M, Blom A W. Risk of cancer in first seven years after metal-on-metal hip replacement compared with other bearings and general population: linkage study between the National Joint Registry of England and Wales and hospital episode statistics. Bmj 2012; 344: e2383.

119. Smith Petersen M N. Arthroplasty of the Hip: A New Method. The Journal of bone and joint surgery 1939; 21: 269.
120. Solheim O, Gershenson D M, Trope C G, Rokkones E, Sun C C, Weedon-Fekjaer H, et al. Prognostic factors in malignant ovarian germ cell tumours (The surveillance, epidemiology and end results experience 1978-2010). European journal of cancer 2014; 50 (11): 1942-50.
121. Statistics Norway,
122. Sudhakar A. History of Cancer, Ancient and Modern Treatment Methods. Journal of cancer science & therapy 2009; 1 (2): 1-4.
123. Sudmann E, Havelin L I, Lunde O D, Rait M. The Charnley versus the Christiansen total hip arthroplasty. A comparative clinical study. Acta orthopaedica Scandinavica 1983; 54 (4): 545-52.
124. Tanday S. Lifetime risk of cancer is more than 50% in Britain. The lancet oncology 2015; 16 (3): e109.
125. Toledo-Pereyra L H. John Charnley—Father of Modern Total Hip Replacement. Journal of Investigative Surgery 2004; 17 (6): 299-301.
126. Tomasetti C, Vogelstein B. Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. Science (New York, NY) 2015; 347 (6217): 78-81.
127. Travis L B, Fossa S D, Schonfeld S J, McMaster M L, Lynch C F, Storm H, et al. Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. Journal of the National Cancer Institute 2005; 97 (18): 1354-65.
128. Urban R M, Jacobs J J, Tomlinson M J, Gavrilovic J, Black J, Peoc'h M. Dissemination of wear particles to the liver, spleen, and abdominal lymph nodes of patients with hip or knee replacement. The Journal of bone and joint surgery American volume 2000; 82 (4): 457-76.
129. Urban R M, Tomlinson M J, Hall D J, Jacobs J J. Accumulation in liver and spleen of metal particles generated at nonbearing surfaces in hip arthroplasty. The Journal of arthroplasty 2004; 19 (8 Suppl 3): 94-101.
130. van der Sluis I M, van den Heuvel-Eibrink M M. Osteoporosis in children with cancer. Pediatric Blood & Cancer 2008; 50 (S2): 474-8.
131. Van Noorden R, Maher B, Nuzzo R. The top 100 papers. Nature 2014; 514 (7524): 550-3.
132. Vikse B E, Irgens L M, Leivestad T, Skjaerven R, Iversen B M. Preeclampsia and the risk of end-stage renal disease. The New England journal of medicine 2008; 359 (8): 800-9.
133. Visuri T, Pukkala E, Paavolainen P, Pulkkinen P, Riska E B. Cancer risk after metal on metal and polyethylene on metal total hip arthroplasty. Clinical orthopaedics and related research 1996; (329 Suppl): S280-9.
134. Visuri T, Pukkala E, Pulkkinen P, Paavolainen P. Decreased cancer risk in patients who have been operated on with total hip and knee arthroplasty for primary osteoarthrosis: a meta-analysis of 6 Nordic cohorts with 73,000 patients. Acta orthopaedica Scandinavica 2003; 74 (3): 351-60.
135. Visuri T, Pulkkinen P, Paavolainen P, Pukkala E. Cancer risk is not increased after conventional hip arthroplasty. Acta orthopaedica 2010; 81 (1): 77-81.
136. Visuri T I, Pukkala E, Pulkkinen P, Paavolainen P. Cancer incidence and causes of death among total hip replacement patients: a review based on Nordic cohorts with a special emphasis on metal-on-metal bearings. Proceedings of the Institution of Mechanical Engineers Part H, Journal of engineering in medicine 2006; 220 (2): 399-407.

137. Wagner P, Olsson H, Lidgren L, Robertsson O, Ranstam J. Increased cancer risks among arthroplasty patients: 30 year follow-up of the Swedish Knee Arthroplasty Register. European journal of cancer 2011; 47 (7): 1061-71.
138. Waldenstrom A C, Olsson C, Wilderang U, Dunberger G, Lind H, Alevronta E, et al. Relative importance of hip and sacral pain among long-term gynecological cancer survivors treated with pelvic radiotherapy and their relationships to mean absorbed doses. International journal of radiation oncology, biology, physics 2012; 84 (2): 428-36.
139. Web of Science,
140. Willert H G, Broback L G, Buchhorn G H, Jensen P H, Koster G, Lang I, et al. Crevice corrosion of cemented titanium alloy stems in total hip replacements. Clinical orthopaedics and related research 1996; (333): 51-75.
141. Wodarz D, Zauber A G. Cancer: Risk factors and random chances. Nature 2015; 517 (7536): 563-4.
142. Woodman J L, Jacobs J J, Galante J O, Urban R M. Metal ion release from titanium-based prosthetic segmental replacements of long bones in baboons: a long-term study. Journal of orthopaedic research : official publication of the Orthopaedic Research Society 1984; 1 (4): 421-30.
143. World Health Organization, World Cancer Report 2014, 2014
144. Yamamoto Y, Iwase H. Safety profiles of aromatase inhibitors and selective estrogen-receptor modulators in the treatment of early breast cancer. Int J Clin Oncol 2008; 13 (5): 384-94.
145. Yurut-Caloglu V, Durmus-Altun G, Caloglu M, Usta U, Saynak M, Uzal C, et al. Comparison of protective effects of L-carnitine and amifostine on radiation-induced toxicity to growing bone: histopathology and scintigraphy findings. Asian PacJCancer Prev 2010; 11 (3): 661-7.
146. Zahl P H, Jorgensen K J, Gotzsche P C. Overestimated lead times in cancer screening has led to substantial underestimation of overdiagnosis. British journal of cancer 2013; 109 (7): 2014-9.
147. Zahl P H, Maehlen J. Overdiagnosis of breast cancer after 14 years of mammography screening. Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke 2012; 132 (4): 414-7.
148. Zhang Y, Kiel D P, Kreger B E, Cupples L A, Ellison R C, Dorgan J F, et al. Bone mass and the risk of breast cancer among postmenopausal women. The New England journal of medicine 1997; 336 (9): 611-7.

