A POPULATION-BASED ANALYSIS OF THE RISK OF HIP FRACTURE IN MEN WITH PROSTATE CANCER EXPOSED TO RADIATION AND ANDROGEN DEPRIVATION THERAPY

by

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Abstract

Prostate cancer is frequently diagnosed in elderly men and, despite the largely unproven survival benefits of treatment, the majority receive treatment. Treatment options include surgery, radiation, and/or androgen deprivation therapy (ADT). Risks associated with treatment include hip fracture. Current understanding suggests that hip fracture is a frequent cause of morbidity and mortality in the elderly, and both radiation treatment and ADT can increase the risk of hip fracture. It is important to understand these risks so they can be minimized and the morbidity of treatment reduced.

The objectives of this study were to estimate the risk of hip fracture as a major adverse outcome of treatment for prostate cancer among elderly men. The specific objectives include estimating: 1) the risk of hip fracture and the dose-risk relationship among patients receiving curative radiation treatment, and 2) the risk of hip fracture associated with palliative ADT and relapsed ADT compared to curative ADT.

The cancer diagnosis and treatment records of 32,673 men were linked to their hospital discharge abstracts. The risk of hip fracture was estimated using Cox regression and the estimates were adjusted for age, comorbidity, income, and year of diagnosis.

The risk of hip fracture was 59% higher among men who received curative radiation when compared to men who received curative surgery. The risk of hip fracture fell by 6% with each one Gy increase in radiation dose between 55 and 81 Gy Biological Equivalent Dose to the hip-bone. The risk of hip fracture for subjects in the palliative ADT and relapsed ADT categories was 5.98 and 5.77 times the risk in comparison to men who received curative ADT treatment.

Curative radiation treatment is associated with an increased risk of hip fracture when compared to curative surgery. The risk of hip fracture is greater with ADT for palliation and relapsed cancer than with curative treatment. Current treatments for prostate cancer contain significant risk of hip fracture for elderly men and these risks should be considered as part of the treatment decision.

Contents

List of Tables

List of Figures

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Dedication

To Dawn, Kate, Jennie, and Craig.

Chapter 1: Introduction

There has been a significant increase in the number of men diagnosed with prostate cancer in the last two decades because of increased use of prostate specific antigen (PSA) testing for early detection of this disease. Accompanying this increased rate of detection is an increase in the number of men receiving treatment for prostate cancer. Treatment options include surgery, radiation, and androgen deprivation therapy. Traditionally, androgen deprivation was accomplished by orchiectomy, and is now most commonly achieved with Luteinizing Hormone Releasing Hormone (LHRH) injections. Approximately 65% of men with prostate cancer will be treated by temporary or permanent androgen deprivation. Androgen deprivation results in an accelerated loss of bone mineral leading to osteoporosis, in a mechanism similar to the development of osteoporosis in women after menopause. It is well established that osteoporosis increases the risk of bone fractures. Osteoporotic bone fractures are now a major cause of morbidity and mortality, and are the fifth leading cause of hospitalization in the elderly in the US.

Approximately 40% of men treated for prostate cancer receive radiation treatment. The prostate is centered between the hip-bones, and the hip-bones are frequently irradiated during prostate cancer radiation treatment. Radiation can increase bone fragility, and may increase the risk of bone fracture.

The increased risk of hip fracture after androgen deprivation therapy (ADT) has been examined in several studies using population health data in men with prostate cancer, but there are few comparable studies on the effects of radiation treatment on hip fracture. In addition, the existing studies of ADT and hip fracture have not distinguished between the distinctly different indications for ADT treatment in men with prostate cancer, which include curative treatment combined with surgery or radiation, treatment for relapsed cancer after surgery or radiation, and palliative treatment of advanced and metastatic disease. It is possible that ADT will have a different impact on the risk of hip fracture depending on the indication for treatment because of differences in age, comorbidity, and other factors in men who receive ADT for different treatment indications.

This study used population health data for men with prostate cancer diagnosed in British Columbia (BC) between 1986 and 2000. The study linked BC Cancer Agency records for

LHRH injections and radiation treatment to hospital separation abstracts for curative prostatectomy, orchiectomy and hip fractures.

The primary objectives of this study were: (1) to measure the association between radiation treatment and the risk of hip fracture in men receiving curative treatment for prostate cancer, (2) to estimate the radiation dose to the hip in men receiving curative treatment for prostate cancer and to determine the relationship between radiation dose to the hip and the risk of hip fracture, and (3) to categorize men with prostate cancer according to the indications for ADT and to examine the relationship between duration of ADT and the risk of hip fracture for these different categories.

Chapter 2: Background

This population-based study examines the associations between prostate cancer treatment and hip fracture. This chapter introduces the concepts of prostate cancer, prostate cancer treatment, and hip fracture, and presents a framework for the concepts underlying the study. Subsequently, the study hypotheses and the rationale for the study design are presented. Finally, the ways in which this study expands on existing work are explained.

2.1: Introduction to Prostate Cancer Epidemiology and Treatment

This section explains who is likely to be diagnosed with prostate cancer, describes how prostate cancer is staged after diagnosis, and discusses the benefits and risks of prostate cancer treatment.

2.1.1: Prostate Cancer Epidemiology

Prostate cancer is the most frequently diagnosed cancer in men. In Canada, one in eight men (12.5%) will be diagnosed with prostate cancer during their lifetime (1). Prostate cancer is predominantly a disease of older men. A 60-year-old man has a 17.5% risk of being diagnosed with prostate cancer during the rest of his life, in contrast, the risk of being diagnosed with prostate cancer before the age of 50 is only 0.2% (2).

Whilst a frequent diagnosis, prostate cancer is an infrequent cause of death; only 1 in 27 men (4%) die from prostate cancer (1). Because of the high incidence and low mortality, there are a large number of men living with a diagnosis of prostate cancer. Currently 0.8% of the Canadian male population are living with this diagnosis (1).

2.1.2: Prostate Cancer Diagnosis, Staging and Prognosis

Prostate cancer is most often diagnosed from trans-rectal core needle biopsies of the prostate. The indications for biopsy are a raised blood level of prostate specific antigen (PSA), or an abnormal prostate on digital rectal exam. Occasionally, prostate cancer is found incidentally after trans-urethral prostatectomy, which is performed to relieve symptoms of prostatic obstruction. Prostate cancer prognosis is strongly associated with the stage and grade of the cancer at diagnosis. Cancer stage is based on the extent of cancer at diagnosis, and is classified according to the international Tumour, Node, and Metastasis (TNM) staging system (Appendix A). At diagnosis, 91% of prostate tumours are localized within the prostate capsule (stage T1 or T2), 5% are locally advanced, having spread outside of the prostate capsule (stage

T3 or T4), and 4% have metastasized (stage M1), most commonly to bone (3). Lymph node involvement (stage N1) is imprecisely staged in prostate cancer, because pelvic lymph nodes are not reliably visualized on CT scans, and most men do not have lymph node biopsies.

A pathologist assigns cancer grade after microscopic examination of the tissue. The pathologist grades the degree of differentiation of the cancer from normal prostate tissue using the Gleason grading system (Appendix A). At diagnosis, 66% of prostate cancers are well differentiated (grade 2-6), 25% are moderately differentiated (grade 7), and 9% are poorly differentiated (grade 8-10) (4). Therefore, the majority of prostate cancers are low grade, well differentiated (grade 2-6) and localized to the prostate (stage T1-2). These cancers are extremely indolent, with almost 100% survival at twenty years after diagnosis (5). In contrast, survival with high grade poorly differentiated cancers is less than 10% at twenty years, irrespective of stage (5).

2.1.3: Prostate Cancer Treatment

Prostate cancer is treated predominantly with surgery, radiation, and androgen deprivation therapy (ADT). In Canada, a small number of men are treated by cryotherapy (freezing of the prostate) or high-intensity focused ultrasound (HIFU). Not all men require treatment. Because prostate cancer often progresses very slowly and many men diagnosed with prostate cancer are elderly, they are more likely to die from causes other than prostate cancer. These men are managed by "watchful waiting" or "active surveillance", which is observation without treatment until the cancer causes symptoms.

The treatment recommendations for radiation, surgery, ADT or watchful waiting are based on the stage and grade of the prostate cancer and on the age and comorbidity of the patient. Approximately one-third of men with localized prostate cancer receive curative treatment with radiation and one-third receive curative surgery (6). Of the men not treated with curative surgery or radiation because of comorbidity, approximately one-third receive ADT immediately after diagnosis, in the absence of symptoms (7).

Despite the frequent use of curative radiation and surgery for localized prostate cancer, there is only one randomized study that has looked at whether treatment of localized prostate cancer improves survival when compared to no treatment. This was a study of 695 men who were randomly assigned to prostatectomy or watchful waiting (8). During a median of 8.2 years of follow-up, 83 men in the prostatectomy group and 106 men in the watchful-waiting group died of any cause (P=0.04), but fewer than half of all deaths were due to prostate cancer. The

implications of these findings are that the survival benefits of curative treatment for localized prostate cancer are likely to be small because prostate cancer is a slowly progressive disease and most men diagnosed with prostate cancer do not die from prostate cancer.

There are no randomized studies comparing curative radiation treatment of localized prostate cancer to no treatment. However, there are several studies of intermediate and high-risk localized prostate cancers comparing radiation treatment alone to radiation treatment combined with ADT (9-11). These studies have shown improved survival with radiation in combination with ADT for localized high-risk prostate cancers and ADT is now routinely administered together with curative radiation for treatment of localized prostate cancer.

Men with a short life expectancy or with locally advanced or metastatic cancer may be treated with ADT alone, with palliative radiation or surgery being used, if necessary, to treat symptoms such as urinary obstruction, pain, or bleeding. ADT slows the progression of prostate cancer and shrinks prostate tumours by reducing the production of testosterone. Without testosterone, prostate cancer cells die or become quiescent. ADT is administered either by orchiectomy (surgical removal of the testicles), or by Luteinizing Hormone Releasing Hormone (LHRH) injections that suppress testosterone production by the testicles. Traditionally, the only indication for orchiectomy for prostate cancer was palliation of symptoms of advanced disease. However, since the mid-1990s, orchiectomy has generally been replaced by the use of LHRH injections, and the indications for ADT have expanded to include treatment combined with curative radiation or surgery, treatment of asymptomatic cancer which has recurred after curative radiation or surgery, as well as palliation of locally advanced or metastatic cancer (12, 13). This latter group includes men without symptoms who are not suitable for curative treatment because of comorbidity and a short life expectancy (7). It is now estimated that 65% of men with prostate cancer will receive ADT at some point during their prostate cancer treatment (14).

The quality of the evidence supporting the use of ADT varies widely for different treatment indications. Randomized trials have shown a survival benefit for ADT together with curative radiation (9-11, 15-18), and also for ADT for metastatic cancer (19). No survival benefit has been demonstrated for ADT together with prostatectomy (20-26) and no randomized trials have been completed of ADT as primary treatment for localized cancer, or for relapsed cancer after curative radiation or surgery.

The duration of ADT also varies widely by treatment indication. ADT together with curative radiation for localized prostate cancer is administered for periods of 6 months to 3 years

(9, 11) while the median duration of ADT for metastatic cancer is two years (19). The median duration of ADT for relapsed cancer after surgery is thirteen years (27).

ADT becomes ineffective when prostate cancer starts to progress despite the absence of testosterone. This is called the hormone resistant or androgen-independent phase of prostate cancer. Men treated with ADT for metastatic prostate cancer develop androgen independence after one to two years (19), and androgen independence develops after a median of eight years of ADT for relapsed cancer after surgery (27).

In an attempt to delay the onset of androgen independence, LHRH injections are sometimes administered intermittently rather than continuously (28). Intermittent ADT allows recovery of testosterone after each cycle of ADT. Androgen deprivation commences when serum testosterone reaches castrate levels, which occurs 12 hours after orchiectomy (29) and an average of one month after administration of an LHRH injection (30). LHRH injections are depot formulations that produce a sustained suppression of testosterone for 0.5, 1, 2, 3, 4 or 6 months, depending on the dose and formulation that is administered. The duration of ADT exposure is lifelong after orchiectomy, but serum testosterone levels recover after LHRH injections are discontinued (28). In 13 men who received LHRH injections prior to prostatectomy, the median time to return of normal serum testosterone levels was six months after a single 3-month injection (31). A median time of six months to testosterone recovery was also observed after six months of LHRH injections in 80 men with prostate cancer that had recurred after radiation or surgery (32). In a study of 267 men who received LHRH injections with curative radiation for localized prostate cancer, the median time to normalization of testosterone was ten months after a median duration of ADT of eleven months (ADT duration range 3 - 35 months), and the time to testosterone recovery was not significantly associated with the duration of ADT (33). Trials are currently underway to determine whether intermittent ADT leads to longer survival compared to continuous ADT.

2.1.4: Side Effects of Prostate Cancer Treatment

Although there is a paucity of data regarding the benefits of prostate cancer treatment, there is ample evidence that these treatments are associated with significant side effects. The most common untoward effects of surgery are impotence and urinary incontinence, which are reported by 77% and 14% of men respectively (34). The most commonly reported side effects of radiation treatment are impotence, fecal urgency, and diarrhea, which affect 73%, 33% and 29% of men respectively (34). The side effects of ADT include hot flashes, weight gain, fatigue,

forgetfulness, emotional lability, loss of libido, and loss of bone mineral density (35). Weight gain may precipitate the metabolic syndrome, with an increased risk of heart attack and stroke. The loss of bone mineral density associated with ADT increases as the duration of ADT exposure increases (36).

As discussed previously, prostate cancer predominantly affects older men, and these men are likely to live many years after diagnosis and treatment. Therefore, it is important to consider treatment side effects that affect men's health as they age. Hip fractures have a significant impact on the health of elderly men. The rate of hip fracture in men increases exponentially with age, rising from 0.9 per 1,000 men at age 65 to 26.0 per 1,000 at age 95 (37). There is evidence to suggest that both radiation and ADT can increase the risk of hip fracture in men treated for prostate cancer.

2.1.4.1: Radiation Effects on the Hip-bone

The radiation dose that is administered to cure prostate cancer typically varies from 50 to 74 Gray. Gray, abbreviated Gy, are the System International (S.I.) units of radiation dose. Radiation treatments are administered in a series of small doses (or fractions) of approximately two Gy each, and a curative course of radiation treatment for prostate cancer typically consists of 20 to 37 fractions administered daily over four to seven weeks. The Biological Equivalent Dose formula is used to convert different dose/fractionation schemes into radiation units (Gy BED) with equivalent biological effects on normal tissue and tumours (38).