15. Appendices

All appendices are in Norwegian.

Appendix 1	Approval from Regional Etisk Komite
Appendix 2	Approval from Norsk Samfunnsvitenskapelig Datatjeneste
Appendix 3	Approval from Datatilsynet
Appendix 4	Approval from Sosial- og helsedirektoratet
Appendix 5	Registration form from the Cancer Registry of Norway (solid tumour)
Appendix 6	Registration form from the Cancer Registry of Norway (non-solid tumour)
Appendix 7	Operation form from the Norwegian Arthroplasty Register

UNIVERSITETET I BERGEN
Det medisinske fakultet
Harald Hårfagresgt. 1,
Postboks 7804, 5020 BERGEN

UNIVERSITY OF BERGEN
Faculty of Medicine
Harald Hårfagresgt. 1
P.O. Box 7804, N-5020 BERGEN

Regional komité for medisinsk forskningsetikk
Vest-Norge (REK Vest)
Postadr.: Universitetet i Bergen, Postboks 7804, 5020Bergen
Besøksadr.: Haukeland Universitetssjukehus, Sentralblokken, 2. etasje, rom 4617
Tlf: 55 97 84 97 / 55 97 84 98 / 55 97 84 99
E-post: rek-vest@uib.no

http://www.etikkom.no/REK/

Bergen, 12.09.06.
Sak nr. 06/8523

Dr. philos. Stein Atle Lie
Unifob Helse
Christiesgate 13
5015 BERGEN

Ad prosjekt: Kreftpasienter og totale hofteleddproteser (170.06).

Det vises til din søknad om etisk vurdering datert 14.06.06. REK Vest vurderte studien i møte den 31.08.06.

Komiteen mener dette er en godt fundert studie og har ingen merknader.
Studien er da endelig klarert fra denne komité sin side.

Vi ønsker dere lykke til med gjennomføringen og minner om at komiteen setter pris på en sluttrapport, eventuelt en kopi av trykt publikasjon når dette foreligger.

Vennlig hilsen

Arnold Berstad
leder

Arne Salbu
sekretær

Norsk samfunnsvitenskapelig datatjeneste AS
NORWEGIAN SOCIAL SCIENCE DATA SERVICES

Harald Hårfagres gate 29
N-5007 Bergen
Norway
Tel: +47-55 58 21 17
Fax: +47-55 58 96 50
nsd@nsd.uib.no
www.nsd.uib.no
Org.nr. 985 321 884

Stein Atle Lie
Nasjonalt register for leddproteser
Ortopedisk klinikk
Haukeland Universitetssykehus
5021 BERGEN

Vår dato: 31.08.2006 Vår ref: 14970/GT Deres dato: Deres ref:

TILBAKEMELDING PÅ BEHANDLING AV PERSONOPPLYSNINGER

Vi viser til melding om behandling av personopplysninger, mottatt 14.06.2006. Meldingen gjelder prosjektet:

14970	*Kreftpasienter og totale hofteleddproteser*
Behandlingsansvarlig	*Helse Bergen HF, ved institusjonens øverste leder*
Daglig ansvarlig	*Stein Atle Lie*
Student	*Eva Dybvik*

Personvernombudet har vurdert prosjektet og finner at behandlingen av personopplysninger utløser konsesjonsplikt i henhold til personopplysningsloven § 33 1. ledd.

I henhold til avtalen med *Helse Bergen HF* er meldingen behandlet og innstilling sendt til Datatilsynet for vurdering av konsesjonsspørsmålet. Det er anbefalt at prosjektet gis konsesjon. Kopi av vår innstilling til Datatilsynet følger vedlagt.

Det gjøres oppmerksom på at det skal gis ny melding til personvernombudet dersom prosjektet endres i forhold til de opplysninger som ligger til grunn for personvernombudets vurdering og søknad til Datatilsynet. Endringsmeldinger gis via et eget skjema, http://www.nsd.uib.no/personvern/endringsskjema. Det skal også gis melding etter tre år dersom prosjektet fortsatt pågår. Meldinger skal skje skriftlig til ombudet.

Personvernombudet har lagt ut opplysninger om prosjektet i en offentlig database, http://www.nsd.uib.no/personvern/register/

Personvernombudet vil ved prosjektets avslutning, 31.12.2009 rette en henvendelse angående status for behandlingen av personopplysninger.

Personvernombudet gjør oppmerksom på at datainnsamling ikke kan startes før konsesjon fra Datatilsynet foreligger.

Dersom noe er uklart ta gjerne kontakt over telefon.

Vennlig hilsen

Bjørn Henrichsen

Geir Teigland

Kontaktperson: Geir Teigland tlf: 55 58 33 48

Vedlegg: Prosjektvurdering

✓ Kopi:Eva Dybvik, Inndalsveien 32, 5063 BERGEN

Personvernombudet for forskning, NSD

Prosjektvurdering - Kommentar

14970

FORMÅL
Prosjektet har som hovedmål å øke kunnskapen om sammenhengen mellom kreft og behovet for hofteprotese. Et sekundærmål er å identifisere risikoen for postoperative komplikasjoner sammenlignet med en kontrollgruppe. Som tertiærmål vil en undersøke om kreftbehandling påvirker "levetiden" for en hofteprotese hos pasienter som har fått innsatt en protese før kreftdiagnosen.

UTVALG
Studiens datamateriale består av en kobling mellom data i Kreftregisteret og Leddproteseregisteret. Ca. 1 000 000 pasienter er registrert i Kreftregisteret, 90 000 i Leddproteseregisteret.

DATAMATERIALET, REGISTRERING OG OPPBEVARING
Materialet kobles ved hjelp av personnummer, koblingen foretas av Kreftregisteret som utleverer fil uten personnummer til forsker. Datafilen vil etter kobling foreligge indirekte personidentifiserende (se vedlagt variabelliste).

Datamaterialet vil oppbevares på nettverkstilkoblet pc ved virksomheten. Utover prosjektleder består prosjektgruppen av Ove Furnes, Sophie D. Fosså, Olav Reikerås, Dag Rune Olsen og Clement Trovik.

Ved prosjektslutt 31.12.2009 skal datamaterialet anonymiseres ved at indirekte personidentifiserende opplysninger slettes eller omkodes (grovkategoriseres).

VURDERING AV ANDRE INSTANSER
Prosjektleder opplyser at det er søkt Sosial- og Helsedirektoratet (SHdir) om dispensasjon fra taushetsplikten, og at prosjektet er forelagt Regional komité for medisinsk forskningsetikk (REK) for vurdering. Det forutsettes at SHdir godkjenner og at REK tilrår prosjektet, personvernombudet ber om ettersendelse av kopi av tilbakemeldingene fra disse instansene.

KOMMENTAR
Personvernombudet finner at behandlingen kan finne sted med hjemmel i personopplysningsloven §§ 8 d og 9 h.

Omkring 60% av kreftpasienter lever minimum 5 år og har dermed risiko for å utvikle seneffekter av gjennomgått kreftbehandling. Forskning på seneffekter har i stor grad vært konsentrert om kartlegging av kardiovaskulære og gonadale senbivirkninger, mens det har vært mindre fokus omkring bivirkninger knyttet til muskler og skjellett. Prosjektleder opplyser at det imidlertid er flere forhold ved kreftbehandling som kan føre til at kreftoverlevende kan ha økt risiko for å utvikle problemer knyttet til skjellettet.

Ny kunnskap om kreftbehandlings innvirkning på muskler og skjelett kan danne grunnlag for bedre og mer målrettet oppfølging av kreftoverlevende, også i forhold til plager som inntil nå ikke er satt i direkte sammenheng med kreftsykdommen og behandlingen av denne.

Behandlingen vurderes av personvernombudet å være nødvendig. Det vurderes videre at den samfunnsmessige interessen i at behandlingen finner sted klart overstiger ulempen behandlingen medfører for hver enkelt registrerte. Personvernulempen for de registrerte synes betraktelig redusert ved at det i prosjektet ikke forekommer direkte personidentifiserende opplysninger.

Ombudet finner at prosjektleder kan unntas fra sin informasjonsplikt overfor utvalget på bakgunn av dets størrelse og vanskeligheten det ville medføre å gi slik informasjon, jf. helseregisterloven § 24 annet ledd pkt. 2.

ANBEFALING
Personvernombudet anbefaler at det for prosjektet gis konsesjon til å behandle helseopplysninger i henhold til personopplysningsloven § 33.

Datatilsynet

Helse Bergen HF
Postboks 1

5021 BERGEN

Deres ref.	Vår ref. (bes oppgitt ved svar)	
Stein Atle Lie	06/01218-2 /cbr	20. september 2006

KONSESJON TIL Å BEHANDLE HELSEOPPLYSNINGER

Datatilsynet viser til Deres søknad av 31. august 2006 om konsesjon til å behandle helseopplysninger.

Datatilsynet har vurdert søknaden og gir Dem med hjemmel i helseregisterloven § 5, jf. personopplysningsloven § 33, jf. § 34, jf kreftregisterforskriften § 35, konsesjon til å behandle helseopplysninger til følgende formål: *"Kreftpasienter og hofteleddsproteser"*.

Databehandlingsansvarlig er Helse Bergen HF ved øverste leder. Gjennomføringen av det daglige ansvaret kan delegeres.

Konsesjonen er gitt under forutsetning av at behandlingen foretas i henhold til søknaden og de bestemmelser som følger av helseregisterloven med forskrifter.

Dersom det skjer endringer i behandlingen i forhold til de opplysninger som er gitt i søknaden, må dette fremmes i ny konsesjonssøknad. Det presiseres at konsesjonen, i samsvar med søknaden, er tidsbegrenset til **31.12.2009**. Personidentifiserbare data må da slettes eller anonymiseres.

Datatilsynet tar forbehold om at konsesjonen kan bli trukket tilbake eller at nye og endrede vilkår kan bli gitt dersom dette er nødvendig ut fra personvernhensyn.

Postadresse:	Kontoradresse:	Telefon:	Telefaks:	Org.nr:	Hjemmeside:
Postboks 8177 Dep 0034 OSLO	Tollbugt 3	22 39 69 00	22 42 23 50	974 761 467	www.datatilsynet.no

Dette vedtak kan påklages til Personvernnemnda i medhold av forvaltningsloven kapittel IV. Eventuell klage må sendes til Datatilsynet senest tre uker etter mottaket av dette brev.

Med hilsen

Hanne P. Gulbrandsen
seniorrådgiver

Cecilie L. B. Rønnevik
rådgiver

Kopi: Norsk samfunnsvitenskapelig datatjeneste AS, Harald Hårfagres gate 29, 5007 BERGEN (14970/GT)

Stein Atle Lie
Unifob Helse
Christiesgt. 15
5015 Bergen

Deres ref:
Saksbehandler: imp
Vår ref: 06/2834
Arkivkode:
Dato: 03.08.2006

Ad. søknad om dispensasjon fra taushetsplikt i forbindelse med forskning for prosjektet "Kreftpasienter og totale hofteleddsproteser"

Det vises til søknad av 14.06.06, om dispensasjon fra taushetsplikten i forbindelse med overnevnte forskningsprosjekt.

Det søkes om dispensasjon fra taushetsplikten for tilgang og kobling av data fra Kreftregisteret og Leddproteseregisteret. Antall pasienter som omfattes av prosjektet er ca 1 million som er registrert i Kreftregisteret og ca 90 000 som er registrert i Leddproteseregisteret.

Formålet med prosjektet er å øke kunnskapen om langtidsvirkninger av kreftbehandling. Det ønskes å se nærmere på kreftpasientens risiko for å få innsatt totalprotese i hofteleddet og eventuelt kreftsykdommens påvirkning på protesens holdbarhet.

Sosial- og helsedirektoratets vurdering:

Med hjemmel i hlspl. § 29 og fvl. § 13 innvilger Sosial- og helsedirektoratet søknad om dispensasjon fra taushetsplikt for tilgang og kobling av data fra Kreftregisteret og Leddproteseregisteret.