During radiation treatment, the hip-bone receives part of the radiation dose that is delivered to the prostate, and this radiation causes bone injury by two mechanisms. Firstly, blood vessel walls become thickened after radiation, resulting in a reduction of blood flow and a fall in bone tissue oxygenation. Secondly, radiation reduces the number of bone-forming cells, leading to a reduction in new bone formation (39). These radiation injuries lead to bone atrophy. The degree of atrophy increases with increasing radiation dose (39), and this radiation-induced atrophy reduces bone strength (39).

Although the microscopic changes in bone tissue that lead to bone atrophy after radiation are well documented, the relationship between radiation dose and bone strength is less clear. The tensile strength of cadaveric bone is reduced when exposed to high doses of radiation, but these doses are many times higher than the radiation dose received by the hip during prostate cancer treatment (40). Studies of bone strength in irradiated rodents have produced conflicting

results in the dose ranges that are used to treat prostate cancer (41, 42). Some studies have shown an increase in bone strength, whereas others have shown a decrease (39).

Most reports of hip fracture associated with radiation treatment to the pelvis have been isolated cases, predominantly in women who received radiation treatment for pelvic malignancies (43-47). There is one population-based study of pelvic fractures in women with pelvic malignancies that compared fracture rates in irradiated and non-irradiated women (48). This study reported a hazard rate for pelvic fractures of 3.16 for anal cancer, 1.66 for cervical cancer, and 1.65 for rectal cancer, after controlling for race, age, and cancer stage, and 90% of the pelvic fractures were hip fractures. The study did not report on the rate of hip fracture with respect to the radiation dose received by the hip-bone. There are no comparable population-based studies of hip fracture after pelvic radiation in men.

The radiation dose-response curve is the graphical plot of the relationship between radiation dose and the biological effect measured at that radiation dose. In general, there is little biological effect in most subjects up to a threshold dose, and the slope of the response curve is relatively flat up to the threshold dose. Above the threshold dose, the response curve rises and is approximately linear up to a saturation dose. Above the saturation dose, the response curve flattens again, because the biological effect occurs in almost all subjects at radiation doses above the saturation dose. Thus the radiation response curve resembles an "S" shape, which is termed a sigmoid dose-response curve (49).

There is very little epidemiological data on the dose-response relationship between radiation dose to the hip-bone and the risk of hip fracture. The US National Cancer Institute sponsored a review of the dose effects of radiation treatment on normal tissues that was published by Emami and colleagues in 1991 (50). They estimated a 5% risk of hip fracture at 5 years after a dose of 52 Gy, and a 50% risk of hip fracture at 5 years after 65 Gy, when radiation treatment is administered at 2 Gy per day. Interpretation of this data suggests a 45% increase in the risk of hip fracture for a 13 Gy increase in radiation dose. However, in their review the authors wrote, "There is no volume data available, and all data are very imprecise." In particular, there was insufficient data to establish a threshold dose below which there is no risk of radiation-related hip fracture. In view of the large number of elderly men who receive radiation treatment for prostate cancer and their long survival after treatment, it is important to further investigate whether there is an increase in hip fractures associated with prostate radiation, and whether a radiation dose-response relationship can be established.

2.1.4.2: ADT Effects on the Hip-bone

ADT suppresses the production of both testosterone and estrogen in men. Both of these hormones are necessary to maintain bone mineralization (51), and their reduction leads to bone mineral loss and osteoporosis. The rate of bone mineral loss in men treated with ADT is similar to that seen in women after menopause (52). It is established that osteoporosis is a risk factor for hip fracture, and that the rate of hip fracture doubles for each 2% loss of bone mineral density (53). Studies of bone mineral density (BMD) after exposure to ADT in men with prostate cancer show a gradual decline in BMD at the hip, which is detectable after 6 months of exposure (52).

There are three population-based studies that reported on hip fractures in men with prostate cancer exposed to ADT (54-56), and two studies that reported on fractures at any site (57, 58). Dickman et al studied men in a Swedish population registry and reported that the risk of hip fracture from diagnosis until death was 1.6 in men exposed to ADT within 6 months of diagnosis, compared to men not exposed to ADT (54). Using the data from a longitudinal study of men in Olmsted County, Minnesota, Melton and colleagues reported a Standardized Incidence Rate of 1.91 for hip fracture in men exposed to ADT compared to the general population (55). Shahinian et al used data from the Surveillance, Epidemiology, and End Results (SEER) program linked to Medicare claims, and found a hip fracture rate of 4.06% during the 12 to 60 months after prostate cancer was diagnosed in men who were exposed to ADT within six months of diagnosis, compared to 2.06% in men who were not exposed to ADT, after adjustment for other prostate cancer treatment (radiation or surgery) (56).

However, none of these studies identified the indications for which ADT was administered. In other words, the men included in these studies will have received ADT for several indications including curative treatment of localized cancer, treatment of cancer that has recurred after radiation or surgery, as well as palliation of symptoms of advanced cancer. It is very likely that men who receive ADT for different treatment indications will differ in age, comorbidity, and other factors such as cancer stage and grade and treatment that may confound the relationship between ADT exposure and hip fracture. In addition, as discussed previously, the median duration of ADT varies widely according to treatment indication, ranging from 6 months to 3 years with curative radiation, to thirteen years with ADT for relapsed cancer after surgery. ADT is being used more frequently as a sole treatment for palliation of newly diagnosed prostate cancer, with potentially many years of exposure to the osteoporotic effects of androgen deprivation (7). Therefore the overall risk of bone mineral loss due to ADT, and subsequent hip fracture, may be greater in the setting of ADT for palliative treatment or for

relapsed cancer than in the setting of curative treatment, even after adjustment for ADT duration. In this case ADT duration would be considered as a control variable rather than as a study variable because the principle variable of interest is the indication for ADT. Because ADT is administered to men with widely different indications, it is important to know whether the risks of fracture associated with ADT are higher or lower in men who receive ADT for different treatment indications.

In summary, prostate cancer is a diagnosis of elderly men. Despite the fact that the benefits of treatment are small or unproven, the majority of men receive treatment for their prostate cancer, and most survive for many years after diagnosis. Given the uncertain benefits of prostate cancer treatment, it is important to consider the risks of treatment because it may be possible to reduce these risks, or to reduce the number of men exposed to these risks. This study focuses on the risks of hip fracture associated with radiation treatment and ADT.

2.2: Introduction to Hip Fracture Epidemiology and Treatment

Hip-bones break when the forces applied to the bone exceed the strength of the bone. Elderly men experience a progressive loss of bone strength and, as they age, they are at increased risk of falling, which applies excessive force to the hip (59). Because of progressive loss of bone strength and increased risk of falls, the rate of hip fracture increases exponentially with age (60). Overall, one in eight Canadian men experience a hip fracture by 80 years of age (60).

Loss of bone mineral density (BMD) is the predominant factor associated with loss of bone strength with aging (53). BMD in men and women is correlated with low levels of estradiol (61). Since estradiol is formed by aromatization of testosterone, the natural decline in testosterone in men with age is also associated with a decline in estradiol (61).

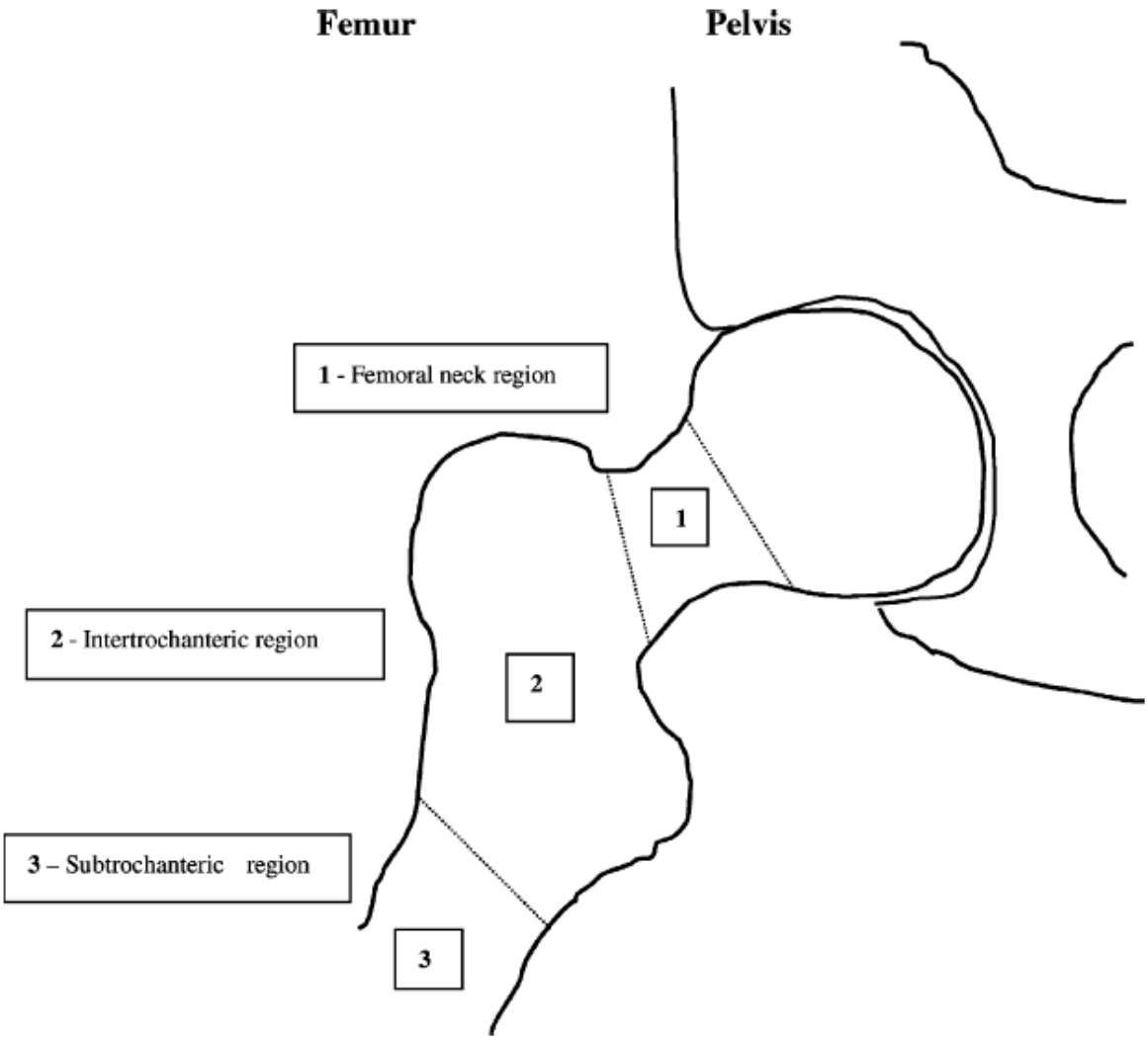
Other factors associated with BMD loss in the elderly are a lack of weight-bearing exercise and diets that are deficient in vitamin D and calcium (62). In addition, many medications that are frequently prescribed in the elderly cause accelerated loss of BMD, such as diuretics, anticonvulsants, and anticoagulants (63).

There are multiple interrelated risk factors for falls in the elderly. These risk factors can be classified as biological and medical, behavioural, socioeconomic, and environmental factors (64). Biological and medical factors relate to health and illness, and include muscle weakness, physical disability, and sensory deficits. Behavioural factors include fear of falling and inappropriate or inadequate use of aids such as canes and walkers. Socioeconomic factors that are related to the risk of falling include poor living conditions, living alone, and lack of support

networks and social interaction. Environmental factors relate to the physical environment and include obstacles and tripping hazards in the home and street, as well as winter snow and ice.

Hip fractures can be classified according to the location of the fracture as: (1) femoral neck fractures (between the greater trochanter and the femoral head), (2) inter-trochanteric fractures (between the greater and lesser trochanter), and (3) sub-trochanteric fractures (at the junction of the proximal shaft of the femur and the lesser trochanter), Figure 2-1 (65). However, the epidemiology and management of hip fractures at these three sites is

Figure 2-1: Hip Fractures as Classified by their Location within the Hip (65)



essentially the same (65). Hip fractures present as acute incapacitating pain that prevents walking and weight bearing (65). Hospital admission and surgery is the usual management,

except for those who are severely debilitated and non-ambulatory, who may be managed with bed rest and analgesia alone (66).

Fractures are classified as pathological when they occur at a site of a bone metastasis. Metastases weaken bone, and increase the risk of fracture. Bone is the commonest site of metastases in prostate cancer, and 85% to 100% of men who die from prostate cancer will have bone metastases at autopsy (67). Melton et al. found that 16% of fractures in men with prostate cancer were pathological (55). Therefore, it is necessary to identify pathological hip fractures in order to estimate the hip fracture risk attributable to ADT separately from the risk attributable to metastatic cancer.

2.3: Study Objectives and Hypotheses

The study had the following objectives:

1. Measure the association between radiation treatment and the risk of hip fracture in men receiving curative treatment for prostate cancer.

2. Estimate the radiation dose to the hip-bone in men receiving curative treatment for prostate cancer and determine the dose relationship between radiation dose to the hip-bone and the risk of hip fracture.

3. Categorize men with prostate cancer according to the indications for ADT and examine the relationship between ADT category and the risk of hip fracture.

The study hypotheses were:

1. Men who are treated with curative radiation for prostate cancer will have a higher risk of hip fracture than men who are treated with curative surgery.The risk of hip fracture in men who receive curative treatment for prostate cancer will increase with increasing radiation dose to the hip-bone.The risk of hip fracture will be higher when ADT is administered for palliation or relapse compared to administration with curative treatment.