Direktoratets dispensasjon gis på følgende vilkår:

- at taushetsplikten i fvl. §§ 13 til 13 e og hlspl, jf. helseregisterloven (hlsregl.) § 15 overholdes
- at opplysningene behandles og oppbevares strengt konfidensielt
- at prosjektet gjennomføres i samsvar med prosjektbeskrivelsen
- at personidentifiserbare data slettes straks det ikke lenger er behov for dem og senest ved prosjektets avslutning den 31.12.09.
- at publikasjoner gis i en slik form at enkeltpersoner ikke kan gjenkjennes

Dispensasjonen gjelder prosjektleder Stein Atle Lie og prosjektmedarbeiderne Eva Dybvik, Ole Furnes, Sophie D. Fosså, Olav Reikerås, Dag Rune Olsen og Clement Trovik. Direktoratet gjør oppmerksom på at dispensasjonen kun gjelder de navngitte personer og at prosjektleder er ansvarlig for at dette overholdes.

Det forutsettes at innhenting, oppbevaring og sletting av opplysninger er i overensstemmelse med Datatilsynets bestemmelser, samt at Regional etisk komité har vurdert og tilrådet prosjektet.

Direktoratet gjør oppmerksom på helseregisterloven § 24 første ledd som pålegger en databehandlingsansvarlig å gi den som er registrert i et helseregister beskjed om innsamling av opplysninger som kommer fra andre kilder enn den registrerte. Til orientering er det direktoratets vurdering at De etter hlsregl. § 24 annet ledd nr. 2, kan unntas fra informasjonsplikten overfor de registrerte om at de aktuelle opplysningene er samlet inn. Antall personer som er omfattet vil gjøre det uforholdsmessig vanskelig å varsle. Videre vil en stor del av pasientene som omfattes være døde.

Direktoratet gjør videre oppmerksom på at brudd på taushetsplikten kan være straffbart i medhold av fvl. § 13 e tredje ledd, hlspl. § 67 og hlsregl. § 34.

Vedtak om dispensasjon fra taushetsplikten kan påklages og klagefristen er tre uker fra mottakelsen av dette brev, jfr. fvl. §§ 28 og 29. Klageinstans er Helse- og omsorgsdepartementet, men en eventuell klage skal rettes til Sosial- og helsedirektoratet. Det følger av fvl. § 18 at en part har rett til å gjøre seg kjent med sakens dokumenter, men mindre annet følger av de unntak loven oppstiller i §§ 18 og 19.

Med vennlig hilsen

Ragnhild Castberg e.f.
fung. avdelingsdirektør

Ida Marie Pedersen
førstekonsulent

KREFT registeret

MELDING TIL KREFTREGISTERET

SOLIDE SVULSTER

Kreftregisteret
postboks 5313 Majorstuen
0304 Oslo

Denne meldingen kan registreres elektronisk. Se baksiden for veiledning

Pasient/behandlingsinstitusjon

Fødselsnummer

Navn

Dato for innleggelse/konsultasjon

Sykehus

Avdeling

Lokalisasjon primærtumor

ICD-10 kode

eller

Tekst

Sideangivelse primærtumor ○ Høyre ○ Venstre ○ Begge ○ Ikke relevant ○ Ukjent

Morfologisk diagnose

Hovedgruppe og type

Ukjent ☐

Klinisk sikker cancer? ○ Ja ○ Nei ○ Usikker

Basis for kreftdiagnosen

Bildediagnostikk (Rtg, UL, CT, MR)	○ Ja	○ Nei
Celleprøve	○ Ja	○ Nei
Vevsprøve	○ Ja	○ Nei
Andre undersøkelser (f.eks. biokjemisk us, skopi, sternalmarg, kirugisk eksplorasjon)	○ Ja	○ Nei

Dersom celle -/vevsprøver er tatt; angi patologilaboratorium

Spesifiser andre undersøkelser

Diagnosedato

Obduksjon ○ Ja ○ Nei

Sykdomsutbredelse på diagnosetidspunktet

Tumor

- ☐ Ingen innvekst
- ☐ Innvekst i naboorgan/-struktur
- ☐ Ukjent

Lymfeknuter

- ☐ Ingen lymfeknutemetastaser
- ☐ Regionale lymfeknutemetastaser
- ☐ Fjerne lymfeknutemetastaser
- ☐ Ukjent

Organ- /fjernmetastaser

- ☐ Ingen organmetastaser
- ☐ Skjelettmetastaser
- ☐ Levermetastaser
- ☐ Annet
- ☐ Lungemetastaser
- ☐ Hjernemetastaser
- ☐ Ukjent

Dersom innvekst i naboorgan/-struktur; beskriv hvor

Dersom regionale; beskriv hvor

Dersom annet; beskriv hvor

Dersom fjerne; beskriv hvor

1950335657

cTNM cT cN cM eller **Stadium**

Primærbehandling

Kirurgisk behandling	○ Ja	○ Nei	○ Ukjent
Hvis ja; type behandling/operasjonsmetode			
Strålebehandling	○ Ja	○ Nei	○ Ukjent
Hormonbehandling	○ Ja	○ Nei	○ Ukjent
Cytostaticabehandling	○ Ja	○ Nei	○ Ukjent
Annen behandling	○ Ja	○ Nei	○ Ukjent
Hvilken behandling			

Kommentar

Melder

Meldedato

Melders

Melder ID

0806335656

Veiledning til utfylling av skjemaet

Dato for innleggelse/konsultasjon
Dato for når denne primære utredning/behandling er utført

Hva som skal meldes
Meldepliktig til Kreftregisteret er alle tilfeller av kreftsykdom, alle svulster i sentralnervesystemet (benigne og maligne), alle endokrine svulster (benigne og maligne), alle svulster i urinblære og alle krefttilfeller tilfeldig oppdaget ved obduksjon. Multiple primære krefttilfeller (synkrone og metakrone) meldes på separate skjemaer. Alle innleggelser for gjennomføring av førstelinjebehandling skal meldes. Ny melding må også sendes ved revisjon av tidligere meldt kreftsykdom (endret eller avkreftet diagnose).

Hvem som skal melde
Klinikere skal melde alle nydiagnostiserte tilfeller av de ovenevnte sykdomstilstander. Klinikere skal melde alle tilfeller hvor det foreligger begrunnet mistanke om kreft. Når flere sykehusavdelinger er involvert i sykdomsutredning og/eller behandling, skal krefttilfellet meldes av alle de aktuelle avdelingene. Ved tvil om meldeplikt bør melding sendes.

Utfylling av skjemaet
Det finnes forskjellige skjemaer for ulike kreftsykdommer. I tillegg til dette skjemaet for solide svulster finnes det skjema for andre kreftformer. Se https://kremt.kreftregisteret.no må benyttes.

Sykdomsopplysninger
Opplysningene skal være om sykdommens art og utbredelse på diagnosetidspunktet.

Dato sykdommen ble bekreftet
Prøvetakingsdato for første positive histologi/cytologi. Dersom vevsprøve ikke er tatt, benyttes den dato man ved hjelp av andre undersøkelser (bildediagnostikk, blodprøve etc.) stiller kreftdiagnosen.

Lokalisasjon primærtumor
Organlokalisasjonen hvor sykdommen faktisk oppsto. Meldepliktig til Kreftregisteret er alle C-diagnoser, med unntak av C44 Basalcellecarcinom. I tillegg skal disse meldes inn:D050, D051, D090, D091, D32, D33, D352, D353, D354, D391, D392, D42, D43, D443, D444, D445, D45. Multiple primære krefttilfeller (synkrone og metakrone) meldes på separate skjemaer. Kun nye kreftilfeller skal meldes. Senere utvikling av metastaser/residiv skal ikke meldes. Alle innleggelser for gjennomføring av førstelinjebehandling skal likevel meldes. Ny melding må også sendes ved revisjon av tidligere meldt kreftsykdom (endret eller avkreftet diagnose).

Morfologisk diagnose
Når det foreligger histologisk undersøkelse av biopsi, operasjonspreparat eller obduksjonspreprarat, ønskes detaljert angivelse av den morfologiske diagnosen, f.eks. "adenokarsinom, edometroid type" (ikke bare "adenokarsinom") eller "malignt melanom, superfisiell spredning" (ikke bare "malignt melanom"). Bruk gjerne allment aksepterte forkortelser.

Sykdomsutbredelse på diagnosetidspunktet
Tumors lokale vekst, regionale spredning og fjernspredning rapporteres basert på all tilgjengelig viten om sykdommen.

Kommentarer.
Dersom uttømmende informasjon om sykdommen ikke kan gis, ønskes oppgitt hvor denne kan innhentes, for eksempel dersom pasienten er henvist til annen avdeling for utredning og/eller behandling.

Elektronisk registrering

Gå inn på: https://kremt.kreftregisteret.no for å registrere denne meldingen elektronisk i stedet for på papir. Ta kontakt med kreftregisteret hvis brukernavn og passord trenges.

MELDING TIL KREFTREGISTERET

Non-solide svulster

Kreftregisteret
postboks 5313 Majorstuen
0304 Oslo

Pasient/behandlingsinstitusjon

Fødselsnr

Navn

Dato for innleggelse/konsultasjon

Sykehus

Avdeling

2436538629

Sykehus spesifiser

Avdeling spesifiser

Sykdomskategori

Hovedgruppe

- ○ Mb. Waldenstrøm **(A)**
- ○ Leukemi **(B)**
- ○ Myelomatose eller lignende plasmacelletumor **(C)**
- ○ Malign histiocytose eller lignende **(D)**
- ○ Myelodysplastisk/Myeloproliferativ sykdom **(E)**
- ○ Myelodysplastisk syndrom (MDS 1-5) **(F)**
- ○ Non - solid tumor av annen eller uklar type **(G)**

Spesifiser hvis hovedgruppe (A) Mb. Waldenstrøm

- ○ Waldenstrøms makroglobulinem med lymfoplasmacyttisk lymfom
- ○ Waldenstrøms makroglobulinem med splenisk marginalsonelymfo
- ○ Waldenstrøms makroglobulinem med B-KLL
- ○ Waldenstrøms makroglobulinem med Ekstranodalt marginalsonelymfom
- ○ Waldenstrøms makroglobulinem
- ○ Annet spesifiser

Spesifiser hvis hovedgruppe (B) (D) (G) morfologisk undergruppe

Ukjent ☐

Spesifiser hvis hovedgruppe (C) myelomatose

- ○ MGUS
- ○ Myelomatos
- ○ Solitær plasmacytom i skjelett
- ○ Solitær plasmacytom utenom skjelett
- ○ Plasmacelleleukemi (<2x10x9/l plc i blod)
- ○ Annet

Spesifiser lokalisasjon i skjelett

Spesifiser organ

Kategoriser myelomatose ○ Asymptomatisk myelomatose ○ Symptomatisk myelomatose ○ Ukjent

Spesifiser hvis hovedgruppe (E) elodysplastisk/Myeloproliferativ sykdom

- ○ Primær myelofibrose, kronisk idiopatisk myelofibrose
- ○ Kronisk myeloproliferativ sykdom uklassifiserbart
- ○ Essensiell trombocytemi
- ○ Polycytemia vera
- ○ Refraktær enemi med ringsideroblaster assosiert med markert trombocytose
- ○ Myeloproliferativ sykdom uklassifiserbar
- ○ Ekstrakutant mastocytom
- ○ Kutan mastocytose
- ○ systemisk mastocytose
- ○ Mastcellesarkom
- ○ Annet

Spesifiser hvis (F) myelodysplastisk syndrom

- ○ Refraktær anemi MDS 1
- ○ Refraktær anemi med ringsideroblaster (RARS), MDS 2
- ○ Refraktær anemi med økning av blaster (RAEB (syn. MDS 3)"
- ○ Refraktær cytopeni med flerlinje-dysplasi (multilineage dysplasia) (RCMD)
- ○ Myelodysplastisk syndrom assosiert med isolert del(5q) kromosomabnormalitet (Syn. 5q-syndrom)
- ○ Myelodysplastisk syndrom, uklassifiserbart. Myelodysplastisk syndrom MDS5
- ○ Myelodysplastisk syndrom UNS, myelodysplasi UNS
- ○ Annet