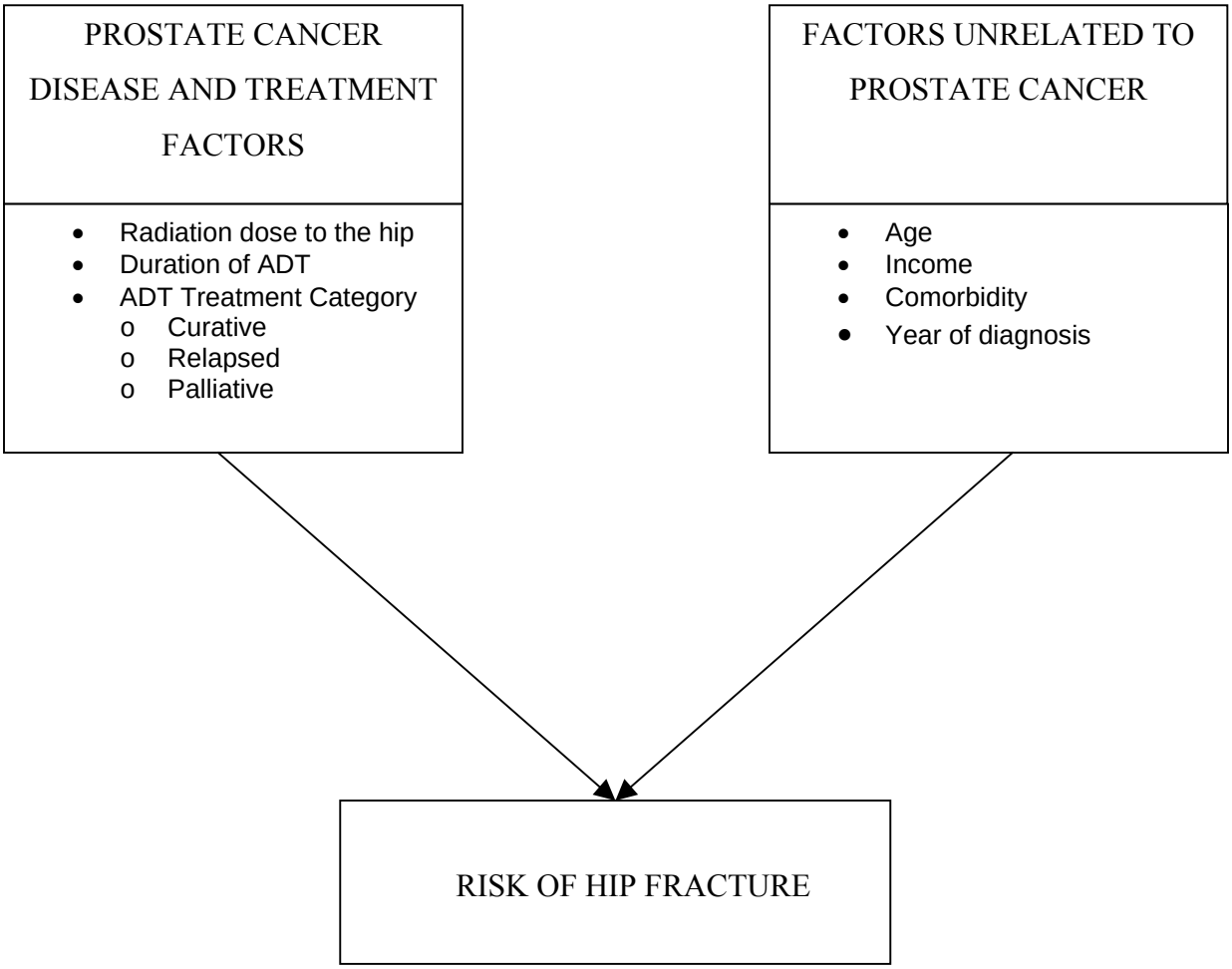
From the literature review, it was hypothesized that two sets of factors would be associated with the risk of hip fracture in men with prostate cancer: (1) factors related to prostate cancer disease and treatment, and (2) factors unrelated to prostate cancer. The first set comprises three factors: (i) radiation dose to the hip, (ii) duration of ADT, and (iii) ADT treatment category, i.e., curative treatment combined with surgery and/or radiation, treatment of relapsed cancer after curative treatment, and palliative treatment without previous curative treatment. The

second set comprises four factors: (i) age, (ii) income, (iii) comorbidity, and (iv) year of diagnosis.

The model in Figure 2-2 presents the broad conceptual framework that was used to generate hypotheses and guide the operationalization of variables. It was hypothesized that both "prostate cancer disease and treatment factors" and "factors unrelated to prostate cancer" would have a direct effect on the outcome of interest, "hip fractures". For example, characteristics such as age, income and health status of an individual would be expected to affect the risk of hip fracture as would characteristics such as intensity of treatment and indication for treatment.

This model is simplistic and does not include many other important influences and relationships. It is likely that "factors unrelated to prostate cancer" have an effect on "prostate cancer disease and treatment factors" in addition to the direct effect on the outcome variable depicted in the model. Furthermore, many other factors that are not captured in this study are

Figure 2-2: Research Framework



expected to have an impact on characteristics of individuals and the treatment of their prostate cancer, as well as on the risk of hip fracture. These effects include social and environmental factors that are likely to affect treatment of prostate cancer and the risk of hip fracture. While these other effects are important to an understanding of the relationship between prostate cancer treatment and the risk of hip fracture, they are beyond the scope of this study and therefore have been omitted from the model.

When comparing the effects of exposure in observational studies, the influence of known and unknown confounders can be reduced by examining groups that are as similar as possible in factors other than the exposure. For example, in men with prostate cancer the influence of confounders are likely to be less when comparing men who have all received curative treatment, such as radiation or surgery, than when comparing men who have received curative treatment to men who have received palliative treatment. Therefore controlling for confounding by restriction was achieved in this study by confining the comparison groups for the effects of radiation on the risk of hip fracture to men who received curative treatment only.

In summary, three general hypotheses formed the basis of this study. The first two hypotheses were that radiation treatment would increase the risk of hip fracture and that the risk would increase with increasing dose to the hip. The third was that the risk of hip fracture would vary according to the indication for ADT.

2.4: Administrative Health Data

This study used population-based administrative health data, comprising BC Hospital Separation Abstracts linked to the BC Cancer Registry and BC Cancer Agency treatment records, for men diagnosed with prostate cancer between 1986 and 2000. The outcome variable was time to hip fracture, and the independent variables were radiation treatment, radiation dose to the hip, and ADT Treatment Category. The effects of age, income, comorbidity, year of diagnosis, and duration of exposure to ADT, were considered as confounding variables. Tumour stage and grade were not available from the data.

Population-based studies using administrative data are ideally suited to examine untoward effects of medical treatments. Randomized prospective studies are invariably underpowered and have insufficient follow-up to be able to measure infrequent side effects, or side effects that occur many years after treatment, whereas administrative data can include many years of data on large numbers of patients. The strengths of administrative data include coverage

of the whole population of interest, and exposure data that is collected independently of outcome data, thus reducing the risk of information bias (68).

There are many potential pitfalls in the use of administrative data. The major shortcoming is that administrative data is generally not collected to answer specific research questions. There may be misclassification of important variables and missing information on potential confounders (69, 70). However, studies have assessed the accuracy and reliability of administrative data for prostatectomies and hip fractures and found an accuracy rate of 89-99% for these diagnoses in administrative data when compared to clinical records (71, 72).

In summary, this study will add new information to enhance the findings of previous studies that have examined the risk of hip fracture in men with prostate cancer. The following chapter will describe the methods employed in the study.

Chapter 3: Methods

This was an observational longitudinal retrospective cohort study with the individual as the unit of analysis. The study population comprised all residents diagnosed with prostate cancer in British Columbia (BC) between 1986 and 2000, and the study period was 1986 to 2001.

The independent variables were: age, income, comorbidity, year of diagnosis, radiation treatment (Yes or No), radiation dose to the hip-bone, ADT duration, and ADT Treatment Category. The dependent variable was time to hip fracture. Exposure to radiation and/or ADT was measured from 1986 to 2000, and hip fractures were measured from 1986 to 2001. Hip fractures were measured for one year longer than exposures in order to allow for a minimum of one year of follow-up.

This chapter describes the sources of data for the study, explains how the files from the data sources were linked and how the study variables were constructed from the fields in the source files, shows what was done to verify the completeness of the source data for ADT exposure and hip fractures, and describes the statistical analysis.

3.1: Data Sources

The two sources of data for this study were the BC Cancer Agency (BCCA) and the Centre for Health Services and Policy Research (CHSPR) at the University of British Columbia (UBC) who provided data from the BC Linked Health Database (BCLHD). The BCCA data files were provided by the BCCA after approval of a data request submitted to the BC Cancer Registrar and the BCCA Data Privacy and Protection Officer. The BCLHD files were provided by CHSPR after approval of a data request submitted to the Ministry of Health. The BCLHD files were anonymised by removal of all personal identifiers including names, addresses, and Personal Health Numbers, and all dates were truncated to month and year only. The Behavioral Research Ethics Board at UBC approved the study. The BCCA and BCLHD files are described in the following sections.

3.1.1: BC Cancer Agency

The BC Cancer Agency has the mandate under the BC Health Act to maintain a provincial Cancer Registry to record all cancers diagnosed in BC for the purpose of cancer research and control. The BCCA is the sole provider of radiation treatment in BC, and the BCCA Radiotherapy File records all radiation treatments that have been administered since

1979. As part of its provincial cancer control mandate, the BCCA is funded by the Ministry of Health to provide all drugs that are used to treat cancer in BC. Cancer drugs are only dispensed by the BCCA or by hospital pharmacies. Hospital pharmacies send a dispensing record to the BCCA for reimbursement of the cost of cancer drugs that they dispense. Since 1986, a dispensing record has been entered in the BCCA Pharmacy File for all cancer drugs that are dispensed by the BCCA or by hospital pharmacies. The BCCA Cancer Registry, Radiotherapy Files, and Pharmacy Files are described in the following sections.

3.1.1.1: Cancer Registry

Cancer is a mandatory reportable disease, and the BCCA maintains a complete registry of all cancers diagnosed in BC since 1969 (73). Cancers are registered from pathology reports, autopsies, death certificates, and clinical cancer report forms, submitted by hospitals and physicians to the Cancer Registry.

BC residents were identified by postal code or the Statistics Canada Standard Geographical Classification (SGC) code of the patient's residence or the registering hospital at the time of diagnosis. The SGC Code is assigned by Statistics Canada based on legislated administrative areas at the provincial and local government levels.

Prostate cancers were identified as adenocarcinoma of the prostate (International Classification of Diseases for Oncology second edition code C61.9 and morphology code 81403) with a diagnosis date between January 1, 1986 and December 31, 2000.

A BCCA unique identification number (Agency ID) is assigned to each person in the Cancer Registry. Because fifteen percent of persons in the cancer registry have more than one cancer diagnosis, a cancer Site Number is also assigned for each cancer site diagnosed for each person in the Cancer Registry. Thus, each cancer site for each person in the cancer registry is identifiable uniquely by the Agency ID and Site Number so that diagnosis and treatment data can be identified for each cancer and for each individual. The fields that were used from the Cancer Registry were the Agency ID, Site Number, birth date, diagnosis date, and death date.

3.1.1.2: Radiotherapy File

The Radiotherapy File was used to identify men in the study population (using the Agency ID and Site Number) who received curative radiation treatment (identified from the data fields, Treatment Intent = "R" and Treatment Type = "R") with a start date between January 1, 1986 and December 31, 2000. The fields that were used from the Radiotherapy File are described in Section 3.4.4.

3.1.1.3: Pharmacy File

The BCCA Pharmacy File was used to identify men in the study population who were dispensed LHRH injections (using the BCCA Drug Identification Number) with a prescription date between January 1, 1986 and December 31, 2000. The BCCA Drug Identification Numbers (DIN) for LHRH injections are listed in Appendix B. The fields that were used from the Pharmacy File are described in Section 3.4.5.

3.1.2: BC Linked Health Database

The BCLHD is a linked longitudinal database that includes all BC residents. The BCLHD is housed at the Centre for Health Services Policy and Research (CHSPR) at UBC. The database files include the Registry file of persons registered with the Medical Services Plan (MSP), the Hospital Separations Abstracts file, and the file of MSP records of payments to providers. The data in the BCLHD are linked at the individual level using a probabilistic linkage that achieves greater than 95% linkage rates (74), thus minimizing the number of BC residents whose data is missing from the BCLHD because of unsuccessful record linkage. The BCLHD files that were used in this study are described in the following sections.

3.1.2.1: MSP Registry

The MSP Registry provided the Statistics Canada neighbourhood income quintile which was used as a proxy for socioeconomic status.

3.1.2.2: Hospital Separations Abstracts File

The Hospital Separations Abstracts file was used to identify men in the study population who were exposed to ADT in the form of bilateral orchiectomy between January 1, 1986 and December 31, 2000, to identify men treated by curative surgery between January 1, 1986 and December 31, 2000, and to identify men with hip fractures that occurred between January 1, 1986 and December 31, 2001.

All BC hospitals submit a Separations Abstract to the Canadian Institute for Health Information (CIHI) after a patient is discharged, transferred, or dies in hospital. This abstract is coded from the medical chart by abstractors who are trained according to CIHI standards and procedures (75). The abstracts are reviewed and edited by CIHI and then computer files of discharge abstracts are distributed to the provinces. The BC Hospital Separations Abstracts obtained for this study included hospital discharges, transfers and deaths with separation dates from April 1, 1985 to March 31, 2002. Since the Separation Abstract is generated at the end of

the hospital admission, it is desirable to have Abstracts that are generated for at least a year after the end of the study period in order to capture subjects with long hospital stays.

3.1.2.3: MSP Payments File

The MSP Payments files record payments to BC health care practitioners for insured services. Health care practitioners include BC physicians who bill MSP a fee for service provided. A small number of hospital and clinic-based physicians do not bill fee-for-service because they are funded by sessional payments and negotiated contracts. These physicians are mainly radiologists, pathologists, psychiatrists, oncologists, emergency room physicians, and public health officers. Insured services cover all medical care provided by physicians, excluding cosmetic surgery and care funded by automobile accident insurance (ICBC) and the Workers Compensation Board (WCB). The MSP Payments files obtained for this study included physician billing records with date of service provided from April 1, 1985 to March 31, 2002.

3.2: Constructing the File Linkage

The study population was identified from the BCCA Cancer Registry. A file of identifiers from this population was sent to the British Columbia Ministry of Health (MOH), and the MOH matched these identifiers to the MSP records. The identifiers were family name, first name, second name, sex, birth date, Personal Health Number (PHN), death date, and postal code.

Because second name and postal code are not reliably recorded in the BCCA data, and to allow for incomplete recording of date of birth and date of death, a second match was performed using family name, first initial, sex, month and year of birth, PHN, and month and year of death.

Ideally, the matched records will be a random sample of the initial study population. However, it is possible that the characteristics of the matched and unmatched records will differ in a systematic way, and these differences may lead to biased estimates that are derived using the matched records only. Therefore, the BCCA records of the matched and unmatched subjects in the study population were compared in order to determine whether they differed systematically. The data items that were used for this comparison were: age at diagnosis, age at death, year of diagnosis, receipt of curative radiation treatment, and receipt of LHRH injections.

After the match was complete, a file of temporary IDs was created for the matched records in the BCCA population, and these temporary IDs were provided to the MOH. The MOH provided a crosswalk file linking the temporary IDs to scrambled MOH identifiers. The scrambled MOH identifiers replaced the temporary IDs in the BCCA population, and the file of

temporary IDs and the crosswalk file were erased. This assured the anonymity of the linked data.

The MOH sent the file of scrambled identifiers to CHSPR who subsequently provided the anonymised MSP Registry, Hospital Separations Abstracts, and MSP Payments files. These files were linked to the anonymised BCCA files using the scrambled identifiers.