Basis for kreftdiagnosen

Fødselsnummer

Hovedgruppe

- ☐ Benmargsutstryk
- ☐ Blodutstryk
- ☐ Blodprøve
- ☐ Spinalvæskeundersøkelse
- ☐ Benmargsbiopsi
- ☐ Biopsi UNS
- ☐ Cytologi UNS
- ☐ Serum -og/eller urinelektroforese
- ☐ Annet
- ☐ Ingen

Hvis annet

- ☐ Cytokjemi
- ☐ Immunfenotyping/immunhistokjemi
- ☐ Cytogenetisk undersøkelse
- ☐ Karyotyping
- ☐ Molekylærgenetisk undersøkelse
- ☐ Annet
- ☐ Ikke utført

Bildediagnostikk

○ Ja ○ Nei

Dato sykdommen ble bekreftet

Patologilaboratorium

7726538626

Spesifiser annen prøve

Primærbehandling

Kirurgisk behandling

○ Ja ○ Nei ○ Ukjent

Strålebehandling

○ Ja ○ Nei ○ Ukjent

Cytostaticabehandling

○ Ja ○ Nei ○ Ukjent

Annen behandling

○ Ja ○ Nei ○ Ukjent

Spesifiser kirurgi

Spesifiser annen behandling

Kommentar

Kommentar

Meldedato

Melders navn

Melder ID

Veiledning til utfylling av skjemaet

Hvem som skal melde: Meldepliktig til kreftregisteret er alle tilfeller av kreftsykdom, alle forstadier til kreft, alle histologisk benigne svulster i sentralnervesystemet , alle benigne endokrine svulster, alle svulster i urinblære og alle krefttilfeller tilfeldig oppdaget ved obduksjon. Multiple primære krefttilfeller (synnkrone og metakrone) meldes på separate skjemaer. Det er som hovedregel bare nødvendig å rapportere **nye sykdomstilfeller.** Alle innleggelser for gjennomføring av førstelinjebehandling skal likevel meldes. Ny melding må også sendes ved revisjon av tidligere meldt kreftsykdom (endret eller avkreftet diagnose).

Hvem som skal melde:

Klinikere og patologilaboratorier skal melde alle nye diagnostiserte tilfeller av de ovenfor nevnte sykdomstilstander. Klinkikere skal i tillegg melde alle tilfeller hvor det foreligger begrunnet mistanke om kreft. Når flere sykehusavdelinger er involvert i sykdomsutredning og/eller behandling, skal krefttilfellet meldes av alle de aktuelle avdelingene. Ved tvil om meldeplikt bør melding sendes.

Utfylling av skjemaet:

Det finnes forskjellige skjemaer for ulike kreftsykdommer. I tillegg til dette skjemaet for non-solid svulst finnes skjema for solid svulst og spesialskjemaer for brystkreft, ovariekreft og malignt lymfom/kronisk lymfatisk leukemi. Riktig skjema må benyttes. Operasjonsbeskrivelse må vedlegges hvis det er utført kirurgisk behandling.

Dato for innleggelse/konsultasjon:

Dato for når denne primære utredning/behandling er utført

Dato sykdommen ble bekreftet:

Prøvetakingsdato for første positive histologi/cytologi. Dersom vevsprøve ikke er tatt, benyttes den dato man ved hjelp av andre undersøkelser(billeddiagnostikk, blodprøve etc) stiller kreftdiagnosen.

Sykdomskategori og morfologisk undergruppe:

Hovedkategori av non-solide svulster som sykdomstilfellet tilhører angis ved avkrysning (leukemi, myelomatose, etc.). I tillegg angis *morfologisk undergruppe* med den grad av nøyaktighet som de tilgjengelige diagnostiske hjelpemidler har git anledning til.

Sykdommens lokalisasjon/debutorgan: For non-solide svulster med begrenset utbredelse på diagnosetidspunktet, kan det være mulig å angi i hvilket organ eller hvilken region sykdommen hadde sitt utspring, f.eks. non-Hodgkin lymfom i magesekk eller hodgkin lymfom med affeksjon bare av lymfeknuter på halsen

Basis for kreftdiagnosen:

De diagnostiske prosedyrer som danner grunnlaget for diagnosen, avkrysses. For undersøkelser utført i patologi-laboratorium anføres remissenummer og år samt laboratorium ansvarlig for undersøkelsen.

Nasjonalt Register for Leddproteser
Ortopedisk klinikk, Helse Bergen HF
Haukeland universitetssjukehus
Møllendalsbakken 11, 5021 BERGEN
Tlf 55973742/55973743

F.nr. (11 sifre).....

Navn:.....
(Skriv tydelig ev. pasient klistrelapp – **spesifiser sykehus**.)

Sykehus:.....

HOFTEPROTESER

ALLE TOTALPROTESER I HOFTELEDD REGISTRERES. Innsetting, skifting og fjerning av totalproteser i hofteledd, samt kantplastikk, bløtdelsrevisjon for infisert protese og hemiproteser på annen indikasjon enn fraktur/fraktursekvele. Hemiprotese for fraktur/fraktursekvele registreres på Hoftebruddskjema.

TIDLIGERE OPERASJON I AKTUELLE HOFTE (ev. flere kryss)
- ☐ 0 Nei
- ☐ 1 Osteosyntese for fraktur i prox. femurende
- ☐ 2 Hemiprotese pga. fraktur
- ☐ 3 Osteotomi
- ☐ 4 Artrodese
- ☐ 5 Totalprotese(r)
- ☐ 6 Annen operasjon .....