3.3: Study Cohorts

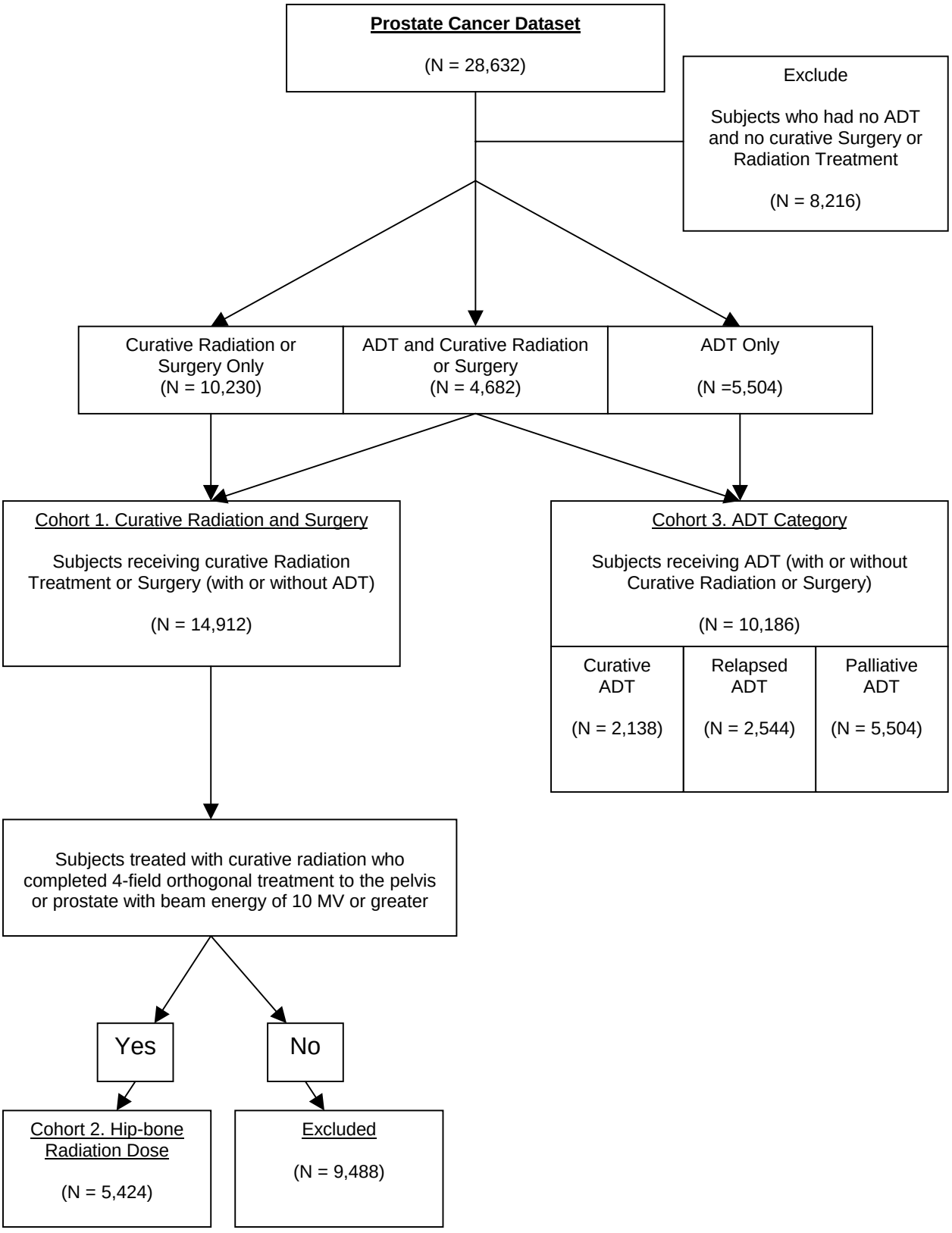
The study population was split into three overlapping cohorts, Figure 3-1. Each cohort included subjects of interest in answering a particular study question. Subjects could be included in more than one cohort. These cohorts, and the study questions addressed by analysis of each cohort, were:

Cohort 1. Curative Radiation and Surgery. This cohort comprised all men in the study population who were treated with curative radiation or surgery. Some of the men in this cohort also received ADT. This cohort was assembled to analyze the effect of radiation treatment on the time to hip fracture for men treated with curative radiation and surgery. The cohort was restricted to men who received curative treatment for prostate cancer in order to reduce the effect of confounding variables that influence both the selection of men for treatment and the risk of hip fracture.

Cohort 2. Hip-bone Radiation Dose. This cohort comprised all men in the study population who received curative radiation treatment, whose radiation dose to the hip-bone could be accurately estimated from the radiation treatment data. Some of the men in this cohort also received ADT. This cohort was assembled to determine the threshold dose, and the radiation dose-response relationship above the threshold dose, for the effect of radiation to the hip-bone on the time to hip fracture.

Cohort 3. ADT Category. This cohort comprised all men in the study population who received ADT. Some of the men in this cohort also received curative radiation and surgery. The cohort was divided into three mutually exclusive categories. The Curative ADT Category comprised men who received ADT combined with curative radiation or surgery. The Relapsed ADT Category comprised men who received ADT for prostate cancer that relapsed after curative radiation or surgery. The Palliative ADT Category comprised men who only received ADT for palliative treatment, without curative radiation or surgery. The ADT Cohort was assembled to

Figure 3-1: Creating the Curative Radiation and Surgery, Hip-bone Radiation Dose, and ADT Category Cohorts



analyze whether the rate of hip fracture varied by ADT Category.

3.4: Study Variables

The independent and dependent variables in this study were created from data fields in the linked files from the Cancer Registry, BCCA Pharmacy, BCCA Radiotherapy, MSP Registry, and Hospital Separations Files. The independent variables were: age, income, comorbidity, radiation treatment (Yes or No), radiation dose to the hip-bone, ADT duration and ADT Category. The dependent variable was time to hip fracture. The operational definitions of the study variables are summarized in Table 3.1.

Table 3.1: Operational Definitions of Study Variables

Variable	Data Source	Time-dependent	Properties	Operational Definitions
Age at Diagnosis	Cancer Registry	No	Continuous	Age at diagnosis of prostate cancer
Year of Diagnosis	Cancer Registry	No	Discrete, Interval	Calendar year of the cancer diagnosis
Income Quintile	MSP Registry	No	Discrete, Ordinal	Neighbourhood income quintile derived by Statistics Canada from Census data
Charlson Comorbidity Score	Hospital Separations Abstracts	No	Discrete, Ordinal	Comorbidity score derived from Hospital Separations diagnoses from 6 months before to 6 months after the date of diagnosis of prostate cancer
Curative Radiation or Surgery	BCCA Radiotherapy File and Hospital Separations Abstracts	No	Discrete, Ordinal	Curative treatment received: Radiation or Surgery
Radiation Dose to Hip-bone	BCCA Radiotherapy File	No	Continuous	Radiation dose to the hip-bone derived from radiation dose to the prostate, fractionation, radiation beam energy, radiation beam size, radiation beam arrangement, and patient size. Administered on start date of first radiation treatment
Duration of Androgen Deprivation Therapy (ADT)	BCCA Pharmacy File, Hospital Separations Abstracts	Yes	Continuous	Sum of net duration of LHRH injections plus time since orchiectomy

Variable	Data Source	Time-dependent	Properties	Operational Definitions
ADT Category	BCCA Radiotherapy File, BCCA Pharmacy File, Hospital Separations Abstracts	No	Discrete, Ordinal	ADT categorized as: 1. Curative ADT 2. Relapsed ADT 3. Palliative ADT
Hip Fracture	Hospital Separations Abstracts	Yes	Discrete	First non-pathological hip fracture occurring after diagnosis of prostate cancer

Table 3.2 shows which variables were included in each study cohort.

Table 3.2: Variables Included in the Study Cohorts

Variable	Cohort 1 Curative Radiation and Surgery Cohort	Cohort 2 Hip-bone Radiation Dose Cohort	Cohort 3 ADT Category Cohort
Age at Diagnosis	√	√	√
Year of Diagnosis	√	√	√
Income Quintile	√	√	√
Charlson Comorbidity Score	√	√	√
Curative Radiation or Surgery	√		√
Radiation Dose to Hip-bone		√	
Duration of Androgen Deprivation Therapy (ADT)	√	√	√
ADT Treatment Category			√
Hip Fracture	√	√	√

The following sections describe how the variables were constructed.

3.4.1: Age at Diagnosis and Year of Diagnosis

Age at diagnosis was calculated using the date of birth and the date of diagnosis fields from the Cancer Registry. Year of diagnosis was the year in which the prostate cancer was diagnosed.

3.4.2: Income Quintile

The Enumeration Area (EA) income quintile is assigned by Statistics Canada using the method developed by Ng et al. that uses family income and family size from census data (76). The method of Ng et al. calculates an Income Per-Person Equivalent (IPPE), which accounts for the economies of scale when more than one person shares a household, Appendix C.

3.4.3: Charlson Score

Comorbidity was assigned using the Charlson Score (77). The Charlson Score was calculated from the weighted Charlson Comorbidity Index (CCI), based on the Deyo implementation (78). The comorbidities scores that are included in the Charlson Comorbidity Index are listed in Appendix D.

Two SAS ® CCI calculation algorithms were obtained for this study. One algorithm was downloaded from the website of the Surveillance Epidemiology and End Results (SEER) program of the US National Cancer Institute (79), and the other was obtained from CHSPR (80).

The SEER program is part of the cancer epidemiology program of the US National Cancer Institute, which maintains a cancer registry for the United States.

The SEER algorithm used ICD9-CM diagnosis codes, whereas the BC data uses ICD9 diagnosis codes. CM is an abbreviation for Clinical Modification, and the ICD9-CM codes are an enhancement of the ICD9 codes to increase the number of diagnostic categories. The ICD9-CM codes were modified to the equivalent ICD9 diagnosis codes in the BC Hospital Separations Abstracts. The SEER implementation was also modified to exclude procedure codes for peripheral vascular disease that are not present in the BC data, and not implemented in the CHSPR algorithm. Both algorithms were modified to allow for 16 diagnosis codes in the BC Hospital Abstracts between 1986 and 2001, and 25 diagnosis codes after 2001. Diagnoses classified as principal diagnosis (code M), pre-admission comorbidities (code 1), post-admission comorbidities (code 2), and secondary diagnoses (code 3), were included in the comorbidity score. A diagnosis of prostate cancer was not included in the comorbidity score.

The Charlson Score was calculated for hospital admission dates from 6 months before, to 6 months after the diagnosis date of prostate cancer. The SAS coding was verified by running both implementations of the algorithm on the Hospital Separations Abstracts and ensuring that each algorithm assigned the same comorbidity score to every subject in the study. Subjects with no admissions from 6 months before, to 6 months after the diagnosis date where assigned a missing Charlson score. These subjects were included in the indicator variables for Charlson score so that these subjects were not excluded from the multivariate analysis.

3.4.4: Radiation Dose to Hip-bone

The prostate is situated approximately centrally in the pelvis, midway between the hip-bones laterally, the pubic bone anteriorly and the sacrum posteriorly. Radiation treatment of prostate cancer may include the pelvic lymph nodes that are adjacent to the prostate, depending on the risk of involvement of these lymph nodes by cancer. The hip-bones are irradiated when either the prostate or the pelvis is treated, and the radiation dose to the hip-bone is a percentage of the radiation dose delivered to the prostate or pelvis. This percentage depends on the size of the pelvis, the radiation treatment technique, the beam energy, and the size of the radiation beams.

The radiation dose to the hip-bone was estimated using data from three sources. These were: (1) The BCCA Radiotherapy File, (2) Measurements made for this study from a sample of men who were treated with radiation for prostate cancer, and (3) Data in the published literature. The methods used to estimate the radiation dose to the hip-bone are explained in the following sections.

3.4.4.1: Pelvic Measurements

The percentage of the prostate radiation dose that is delivered to the hip-bone varies according to the dimensions of the pelvis. The relevant dimensions are the distances between the skin surfaces and between the hip-bones and the prostate. Pelvic dimensions are not recorded in the BCCA Radiotherapy File, therefore a study was performed to estimate the pelvic dimensions for the subjects in the study population. The BCCA Research Ethics Board approved this study.

The study involved measuring the distances between the skin surfaces, the hip-bones, and the prostate from the CT scans of one hundred men treated consecutively for prostate cancer at the BCCA Vancouver Island Cancer Clinic (VICC). These measurements were made at the level of the middle of the prostate. These measurements were: (1) the distance between the skin surfaces from front to back of the pelvis (Anterior Posterior (AP) separation), (2) the distance

between the skin surfaces from side-to-side (lateral separation), and (3) the distance between the centres of the hip-bones (mid-hip separation).

3.4.4.2: Treatment Technique

The treatment technique describes the position of the radiation beams around the prostate. Between 1986 and 2000, the treatment techniques for prostate cancer in BC used three to five stationary beams, or a combination of stationary beams and moving beams. The moving beams are called "Arcs". The radiation treatment record in the BCCA Radiotherapy file includes a description of the radiation technique that was used to treat each subject in the study.

3.4.4.3: Beam Energy

Between 1986 and 2000, the radiation beam energies that were used for prostate cancer in BC varied from 1.2 million electron-volts (MV) for Cobalt radiotherapy to 30 MV for linear electron accelerators (LINACS). The radiation beam energy is recorded in the BCCA Radiotherapy File.

3.4.4.4: Field Size

The size of the radiation beam that is used to treat the prostate is called the field size. The field size is determined by the prostate size plus a margin. The margin allows for prostate movement during radiation treatment, and for the dose fall-off at the edge of the radiation beam which is called the penumbra of the radiation beam. Radiation field size is not recorded in the BCCA Radiotherapy File, therefore the field size estimates were taken from the literature. Pilepich et al. published a study in 1982 which estimated the field sizes required to treat prostate cancer (81). They measured the prostate size from CT scans of 100 men treated consecutively with radiation for prostate cancer. Pilepich found that a volume of 6.2 x 7.0 x 6.6 cm encompassed 95% of the prostates in his study. These dimensions were increased by 1.5 cm in all six directions to allow for patient movement and penumbra and, after rounding up to the nearest whole number, the radiation field sizes were 10 x 10 x 10 cm. A range of field sizes of 9 x 9 x 9 cm, 10 x 10 x 10 cm, and 11 x 11 x 11 cm were explored in estimating the dose to the hip in order to determine the sensitivity of the estimated dose to changes in the radiation field size.

3.4.4.5: Estimating the Radiation Dose to the Hip-bone

Radiation exposure is quantified in physical units of Roentgen, Rads or Gray. Roentgen are units of electrostatic potential created by radiation ionization of air, while Rads are units of energy deposited by radiation ionization of tissue. Gray, abbreviated Gy, are the System

International (S.I.) equivalent of Rads, where one Gray equals 100 Rads. Roentgen units are now obsolete in radiotherapy, and Gray have replaced Rads as the unit of radiation dose.

The biological effect of radiation treatment depends on the dose/fractionation schedule determined by the total dose (D) and the number of radiation fractions (N) that are administered. The Biological Equivalent Dose (BED) standardizes the biological effect of different dose/fractionation schedules (38), where:

$$BED = D \times [\, 1 + (D / N) / (\alpha / \beta) \,]$$

The α / β ratio in this equation is a constant that is derived experimentally for each biological tissue. The α / β ratio for the hip-bone is approximately 3 Gy (38).

The SomaVision ® radiation planning system at the Vancouver Island Cancer Clinic (VICC) was used to estimate the percentage radiation dose to the hip-bone using the pelvic measurements from men treated for prostate cancer at VICC, the beam energies and treatment techniques from the BCCA Radiotherapy File, the field sizes from the Pilepich study, and the Biological Equivalent Dose for each subject calculated from the dose and number of fractions from the BCCA Radiotherapy File.

3.4.4.6: Estimating the Radiation Dose-Response Relationship

Only subjects whose radiation dose to the hip-bone could be accurately determined from the administrative data were included in the estimation of the dose-response relationship for hip fracture. How these subjects were selected for inclusion is described in Chapter 4, Section 4.2.1.3.

As discussed in Chapter 2, the shape of the radiation dose-response curve is not linear over the whole range of radiation dose, but is typically sigmoid shaped, with a threshold dose below which no effect is seen, and an approximately linear dose-response up to a saturation dose, above which an effect is almost always observed. This study attempted to estimate the threshold dose for hip fracture, and the radiation dose-response relationship for hip fracture between the threshold dose and the saturation dose.

3.4.5: Duration of ADT

Androgen deprivation therapy (ADT) comprises administration of Luteinizing Hormone Releasing Hormone (LHRH) injections and/or bilateral orchiectomy (surgical removal of both testicles).

LHRH injections were identified from their Drug Identification Number (DIN) and drug names in the BCCA Pharmacy File. The DIN numbers and drug names are listed in Appendix B.

LHRH injections are sustained-release formulations and the duration of androgen suppression for each injection is 0.5, 1, 2, 3, 4, or 6 months, depending on the formulation dispensed. The duration of androgen suppression from LHRH injections was the sum of the duration of androgen suppression of each LHRH prescription dispensed. After discussion with BCCA Pharmacy staff, it was determined that a negative value in one or both of the fields "Quantity Dispensed" and/or "Costing" in the BCCA Pharmacy File represented a correction to the dispensing record. Therefore, negative LHRH durations were calculated for these records, and the negative duration was added to the positive duration to obtain the net LHRH duration.

LHRH injections can be administered continuously or intermittently. Testosterone levels recover when LHRH injections are stopped, therefore, if LHRH injections are not administered continuously, then testosterone will recover between injections. The cumulative LHRH duration was reduced for each month when there was a gap between the end of the duration of an LHRH injection and the administration of the next LHRH injection where the LHRH administration dates were taken to be the dispensing dates. This reduction was to allow for testosterone recovery after stopping LHRH injections. The amount of this reduction was one month for each month that an LHRH injection was not dispensed. The effect of varying this reduction from 0.5 to 2 months was investigated in the analysis. This was done to test the sensitivity of the effect of ADT duration from LHRH injections on the risk of hip fracture.

For the analysis of ADT Duration from LHRH injections as a time-dependent variable in each year after diagnosis, the cumulative maximum LHRH exposure (accumulated in months then divided by 12 during that year) was assigned to the ADT duration for that year.

Orchiectomies were identified by Canadian Classification of Procedures (CCP) codes 7431 (Removal of Both Testes) and 7432 (Removal of Remaining Testis) in the Hospital Separations Abstracts file. ADT is continuous after orchiectomy. For the analysis of ADT Duration from orchiectomy as a time-dependent variable in each year after diagnosis, the cumulative ADT Duration from orchiectomy increased by one year after each year following orchiectomy.

ADT duration commenced at the date of the first LHRH prescription in the BCCA Pharmacy File or the date of the procedure code for orchiectomy in the Hospital Separations Abstracts, whichever occurred earlier. If orchiectomy was preceded by LHRH injections, then

the duration of ADT from LHRH injections was added to the duration of ADT exposure after orchiectomy. There are no clinical indications for administering LHRH injections to men who have had an orchiectomy and, when this occurs, there is no additive effect for ADT exposure. Therefore, LHRH injections administered after orchiectomy were ignored when calculating duration of ADT exposure.

3.4.6: ADT Treatment Category

Subjects who received ADT were assigned to one of three ADT Categories:

1. Curative ADT comprised men who received ADT combined with curative radiation or surgery.

2. Relapsed ADT comprised men who received ADT for prostate cancer that relapsed after curative surgery radiation or surgery, and who did not receive curative ADT. (Men who received curative ADT and subsequently relapsed were included in Category 1.)

3. Palliative ADT comprised men who did not receive curative radiation or surgery, who received ADT for palliative treatment of prostate cancer.

In order to assign subjects to ADT Category 1 or 2, it was first necessary to identify subjects who received curative radiation or surgery. Curative radiation was identified by code "R" (Radical or curative radiation treatment) or by code "A" (Adjuvant radiation treatment given after curative surgery) in the Treatment Intent field in the BCCA Radiotherapy File. Surgery for curative prostatectomy was identified from the Canadian Classification of Procedures (CCP) code in the Procedure Code fields in the Hospital Separations Abstracts files. The CCP codes that were used to identify curative prostatectomy are shown in Table 3.3.

Table 3.3: Procedure Codes for Prostatectomy in the Hospital Separations File

Canadian Classification of Procedures (CCP) Code	Description of Surgical Procedure
722	Suprapubic Prostatectomy
723	Retropubic Prostatectomy
724	Radical Prostatectomy
7252	Perineal Prostatectomy

The second step in assigning subjects to ADT Category 1 or 2 was to separate ADT combined with curative surgery or radiation (ADT Category 1), from ADT for relapsed prostate cancer after curative surgery or radiation, without curative ADT (ADT Category 2). Based on the published studies of ADT combined with curative surgery or radiation (9, 11), ADT combined with curative surgery was defined as ADT started before, and ended less than three months after, the prostatectomy procedure date in the Hospital Separations Abstracts files. ADT combined with curative radiation was defined as ADT started before three months after, and ended before three years after, the end date of curative radiation in the BCCA Radiotherapy file. Subjects who started ADT within these dates were assigned to ADT Treatment Category 1. Subjects who started ADT after these dates were assigned to ADT Category 2.

Subjects in the study population who did not receive curative surgery or radiation, and who were exposed to ADT were assigned to ADT Category 3.

3.4.7: Hip Fracture

In estimating the risk of hip fracture associated with exposure to ADT and radiation, it is necessary to account for the delay between onset of exposure, and subsequent loss of bone mineral density sufficient to weaken the hip-bone and increase the risk of hip fracture. If this delay is not accounted for, then hip fractures before sufficient loss of bone mineral density has occurred will be misattributed to the exposure. Values for this delay of 6, 12, and 18 months were explored to determine the change in the effect of duration of ADT exposure on the risk of hip fracture. A delay of 12 months was used for the main results.

The Hip Fracture variable was defined as the presence of an ICD-9 diagnosis code for hip fracture in the Hospital Separations Abstracts. The ICD-9 codes for hip fracture are 820 to 820.9. Subjects were considered at risk of hip fracture until first hip fracture, and were censored at the earliest of the date of death, or the end of the study period.

The ICD-9 code for pathological fracture (733.1) does not identify the site of the pathological fracture. Therefore, all subjects with a diagnosis of pathological fracture were excluded from the study cohorts in order to reduce the probability of including pathological hip fractures with hip fractures associated with radiation exposure or ADT exposure. The analysis was subsequently repeated with the inclusion of these subjects in order to estimate the impact of including pathological hip fractures on the effect of radiation on the rate of hip fracture.

3.5: Verification of the Data for LHRH injections and Hip Fractures

As far as is known, this is the first study to examine LHRH injections using BC administrative health data, and the first study to categorize the indications for ADT using administrative health data. Therefore, studies were performed to verify the completeness of recording of LHRH injections, the accuracy of categorizing the treatment indications for LHRH injections, and the recording of hip fractures.

Two verification studies were performed. The first study examined clinical records of men treated for prostate cancer, and compared information on use of LHRH injections in the clinical records with prescription records for LHRH injections in the BCCA Pharmacy File. The second verification study compared information on hip fractures in the MSP Payments files to the information on hip fractures in the Hospital Separations Abstracts files.

Two random samples were selected to verify the LHRH prescription information in the BCCA Pharmacy File. The first sample was 200 subjects who were randomly selected from subjects in the study population who were recorded in the Pharmacy File as having received a prescription for a LHRH injection. The second sample was 200 subjects who were randomly selected from subjects in the study population with no LHRH prescriptions in the Pharmacy File. These two random samples were combined to form a verification study sample of 400 subjects. The verification study comprised abstracting information from the BCCA treatment charts (for subjects treated at the BCCA), and sending questionnaires to the treating urologists (for subjects not treated at BCCA) to determine whether LHRH injections had been prescribed, and the indications for LHRH injections. The BCCA Research Ethics Board approved this verification study.

Chart information abstracted from the BCCA treatment charts, or information obtained from urologists, was regarded as the gold standard to which administrative information from the prescription records in the Pharmacy File was compared. The simple kappa statistic with 95% confidence intervals was calculated for agreement between the presence or absence of LHRH injections, and the indications for LHRH injections, in the chart information and in the administrative information. A kappa statistic greater than 0.75 was taken to indicate excellent agreement beyond chance, and values between 0.60–0.74 were taken to indicate good agreement.

The second verification study of ADT and hip fractures compared MSP and Hospital Separations Abstracts data. MSP records of physician billings are collected entirely independently from Hospital Separations Abstracts. The presence or absence of diagnosis codes for hip fractures for subjects in the MSP Billing data was compared to the presence or absence of

these codes in the Hospital Separations Abstracts using methods published by Roos and Baron (71, 72).

3.6: Analytic Methods

The start time of the analysis was the date of diagnosis. Subjects were censored if they did not have a hip fracture before the date of death, or before December 31, 2001, which was the end of the study period. Subjects were removed from the analysis if they had a hip fracture before the diagnosis of prostate cancer. The indicator variables income quintile, Charlson score, and year of diagnosis in the univariate models were tested for significance using the model p-value.

The effect of radiation treatment compared to surgery on the time to hip fracture in men treated with curative radiation and surgery was analyzed in Cohort 1. (Curative Radiation and Surgery) using Cox regression (82). The relative risk of radiation treatment was estimated before and after adjustment for age at diagnosis, income quintile, Charlson score, year of diagnosis, and ADT duration as a time-dependent variable.

Cox regression was used to analyse the time to hip fracture for increasing radiation dose to the hip-bone in Cohort 2. (Hip-bone Radiation Dose), for men treated with curative radiation whose radiation dose to the hip-bone could be estimated from the administrative data. The relative risk of radiation dose was estimated before and after adjustment for age at diagnosis, income quintile, Charlson score, year of diagnosis, and ADT duration as a time-dependent variable.

In Cohort 3. (ADT Category), ADT Category was used as a time-dependent variable to analyse the time to hip fracture by ADT Category. The relative risk of ADT Category was estimated before and after adjustment for age at diagnosis, income quintile, Charlson score, year of diagnosis, and ADT duration as a time-dependent variable.

To explore the influence of intermittent LHRH injections on the risk of hip fracture in Cohort 3. (ADT Category), Cox regression multivariate models were used to estimate the effect of ADT Duration as a time-dependent continuous variable on the relative risk of hip fracture after adjustment for age at diagnosis, radiation treatment, income quintile, Charlson score, and year of diagnosis.

To explore the interval between starting ADT and the risk of hip fracture in Cohort 3. (ADT Category), Cox regression multivariate models were used to estimate the effect of ADT Duration as a time-dependent continuous variable on the relative risk of hip fracture, after

adjustment for age at diagnosis, radiation treatment, income quintile, Charlson score, and year of diagnosis.

The ICD-9 code for pathological fracture (733.1) does not identify the site of the pathological fracture. Therefore, all subjects with a diagnosis of pathological fracture were excluded from the study cohorts in order to reduce the probability of including pathological hip fractures with hip fractures associated with radiation exposure or ADT exposure. This was the most conservative way of accounting for the possibility that a hip fracture in a subject with a diagnosis of pathological fracture may have been a pathological hip fracture. To test the impact of this exclusion, the analysis of the effect of radiation treatment on the relative risk of hip fracture in Cohort 1. (Curative Radiation and Surgery) was repeated after including subjects who had a pathological fracture.

All variables in all models had one degree of freedom. A Wald Chi-square statistic and associated p-value was used to test the significance of each parameter in the model. SAS ® version 9.1 was used for the analysis.

To determine the most parsimonious model, variables were removed in turn from the multivariate model if removing the variable caused the estimate for the main independent variable (radiation treatment, radiation dose, or ADT Category) to change by less than 10%. The variables that had been removed were added back into the model after removing a second or subsequent variable, and were retained in the model if adding them back caused the estimate for the independent variable to change by more than 10%.

3.6.1: Informative Censoring

Informative censoring occurs when similar factors affect both censoring (e.g. death) and outcomes (e.g. hip fracture). Since illness severity may be a determinant of both hip fracture and death, subjects censored at death may have a higher risk of hip fracture than men who survived. Survival curves were compared for Radiation Treatment and Surgery, and for the three ADT Categories (Curative, Relapsed and Palliative) to see how differences in the rate of death may have influenced the estimates of the risk of hip fracture (83).

3.6.2: Missing data

A "missing" category was created for missing ordinal data in order to retain subjects with missing data in the analysis. It was recognized that this method of dealing with missing data may introduce bias into the estimates of the independent variables (84).

Chapter 4: Results (1) – Files, Variables, and Verification

The target population was BC men diagnosed with prostate cancer between 1986 and 2000, from which the study population was drawn. The study data consisted of BC Cancer Agency cancer diagnosis and treatment records that were matched to the provincial Medical Services Plan (MSP) records and hospital discharge abstracts.