OPERASJONSDATO (dd.mm.åå) ☐☐.☐☐.☐☐

AKTUELLE OPERASJON (ett kryss)
- ☐ 1 Primæroperasjon (også hvis hemiprotese tidligere)
- ☐ 2 Reoperasjon (totalprotese tidligere)
- ☐ 3 Primær hemiprotese for annen indikasjon enn fraktur/fraktursekvele

AKTUELLE SIDE (ett kryss) (Bilateral opr.= 2 skjema)
☐ 1 Høyre ☐ 2 Venstre

ÅRSAK TIL AKTUELLE OPERASJON (KRYSS AV ENTEN I A ELLER B)

A Primæroperasjon pga. (evt. flere kryss)
- ☐ 1 Idiopatisk coxartrose
- ☐ 2 Rheumatoid artritt
- ☐ 3 Sekvele etter frakt. colli. fem.
- ☐ 4 Sekv. dysplasi
- ☐ 5 Sekv. dysplasi med total luksasjon
- ☐ 6 Sekv. Perthes
- ☐ 7 Sekv. Epifysiolyse
- ☐ 8 Mb. Bechterew
- ☐ 9 Akutt fraktura colli femoris
- ☐ Annet .....
  (f.eks caputnekrose, tidl. artrodese o.l)

B Årsak til reoperasjon (evt. flere kryss)
- ☐ 1 Løs acetabularkomponent
- ☐ 2 Løs femurkomponent
- ☐ 3 Luksasjon
- ☐ 4 Dyp infeksjon
- ☐ 5 Fraktur (i acetabulum)
- ☐ 6 Fraktur (av femur)
- ☐ 7 Smerter
- ☐ 8 Osteolyse i acetab. uten løsning
- ☐ 9 Osteolyse i femur uten løsning
- ☐ 10 Implantatfraktur femurdel
- ☐ 11 Implantatfraktur caput
- ☐ 12 Implantatfraktur kopp
- ☐ 13 Implantatfraktur liner
- ☐ 14 Implantatfraktur annet: .....
- ☐ Annet .....
  (f.eks Girdlestonesituasjon etter tidl. infisert protese)

REOPERASJONSTYPE (ev. flere kryss)
- ☐ 1 Bytte av femurkomponent
- ☐ 2 Bytte av acetabularkomponent
- ☐ 3 Bytte av hele protesen
- ☐ 4 Fjernet protese og satt inn sementspacer
- ☐ 5 Fjernet sementspacer og satt inn ny protese
- ☐ 6 Fjernet protese (Girdlestone eller fjerning av sementspacer)
  Angi hvilke deler som ble fjernet .....
- ☐ 7 Bytte av plastforing
- ☐ 8 Bytte av caput
- ☐ 9 Bløtdelsdebridement for infisert protese
- ☐ Andre operasjoner .....

TILGANG (ett kryss)
- ☐ 1 Fremre (Mellom sartorius og tensor)
- ☐ 2 Anterolateral (Mellom glut. medius og tensor)
- ☐ 3 Direkte lateral (Transgluteal)
- ☐ 4 Bakre (Bak gluteus medius)
- ☐ 5 Annen .....

MINIINVASIV KIRURGI (MIS) ☐ 0 Nei ☐ 1 Ja

LEIE ☐ 0 Sideleie ☐ 1 Rygg

TROKANTEROSTEOTOMI ☐ 0 Nei ☐ 1 Ja

BENTRANSPLANTASJON (ev. flere kryss)
Acetabulum ☐ 0 Nei ☐ 1 Ja ☐ 2 Benpakking
Femur ☐ 0 Nei ☐ 1 Ja ☐ 2 Benpakking a.m. Ling/Gie

BENTAP VED REVISJON (Paprosky's klassifikasjon se baksiden)
Acetabulum ☐ 1 I ☐ 2 IIA ☐ 3 IIB ☐ 4 IIC ☐ 5 IIIA ☐ 6 IIIB
Femur ☐ 1 I ☐ 2 II ☐ 3 IIIA ☐ 4 IIIB ☐ 5 IV

PROTESEKOMPONENTER
(Bruk klistrelapp på baksiden, eller spesifiser nøyaktig)

Acetabulum
Navn/Type .....
ev. katalognummer .....
☐ Med hydroksylapatitt ☐ Uten hydroksylapatitt
☐ 1 Sement med antibiotika – Navn .....
☐ 2 Sement uten antibiotika – Navn .....
☐ 3 Usementert

Femur
Navn/Type .....
ev. katalognummer .....
☐ Med hydroksylapatitt ☐ Uten hydroksylapatitt
☐ 1 Sement med antibiotika – Navn .....
☐ 2 Sement uten antibiotika – Navn .....
☐ 3 Usementert
☐ 4 Resurfacing

Caput
☐ 1 Fastsittende caput
☐ 2 Separat caput - Navn/Type .....
ev. katalognummer .....
Diameter .....

SYSTEMISK ANTIBIOTIKA
☐ 0 Nei ☐ 1 Ja: ☐ 1 Profylakse ☐ 2 Behandling

	Navn	Dosering	Varighet i timer (døgn)
Medikament 1	.....	.....	.....timer (.....døgn)
Medikament 2	.....	.....	.....timer (.....døgn)
Medikament 3	.....	.....	.....timer (.....døgn)

TROMBOSEPROFYLAKSE
☐ 0 Nei ☐ 1 Ja: Første dose ☐ 1 Preoperativt ☐ 2 Postoperativt
Medikament 1 ..... Dosering opr.dag.....
Dosering videre ..... Varighet ..... døgn
Medikament 2 ..... Dosering ..... Varighet ..... døgn

Fast antikoagulasjon
☐ 0 Nei ☐ 1 Ja, type .....

FIBRINOLYSEHEMMER
☐ 0 Nei ☐ 1 Ja, medikament: ..... Dosering .....

OPERASJONSSTUE
- ☐ 1 "Green house"
- ☐ 2 Operasjonsstue med laminær luftstrøm
- ☐ 3 Vanlig operasjonsstue

OPERASJONSTID (hud til hud) .....min

PEROPERATIV KOMPLIKASJON
☐ 0 Nei
☐ 1 Ja, hvilke(n) .....

ASA KLASSE (se baksiden for definisjon)
- ☐ 1 Frisk
- ☐ 2 Asymptomatisk tilstand som gir økt risiko
- ☐ 3 Symptomatisk sykdom
- ☐ 4 Livstruende sykdom
- ☐ 5 Moribund

Lege .....
Legen som har fylt ut skjemaet (navnet registreres ikke i databasen).

RETTLEDNING TIL HOFTEPROTESER

Registreringen gjelder innsetting, skifting og fjerning av totalproteser i hofteledd, samt kantplastikk, bløtdelsrevisjon for infisert protese og hemiproteser på annen indikasjon enn fraktur/fraktursekvele. Hemiprotese for fraktur/ fraktursekvele registreres på Hoftebruddskjema. Ett skjema fylles ut for hver operasjon. Fødselsnummer (11sifre) og sykehusnavn må påføres. Aktuelle ruter markeres med kryss. På eget Samtykkeskjema skal pasienten gi samtykke til rapportering til Leddregisteret. Samtykkeskjema skal lagres i pasientjournal.