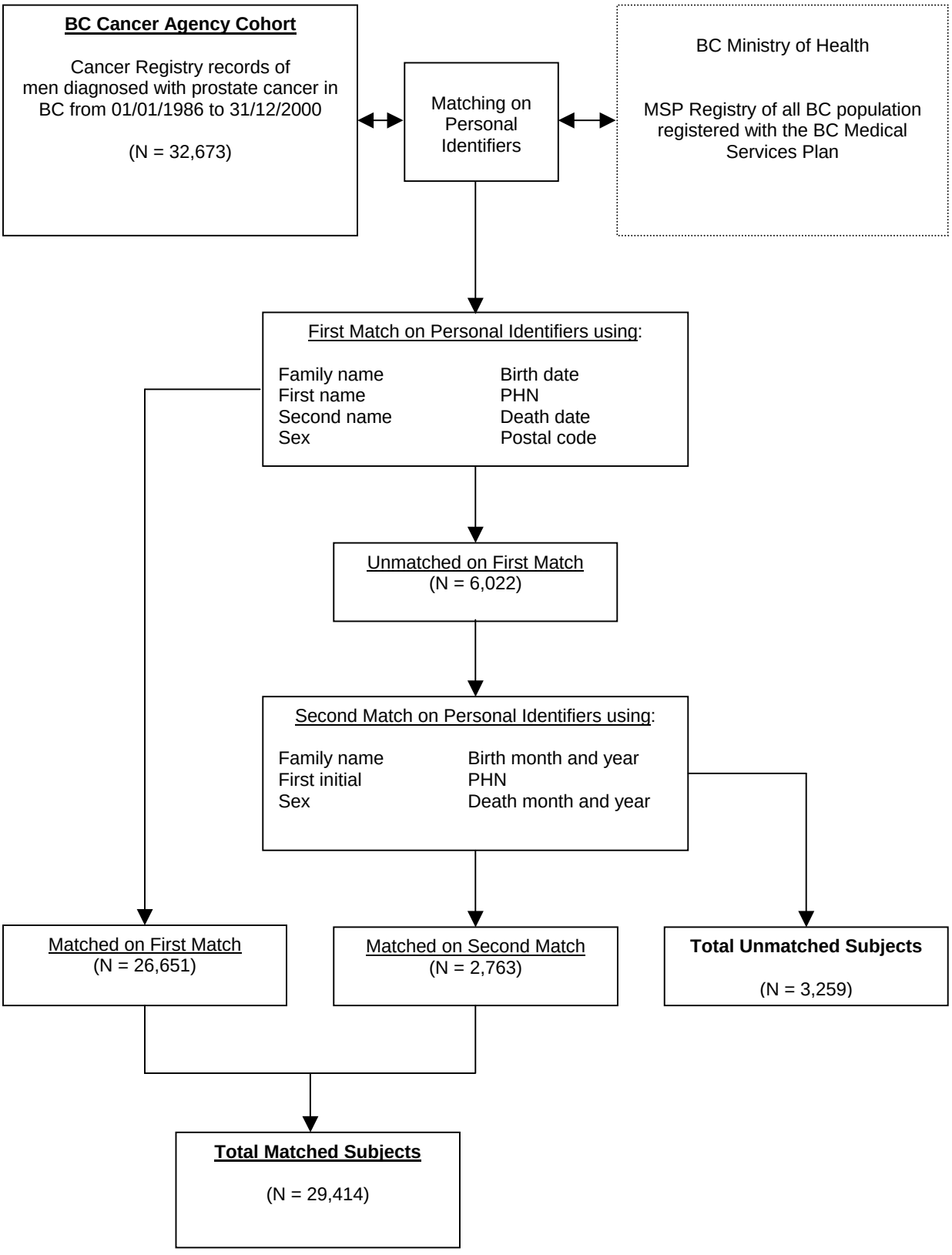
The following sections show the results of the record matching and file linkage, describe the study population and the study variables, and present the results of the verification studies.

4.1: Target Population and Record Linkage

The target population consisted of all BC residents diagnosed with adenocarcinoma of prostate between January 1, 1986 and December 31, 2000. This population comprised 32,673 men from the BC Cancer Registry at the BC Cancer Agency (BCCA). Personal identifiers matched these men with the records in the Medical Services Plan (MSP) Registry at the BC Ministry of Health. The records of men identified in the match were anonymised, and then sent to the Centre for Health Services Policy and Research (CHSPR). CHSPR provided the Hospital Separation Abstracts, Income Quintiles, and MSP Billing records for the matched subjects, which were combined with the BCCA records of cancer diagnosis, radiation treatment, and LHRH treatment to create a Prostate Cancer Dataset. The steps in creating the Prostate Cancer Dataset are summarized in Figure 4-1.

The Ministry of Health, using the full set of personal identifiers, initially matched 26,651 of 32,673 men on all of the identifiers. The identifiers were family name, first name, second name, sex, birth date, Personal Health Number (PHN), death date, and postal code. A further 2,763 of the 6,022 unmatched men were subsequently matched on all of a reduced set of identifiers comprising family name, first initial, sex, month, and year of birth, PHN, and month and year of death. Therefore, a total of 29,414 of the 32,673 men (90% of the target population) were matched.

Figure 4-1: Creating the Matched Dataset



The age at diagnosis, age at death, year of diagnosis of prostate cancer, receipt of curative radiation treatment, and receipt of LHRH treatment, were compared for the matched and unmatched subjects. The matched subjects were younger, lived longer, were more likely to be diagnosed in the later years of the study, and were less likely to receive curative radiation treatment and LHRH injections than the matched subjects, Tables 4.1 to 4.4. The distributions of these variable were all significantly different ($p < .0001$) using the Chi-Square test for Tables 4.1 to 4.3, and the test of proportions for Table 4.4.

Table 4.1: Age at Diagnosis for the Matched and Unmatched Subjects

	Matched Subjects		Unmatched Subjects	
Age Range (years)	N	%	N	%
< 60	2724	9	163	5
60-64	3740	13	326	10
65-69	6096	21	488	15
70-74	6780	23	651	20
75-79	5397	18	651	20
80-84	3091	11	521	16
85 +	1586	5	459	14
Total	29414	100	3259	100

Table 4.2: Age at Death for the Matched and Unmatched Subjects

Age Range (years)	Matched Subjects		Unmatched Subjects	
	N	%	N	%
< 60	177	1	62	2
60-64	405	3	107	4
65-69	1003	7	220	9
70-74	1864	13	388	15
75-79	2917	21	546	22
80-84	3446	24	545	22
85-89	2749	19	398	16
90 +	1546	11	265	10
Total	14107	100	2531	100

Table 4.3: Year of Diagnosis for the Matched and Unmatched Subjects

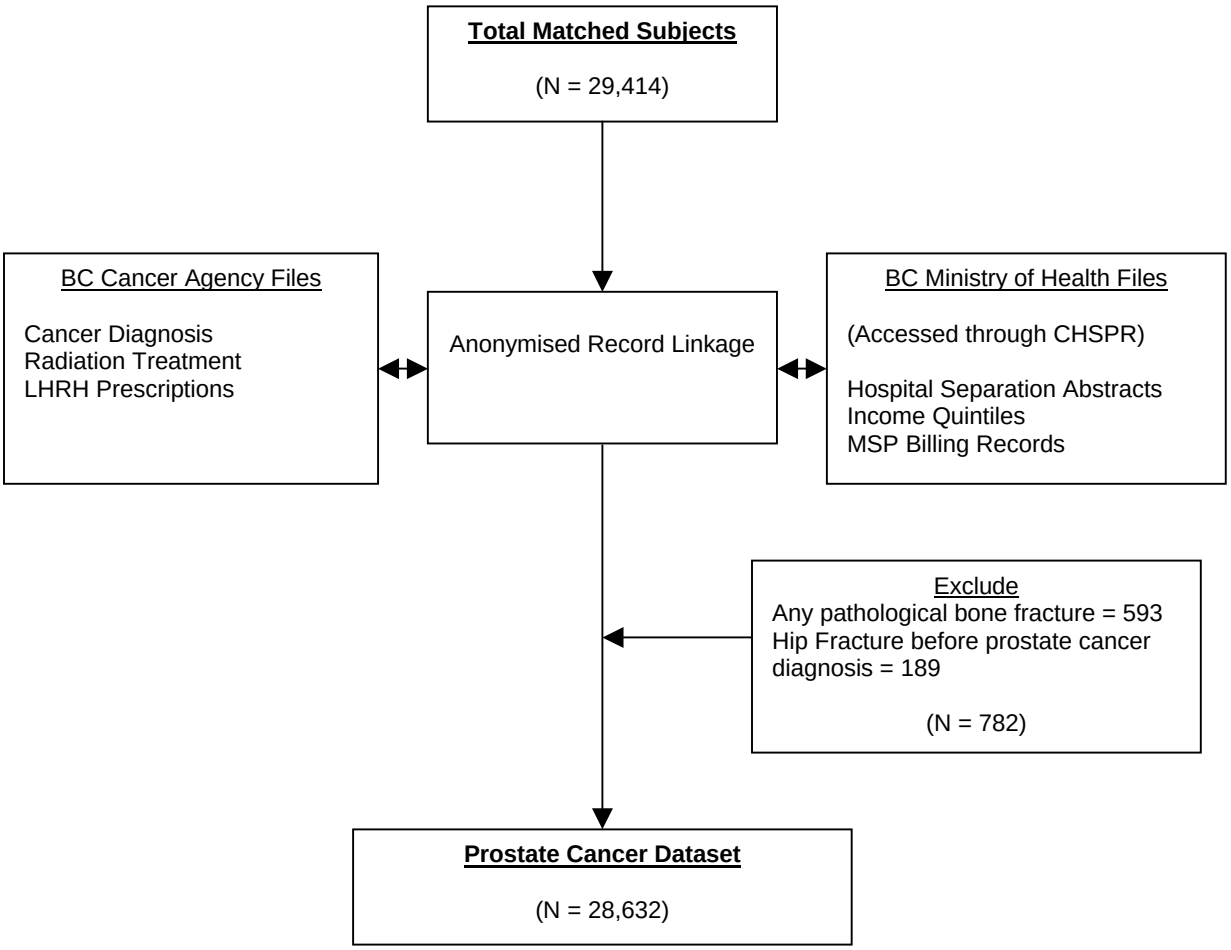
Year of Diagnosis	Matched Subjects		Unmatched Subjects		Total
	N	%	N	%	
1986 – 1991	7885	27	2344	72	10229
1992 – 1996	11468	39	581	18	12049
1997 – 2000	10061	34	334	10	10395
Total	29414	100	3259	100	32673

Table 4.4: Percentage of Matched and Unmatched Subjects receiving Curative Radiation Treatment or LHRH Injections

	Matched Subjects	Unmatched Subjects	p-value
Curative Radiation Treatment	33%	16%	< .0001
LHRH Injections	25%	7%	< .0001

Subsequently excluded from the 29,414 matched subjects were 782 subjects, Figure 4-2. These 782 subjects comprised 593 subjects with a diagnosis of pathological bone fracture recorded in the Hospital Separation abstracts, and 189 subjects who had a hip fracture before their prostate cancer diagnosis. Therefore, the study population was the Prostate Cancer Dataset which comprised 28,632 subjects.

Figure 4-2: Creating the Prostate Cancer Dataset



Excluded from the Prostate Cancer Dataset were 8,216 subjects who did not receive curative radiation or curative surgery or ADT, leaving 10,230 subjects who had curative radiation or surgery, 4,682 subjects who had ADT and curative radiation or surgery, and 5,504 subjects who had ADT without curative radiation or surgery, Figure 3-1, page 21. These three groups were combined in the following ways to form the three study cohorts:

Cohort 1. Curative Radiation and Surgery Cohort (N = 10,230 + 4,682 = 14,912); to compare the effect of radiation treatment, or no radiation treatment, on the risk of hip fracture.

Cohort 2. Hip-bone Radiation Dose Cohort (N = 5,424); a subset of Cohort 1, subjects who received curative radiation that was delivered as 4-field orthogonal treatment to the pelvis or prostate with a beam energy of 10 MV or greater, to determine the threshold dose and the dose-response relationship between radiation dose to the hip-bone and the risk of hip fracture.

The Hip-bone Radiation Dose Cohort only included the 5,424 subjects from the Curative Radiation and Surgery Cohort who received curative radiation delivered as 4-field orthogonal treatment to the pelvis or prostate with a beam energy of 10 MV or greater, because these were the only subjects whose hip-bone radiation dose could be accurately estimated from the administrative data. The process of selecting these subjects is described in Section 4.2.1.3

Cohort 3. ADT Category Cohort (N = 4,682 + 5,504 = 10,186); to determine the effect of ADT treatment Category (Curative, Relapsed, and Palliative ADT) on the relationship between duration of ADT exposure and the risk of hip fracture

4.2: Description of the Study Variables

The study variables that were present in all three of the cohorts were; Age at Diagnosis, Income Quintile, Charlson Comorbidity Score, and Year of Diagnosis. The values of these variables in the three cohorts are compared in the following sections. It was not possible to test the differences between the distributions of these variables within the three cohorts because subjects were included in more than one cohort.

The diagnosis date was taken to be the earliest date of prostate cancer biopsy, radical prostatectomy, orchiectomy, or first LHRH prescription. There were 98, 144, and 454 subjects respectively who had a radical prostatectomy, orchiectomy or their first LHRH prescription before the prostate cancer diagnosis date, and the date differences were greater than one year in

40, 14, and 2 cases respectively. The median age at diagnosis was 72 (range 40-99), 68 (range 40-94) and 71 (range 41-88) years for the ADT Category, Curative Radiation and Surgery, and Hip-bone Radiation Dose Cohorts respectively. The subjects are oldest in the ADT Category Cohort, and youngest in the Curative Radiation and Surgery Cohort, Table 4.5.

The distribution of Income Quintiles was very similar for each cohort, Table 4.6.

The Charlson Score was calculated for hospital admissions from 6 months before, to 6 months after, the diagnosis of prostate cancer. The score was coded as missing if a subject has

Table 4.5: Age Group Frequencies for Age at Diagnosis by Study Cohort

	Cohort 1. Curative Radiation and Surgery		Cohort 2. Hip-bone Radiation Dose		Cohort 3. ADT Category	
Age Range (years)	Frequency	%	Frequency	%	Frequency	%
< 60	1955	13	425	8	920	9
60-64	2604	17	632	12	1199	12
65-69	4057	27	1250	23	2028	20
70-74	3838	26	1811	33	2290	22
75-79	2023	14	1118	21	2053	20
80 +	435	3	188	3	1696	17
Total	14912	100	5424	100	10186	100

Table 4.6: Frequency of Income Quintiles by Study Cohort

	Cohort 1. Curative Radiation and Surgery		Cohort 2. Hip-bone Radiation Dose		Cohort 3. ADT Category	
Income Quintile	Frequency	%	Frequency	%	Frequency	%
1	2764	19	1072	20	2142	21
2	2632	18	993	18	1849	18
3	2694	18	1014	19	1909	19
4	2753	18	979	18	1797	18
5	3336	22	1129	21	1957	19
Missing	733	5	237	4	532	5
Total	14912	100	5424	100	10186	100

Table 4.7: Frequency of Charlson Scores by Study Cohort

	Cohort 1. Curative Radiation and Surgery		Cohort 2. Hip-bone Radiation Dose		Cohort 3. ADT Category	
Charlson Score	Frequency	%	Frequency	%	Frequency	%
0	10473	70	3199	59	5751	56
1	1070	7	307	6	793	8
2	485	3	184	3	419	4
3	359	2	92	2	1130	11
Missing	2525	17	1642	30	2093	21
Total	14912	100	5424	100	10186	100

no hospital admissions during this period. The subjects in the ADT Category Cohort have greater comorbidity than those in the other two cohorts and the subjects treated with radiation alone, in the Hip-bone Radiation Dose Cohort, have the highest number of admissions coded as missing, Table 4.7.