AKTUELLE OPERASJON

Primæroperasjoner: Dette er første totalproteseoperasjon.

Reoperasjon (totalprotese tidligere): Fjerning av protesedeler (f.eks. Girdlestone) må registreres. Kantplastikk (f. eks. PLAD) og bløtdelsrevisjoner for infeksjon registreres selv om protesedeler ikke skiftes.

Primær hemiprotese for annen indikasjon enn fraktur/fraktursekvele: Hemiprotese for fraktur/fraktursekvele registreres på Hoftebruddskjema.

ÅRSAK TIL AKTUELLE OPERASJON

Kryss av under A ved primæroperasjoner og under B ved reoperasjoner. I B må du krysse av for alle årsakene til reoperasjon, eller forklare med fritekst.

REOPERASJONSTYPE

Fjerning av protesedeler (f.eks. Girdlestone) må registreres. Kantplastikk (f. eks. PLAD) og bløtdelsrevisjoner for infeksjon registreres selv om protesedeler ikke skiftes.

TILGANG

Det vises til artikkel: Reigstad A, Blom Hagen T. Snittføring ved totalplastikk i hofteleddet.Tidsskr Nor Laegeforen. 1985 Mar 30;105(9-10):677-9.

BENTRANSPLANTASJON Benpropp som sementstopper regnes ikke som bentransplantat.

PROTESEKOMPONENTER: Acetabulum - Femur - Caput - Trokanterdel og hals hvis disse er separate deler

Bruk helst klistrelappene som følger med protesen. Lim disse på baksiden av skjema. Alternativt, skriv inn protesenavn + katalognummer eller protesenavn + størrelse, materiale, overflatebelegg og design. Sementnavn må anføres.

KOMPLIKASJONER Også operasjoner hvor pasienter dør på operasjonsbordet eller rett etter operasjon skal meldes.Ved stor stor blødning, angi mengde.

ASA-KLASSE (ASA=American Society of Anesthesiologists)

ASA-klasse 1: Friske pasienter som røyker mindre enn 5 sigaretter daglig.

ASA-klasse 2: Pasienter med en asymptomatisk tilstand som behandles medikamentelt (f.eks hypertensjon) eller med kost (f.eks diabetes mellitus type 2) og ellers friske pasienter som røyker 5 sigaretter eller mer daglig.

ASA-klasse 3: Pasienter med en tilstand som kan gi symptomer, men som holdes under kontroll medikamentelt (f.eks moderat angina pectoris og mild astma).

ASA-klasse 4: Pasienter med en tilstand som ikke er under kontroll (f.eks hjertesvikt og astma).

ASA-klasse 5: Moribund/døende pasient

MINIINVASIV KIRURGI (MIS = Minimally Invasive Surgery**)**

Med MIS menes her at kirurgen har brukt kort snitt og at det er brukt spesialinstrument laget for MIS

SYSTEMISK ANTIBIOTIKA

Her føres det på hvilket antibiotikum som er blitt benyttet i forbindelse med operasjonen, f.eks.: Medkament 1: Keflin 2g x 4, med varighet 12 timer.

TROMBOSEPROFYLAKSE

Medikament, dose og antatt varighet av profylaksen skal angis separat for oprerasjonsdagen og senere. Det skal også oppgis om pasienten står fast på antikoagulantia (AlbylE, Marevan, Plavix ol).

FIBRINOLYSEHEMMER

Her føres det på om en benytter blødningsreduserende legemidler i forbindelse med operasjonen (f.eks. Cyklokapron).

BEINTAP VED REVISJON

Femur (Paprosky`s klassifikasjon)

Type I: Minimalt tap av metafysært ben og intakt diafyse.

Type II: Stort tap av metafysært ben, men intakt diafyse.

Type IIIA: Betydelig tap av metafysært ben uten mulighet for proximal mekanisk støtte. Over 4 cm intakt corticalis i isthmusområdet.

Type IIIB: Betydelig tap av metafysært ben uten mulighet for proximal mekanisk støtte. Under 4 cm intakt corticalis i isthmusområdet.

Type IV: Betydelig tap av metafysært ben uten mulighet for proximal mekanisk støtte. Bred isthmus med liten mulighet for cortical støtte.

Acetabulum (Paprosky`s klassifikasjon)

Type I: Hemisfærisk acetabulum uten kantdefekter. Intakt bakre og fremre kolonne. Defekter i forankringshull som ikke ødelegger subchondral benplate.

Type IIA: Hemisfærisk acetabulum uten store kantdefekter, intakt bakre og fremre kolonne, men med lite metafysært ben igjen.

Type IIB: Hemisfærisk acetabulum uten store kantdefekter, intakt bakre og fremre kolonne, men med lite metafysært ben igjen og noe manglende støtte superiort.

Type IIC: Hemisfærisk acetabulum uten store kantdefekter, intakt bakre og fremre kollonne, men med defekt i medial vegg.

Type IIIA: Betydelig komponentvandring, osteolyse og bentap. Bentap fra kl. 10 til 2.

Type IIIB: Betydelig komponentvandring, osteolyse og bentap. Bentap fra kl. 9 til 5.

Kopi beholdes til pasientjournalen, originalen sendes Haukeland universitetssjukehus.

Kontaktpersoner vedrørende registreringsskjema er

Overlege Leif Ivar Havelin, tlf.: 55 97 56 87 og klinikkoverlege Ove Furnes, tlf.: 55 97 56 80

Ortopedisk klinikk, Haukeland universitetssjukehus. Besøksadresse: Møllendalsbakken 11.

Sekretærer i Nasjonalt Register for Leddproteser, Ortopedisk klinikk, Helse Bergen:

Ingunn Vindenes, tlf.: 55 97 37 43 og Ruth Wasmuth, tlf.: 55 97 37 42

Epost nrl@helse-bergen.no

Internet: http://www.haukeland.no/nrl/