Subjects in the ADT Category and Hip-bone Radiation Dose cohorts were diagnosed in later years than the subjects in the Curative Radiation and Surgery Cohort, Table 4.8.

Table 4.8: Year of Diagnosis by Study Cohort

	Cohort 1. Curative Radiation and Surgery		Cohort 2. Hip-bone Radiation Dose		Cohort 3. ADT Category	
Year of Diagnosis	Frequency	%	Frequency	%	Frequency	%
1986 – 1992	5419	36	884	16	3094	30
1993 – 1996	4934	33	2211	41	2626	26
1997 – 2000	4559	31	2329	43	4466	44
Total	14912	100	5424	100	10186	100

4.2.1: Radiation Dose to the Hip-bone

The radiation dose received by the hip-bone is a percentage of the radiation dose delivered to the prostate. This percentage depends on four factors: (1) the radiation beam energy, (2) the treatment technique, (3) the pelvic dimensions, and (4) the size of the radiation fields. The measurements and estimates made for these four factors for the subjects in the Hip-bone Radiation Dose Cohort, and the selection of subjects who were treated with radiation in the Curative Radiation and Surgery Cohort for the Hip-bone Radiation Dose Cohort, are presented in the following sections.

4.2.1.1: Radiation Beam Energy and Treatment Technique

Table 4.9 shows the frequency of beam energy and treatment techniques for the subjects treated with curative radiation to the pelvis or prostate in the Curative Radiation and Surgery Cohort. Note that a subject may be treated with more than one combination of energy and technique, so that the number of treatments was greater than the number of subjects. There are 5,489 4-Field treatments with Beam Energy of 18 MV, and 2,522 4-Field treatments with Beam Energy of 10 MV. Together, these 8,011 treatments comprise 65% of the total 12,270 treatments.

Table 4.9: Frequency of Radiation Beam Energies and Treatment Techniques used for Radiation Treatment in the Curative Radiation and Surgery Cohort

	Treatment Technique			
Beam Energy	4-Field	ARC	Other	Total
18 MV	5489	1707	381	7577
10 MV	2522	1384	246	4152
Cobalt	13	168	27	208
6 MV	77	73	14	164
Pi Mesons	0	0	131	131
4 MV	4	9	8	21
Other	3	10	4	17
Total	8108	3351	811	12270

4.2.1.2: Pelvic Dimensions and Radiation Field Size

The distances between the skin surfaces, the hips and the prostate were measured from the CT scans of one hundred men treated consecutively for prostate cancer at the BCCA Vancouver Island Cancer Clinic. These measurements were made at the level of the middle of the prostate. The measurements were: (1) the antero-posterior distance between the skin surfaces from front to back of the pelvis (AP separation), (2) the lateral distance between the skin surfaces from side to side (lateral separation), and (3) the distance between the centres of the hip-bones (mid-hip separation).

There was very little variation in the dimensions of the internal bony anatomy of the pelvis, with a range of only six centimeters in the mid-hip separation. However, there was much greater variation in the external pelvic dimensions, with a range of nine centimeters in the AP separation, and eleven centimeters in the lateral separation, Table 4.10.

Table 4.10: Pelvic Measurements from 100 Men Treated with Radiation for Prostate Cancer

Measurement	Mean	Std Dev	Minimum	Maximum	Range
AP Separation (cm)	23	19	20	29	9
Lateral Separation (cm)	38	23	33	44	11
Mid-Hip Separation (cm)	22	1	20	26	6

The radiation field size varies according to the size of the prostate that is being treated. As discussed in Chapter 3, Section 3.4.4.4, in the majority of cases the prostate will be encompassed by a field size of 10 x 10 x 10 cm. For the purposes of this study, dose calculations were made for field sizes of 9 x 9 x 9 cm, 10 x 10 x 10 cm, and 11 x 11 x 11 cm, in order to estimate the potential variability in the percentage of radiation dose received by the hip-bones.

4.2.1.3: Estimating the Dose to the Hip-bones

Radiation dose calculations of the radiation dose to the hip-bones were made with the SomaVision ® radiation planning system using the radiation beam energies shown in Table 4.9, for the maximum and minimum range pelvic dimensions shown in Table 4.10, and field sizes of 9 x 9 x 9 cm, 10 x 10 x 10 cm, and 11 x 11 x 11 cm.

Table 4.11: Percentage Dose Change to the Hip-bone for Minimum to Maximum Variation in Pelvic Dimensions and Field Size for Beam Energies using the 4-Field Technique

	Percentage Dose Change to the Hip-bone for Minimum to Maximum variation in:	
Beam Energy	Pelvic Dimensions	Field Size
Cobalt	12.2 %	1.5 %
6 MV	6.1 %	0.6 %
10 MV	4.7 %	0.5 %
18 MV	3.2 %	0.1 %

Table 4.12: Percentage Dose Change to the Hip-bone for Minimum to Maximum Variation in Pelvic Dimensions and Field Size for Beam Energies using the Arc Technique

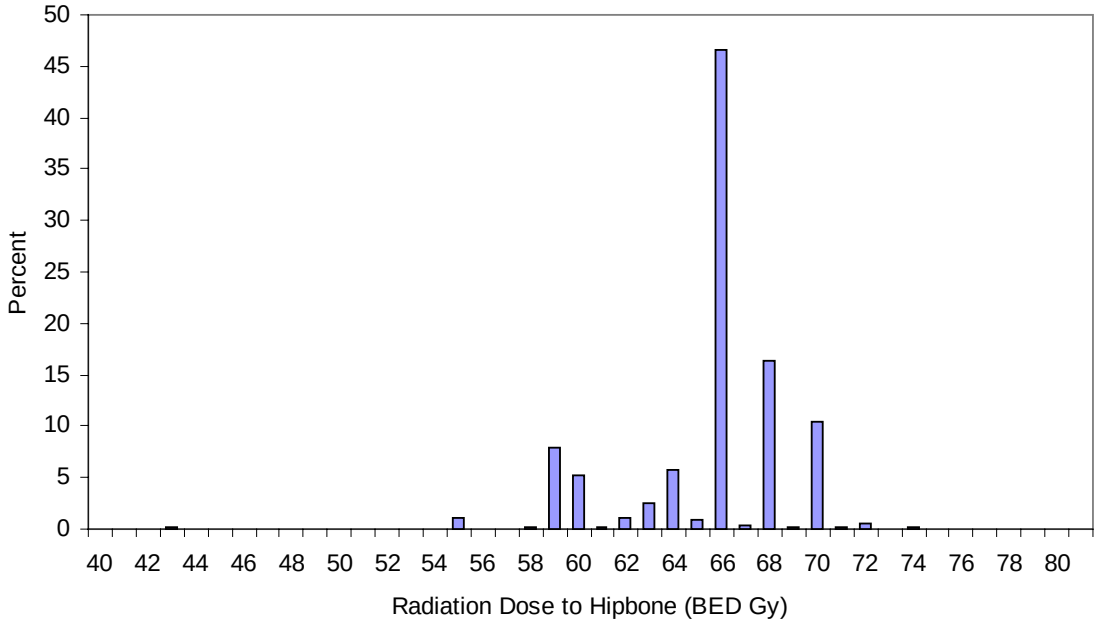
	Percentage Dose Change to the hip-bone for Minimum to Maximum variation in:	
Beam Energy	Pelvic Dimensions	Field Size
Cobalt	10.4	13.8
6 MV	13.0	13.9
10 MV	13.0	13.5
18 MV	13.1	13.1

The percentage variation in radiation dose to the hip-bones was much less for the 4-Field technique, Table 4.11, than the Arc Technique, Table 4.12,. The sum of the percentage variation for the maximum and minimum pelvic dimensions and field size for the subjects who received treatment with beam energies of 10 MV and 18 MV using 4-Field techniques was equal to or less than 5.2%, which is comparable to the dose variation that is accepted in radiation treatment practice, whereas the sum of the percentage variation for the maximum and minimum pelvic dimensions and field size for the subjects who received treatment with Arc techniques was greater than 24% for all energies. Therefore, the subjects included in the Hip-bone Radiation Dose Cohort were restricted to those who received treatment with beam energies of 10 MV or 18 MV and 4 Field techniques to the pelvis and prostate, because these were the only subjects in whom the radiation dose to the hip-bone could be accurately estimated from the administrative data. These comprised 8,011 treatments in 5,424 subjects. The dose to the hip-bone for average-

sized pelvic measurements and field sizes was 60% of the dose to the prostate. This dose was converted to the Biological Equivalent Dose (BED) to account for differences in radiation dose/fractionation using the BED calculation described in Chapter 3, Section 3.4.4.5.

The hip-bone dose ranged from 40 Gy BED to 81 Gy BED with a mean of 65.6 Gy BED and a median of 66 Gy BED, Figure 4-3. The dose distribution frequency in Figure 4-3 was not uniform, because certain radiation dose/fractionation schedules, such as 66 Gy in 33 fractions, are commonly used when treating prostate cancer and other dose/fractionation schedules are not used at all.

Figure 4-3: Frequency of Radiation Dose to the Hip-bone received by Subjects in the Hip-bone Radiation Dose Cohort



A threshold dose of 55 Gy BED to the hip-bone was chosen for the dose-response relationship between radiation dose to the hip-bone and the risk of hip fracture because there were no hip fractures in subjects treated with doses lower than 55 Gy BED. The upper dose level in the study population was 81 Gy BED, so the radiation dose-response relationship was estimated between 55 Gy BED and 81 Gy BED. Threshold dose levels of 50 and 60 Gy BED were also explored in the analysis, to determine the variation in the dose-response relationship with different threshold doses.

4.2.2: Duration of Androgen Deprivation Therapy Exposure

Androgen deprivation therapy (ADT) exposure may result from treatment with LHRH injections or from bilateral orchiectomy. There were 28,245 LHRH prescriptions in the BCCA Pharmacy File, which were dispensed to 5,719 subjects. A procedure code for orchiectomy was found in 4,696 subjects in the Hospital Separation Abstracts. LHRH injections alone were received by 5,490 subjects, and orchiectomy alone by 4,467 subjects, and 229 subjects received both.

The start of ADT from LHRH injections was measured from the date of the first LHRH prescription, and the start of ADT from orchiectomy was measured from the date of the orchiectomy. The duration of LHRH exposure was increased by one month for each month that an LHRH injection was dispensed, and decreased by one month for each month that an LHRH injection was not dispensed. The rate of decrease of duration of LHRH exposure was subsequently varied from 0.5, to 1.0, to 2.0 months for each month that an LHRH injection was not dispensed, in order to explore the effect of this variation on the relationship between the duration of ADT exposure and risk of hip fracture in the ADT cohort. The maximum ADT exposure from LHRH injections was determined for each one year period after LHRH injections were started, and this maximum was assigned as the time-dependent value of duration of LHRH exposure for that year. The time-dependent value of duration of ADT exposure from orchiectomy increased by one year for each year after orchiectomy. ADT exposure from LHRH injections ended at the date of orchiectomy, hip fracture, death, or the study end date, which was December 31, 2001. ADT exposure from orchiectomy ended at the date of hip fracture, death, or the study end date. The duration of ADT exposure from LHRH injections before orchiectomy was added to the duration of exposure from orchiectomy.

The median duration of ADT from LHRH injections was 8 months, range 0.5 to 92 months, with 75% of the subjects exposed to 12 months or less, Figure 4-4.

Figure 4-4: Frequency of Maximum Duration of ADT Exposure from LHRH Injections received by Subjects in the ADT Category Cohort

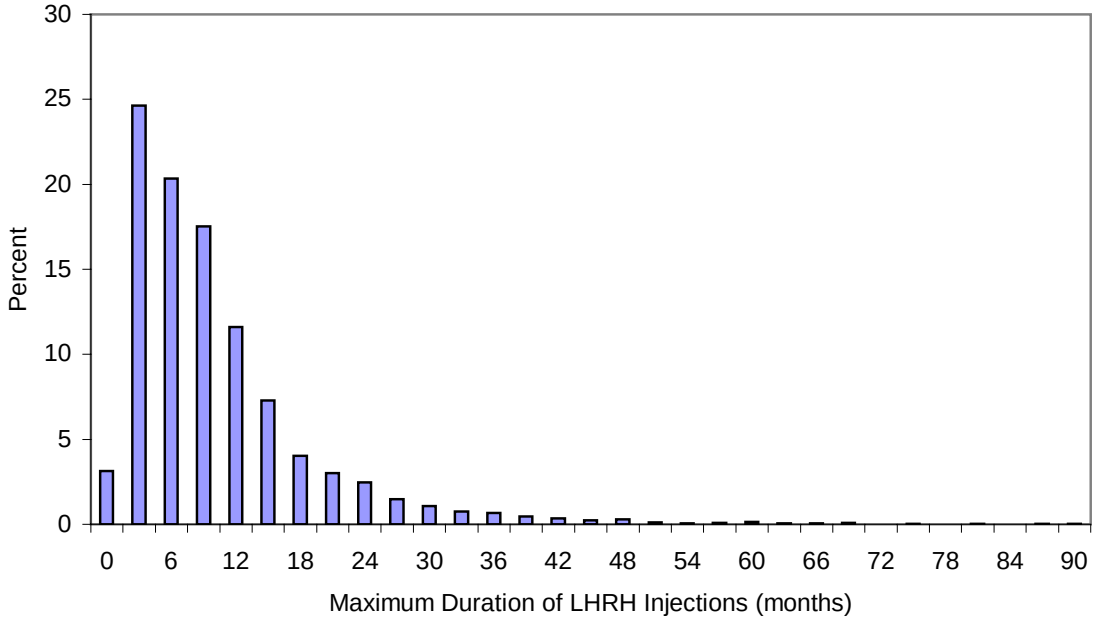
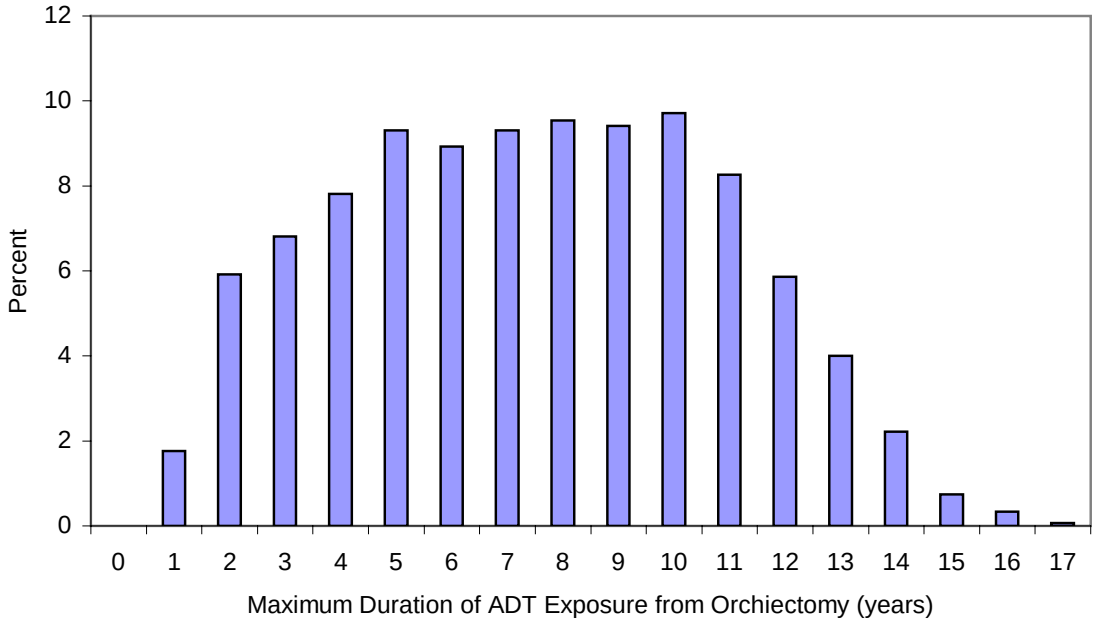


Figure 4-5: Frequency of Maximum Duration of ADT Exposure from Orchiectomy received by Subjects in the ADT Category Cohort



The median duration of ADT exposure from orchiectomy was 7.2 years, range 0.01 to 17.8 years, Figure 4-5.

4.2.3: ADT Category

The three ADT categories were:

1. Curative ADT, combined with curative surgery or radiation.
2. Relapsed ADT, for relapsed cancer after curative surgery or radiation, without curative ADT.
3. Palliative ADT, without curative surgery or radiation.

The assignment of subjects to these categories is shown in Figure 4-6. Comparing the distribution of subjects by age group for the curative, relapsed and palliative categories, subjects who received palliative ADT were older than subjects in the curative and relapsed categories, Table 4.13 ($p < 0.0001$ by the Chi-Square test with 12 degrees of freedom). Subjects who received palliative ADT had higher comorbidity scores, Table 4.14, than subjects in the curative and relapsed categories ($p < 0.0001$ by the Chi-Square test with 8 degrees of freedom). The distribution of Income Quintiles was also different between the three categories, Table 4.15, ($p < 0.0001$ by the Chi-Square test with 10 degrees of freedom). Subjects who received curative ADT were diagnosed in the later years of the study, Table 4.16 ($p < 0.0001$ by the Chi-Square test with 4 degrees of freedom).

Figure 4-6: Assignment of Subjects to ADT Categories

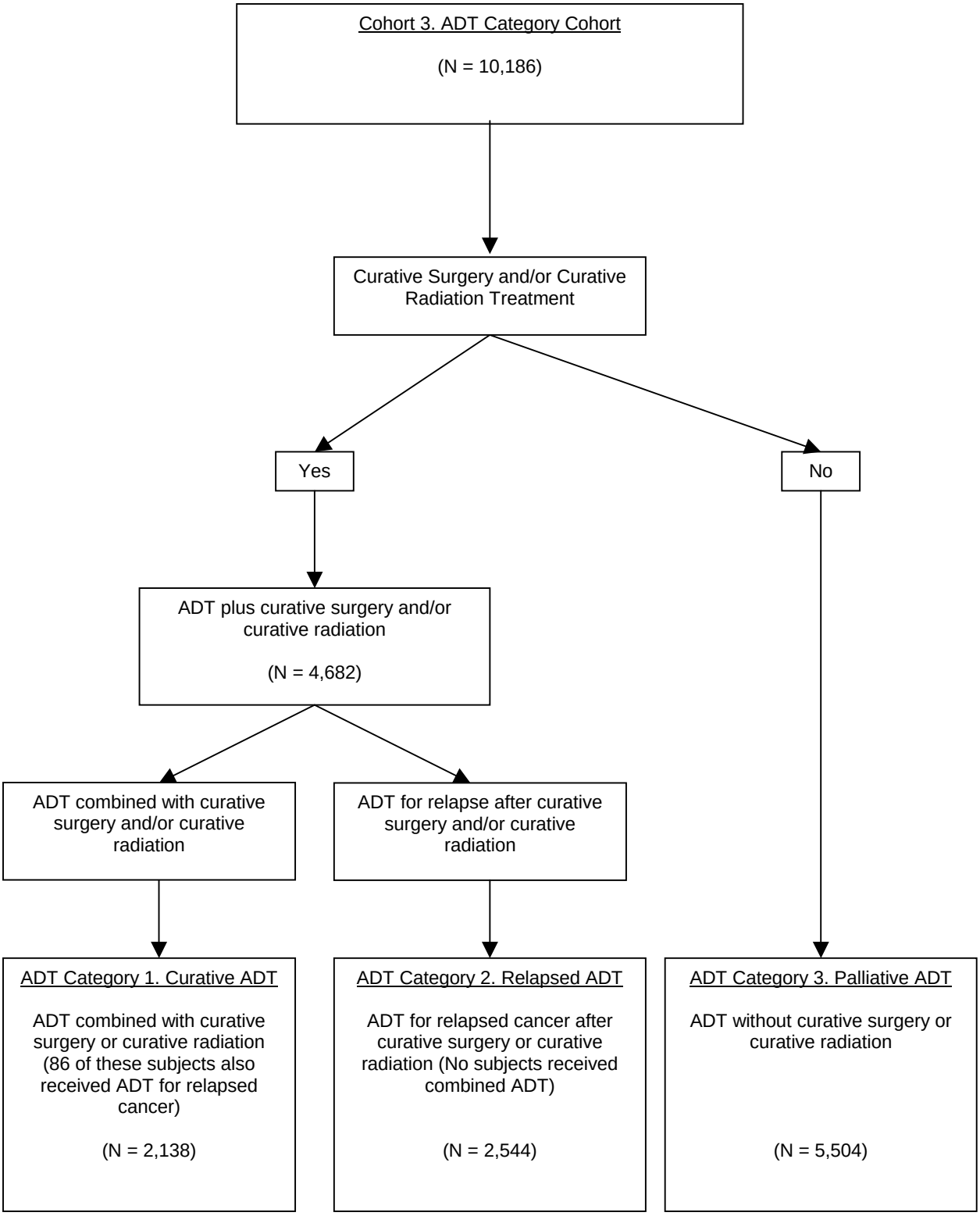


Table 4.13: Age Group Frequencies of Age at Diagnosis for ADT Categories

	All ADT Categories		Curative ADT		Relapsed ADT		Palliative ADT	
Age Range (years)	Frequency	%	Frequency	%	Frequency	%	Frequency	%
< 60	920	9	349	16	255	10	316	6
60-64	1199	12	351	16	391	15	457	8
65-69	2028	20	547	26	714	28	767	14
70-74	2290	22	533	25	685	27	1072	19
75-79	2053	20	312	15	404	16	1337	24
80-84	1203	12	41	2	81	3	1081	20
85 +	493	5	5	0	14	1	474	9
Total	10186	100	2138	100	2544	100	5504	100

(Comparing Curative, Relapsed, and Palliative ADT, Chi-Sq $p<0.0001$ with 12 df)

Table 4.14: Frequency of Charlson Scores for ADT Categories

	All ADT Categories		Curative ADT		Relapsed ADT		Palliative ADT	
Charlson Score	Frequency	%	Frequency	%	Frequency	%	Frequency	%
0	5751	56	1116	52	1892	74	2743	50
1	793	8	102	5	220	9	471	9
2	419	4	57	3	81	3	281	5
3	1130	11	33	2	104	4	993	18
Missing	2093	21	830	39	247	10	1016	18
Total	10186	100	2138	100	2544	100	5504	100

(Comparing Curative, Relapsed, and Palliative ADT, Chi-Sq $p<0.0001$ with 8 df)

Table 4.15: Frequency of Income Quintiles for ADT Categories

	All ADT Categories		Curative ADT		Relapsed ADT		Palliative ADT	
Income Quintile	Frequency	%	Frequency	%	Frequency	%	Frequency	%
1	2142	21	338	16	500	20	1304	24
2	1849	18	378	18	447	18	1024	19
3	1909	19	414	19	465	18	1030	19
4	1797	18	406	19	470	18	921	17
5	1957	19	503	24	536	21	918	17
Missing	532	5	99	5	126	5	307	6
Total	10186	100	2138	100	2544	100	5504	100

(Comparing Curative, Relapsed, and Palliative ADT, Chi-Sq p <0.0001 with 10 df)

Table 4.16: Year of Diagnosis for ADT Categories

	All ADT Categories		Curative ADT		Relapsed ADT		Palliative ADT	
Year of Diagnosis	Frequency	%	Frequency	%	Frequency	%	Frequency	%
1986 - 1992	3094	30	21	1	1491	59	1582	29
1993 - 1996	2626	26	373	17	782	31	1471	27
1997 - 2000	4466	44	1744	82	271	11	2451	45
Total	10186	100	2138	100	2544	100	5504	100

(Comparing Curative, Relapsed, and Palliative ADT, Chi-Sq p <0.0001 with 4 df)

4.3: Verification of LHRH Prescriptions and Hip Fractures

Verification studies were done for the LHRH prescription data in the BCCA Pharmacy Files and for the hip fracture diagnoses in the Hospital Discharge Abstracts.

4.3.1: Verification of LHRH Prescriptions

The LHRH prescription data was verified by comparing the prescription records with clinical information in the BCCA treatment charts and questionnaires sent to community urologists. The presence or absence of clinical information on LHRH prescriptions was compared to the presence or absence of LHRH prescription records in the administrative information. The indications for LHRH treatment (Curative, Relapsed and Palliative) in the

clinical records were compared to the categories of LHRH treatment (Curative, Relapsed and Palliative) derived from the administrative information. Clinical records were available for 323 men for these comparisons, which is a data capture rate of 81%. The Kappa value for agreement was excellent (> 0.75) for all categories of LHRH injections, Table 4:17.

Table 4.17: Agreement between Administrative and Chart Information for LHRH Injections

Category of Use of LHRH Injections	Kappa (95% C.I.)	Present in Administrative Information	Present in Chart Information		
			Yes	No	
All LHRH Injections	0.84 (0.77 - 0.89)	Yes	170	12	182
		No	13	128	141
		Total	183	140	323
Curative LHRH Injections	0.79 (0.70 - 0.88)	Yes	42	7	49
		No	11	263	274
		Total	53	270	323
Relapsed LHRH Injections	0.91 (0.85 - 0.94)	Yes	85	4	89
		No	8	226	234
		Total	93	230	323
Palliative LHRH Injections	0.79 (0.70 - 0.88)	Yes	42	10	52
		No	8	263	271
		Total	50	273	323

4.3.2: Verification of Hip Fractures

The Kappa value showed good agreement between the presence of an ICD-9 hip fracture code in the Hospital Discharge abstracts and the MSP Billing records for the 28,632 subjects in the Prostate Cancer Dataset, Kappa = 0.67 (95% C.I. 0.64 – 0.70), Table 4.18. The comparison was limited to records with diagnosis dates after January 1991, because MSP Billing records only included an ICD-9 diagnostic code after January 1991.

Table 4.18: Agreement between Hospital Separation Abstracts and MSP Billing Records for Hip-Specific Fracture Codes Only

	Hospital Separation Abstracts		
MSP Billing Records	Yes	No	Total
Yes	426	195	621
No	212	27799	28011
Total	638	27994	28632

There are 212 subjects in Table 4.18 who have an ICD-9 code for hip fracture in the Hospital Separation abstracts, but not in the MSP Billing records.

When subjects with the non-specific MSP diagnostic ICD-9 code 821.0 (Fracture Shaft/NOS Femur Closed) are included in the comparison, then the agreement was excellent, Kappa = 0.76 (95% C.I. 0.73 – 0.78), Table 4.19.

Table 4.19: Agreement between Hospital Separation Abstracts and MSP Billing Records including ICD-9 Code 821.0 (Fracture Shaft/NOS Femur Closed)

	Hospital Separation Abstracts		
MSP Billing Records	Yes	No	Total
Yes	569	285	854
No	69	27709	27778
Total	638	27994	28632

4.4: Summary of Study Populations and Study Variables

The match on personal identifiers was successful for 90% of the target population. The unmatched subjects. The matched subjects were younger, lived longer, were more likely to be diagnosed in the later years of the study, and were less likely to receive curative radiation treatment and LHRH injections than the matched subjects.

The study population was divided into three cohorts; the Curative Radiation and Surgery Cohort (N = 14,912) to compare the effect of radiation treatment, or no radiation treatment, on the risk of hip fracture; the Hip-bone Radiation Dose Cohort (N = 5,424); a subset of Cohort 1, subjects who received curative radiation that was delivered as 4-field orthogonal treatment to the

pelvis or prostate with a beam energy of 10 MV or greater, to determine the threshold dose and the dose-response relationship between radiation dose to the hip-bone and the risk of hip fracture; and the ADT Category Cohort (N = 10,186); to determine the effect of ADT treatment Category (Curative, Relapsed, and Palliative ADT) on the relationship between duration of ADT exposure and the risk of hip fracture.

The ADT Category Cohort was divided into three ADT categories; the Curative ADT category comprising subjects who received ADT combined with curative surgery or radiation, the Relapsed ADT category comprising subjects who received ADT for relapsed cancer after curative surgery or radiation, without curative ADT, and the Palliative ADT category, comprising subjects who received ADT without curative surgery or radiation.

The study variables were age at diagnosis, income quintile, Charlson comorbidity score, year of diagnosis, radiation treatment, radiation dose to the hip-bone, ADT duration, ADT category and hip fracture.

Comparison of administrative and clinical data showed excellent agreement for the presence and absence of LHRH prescriptions, and for the indications for LHRH prescriptions. The presence of hip fracture codes in the Hospital Discharge Abstracts showed good to excellent agreement with the presence of hip fractures codes in the MSP data.

Chapter 5: Results (2) – Analysis

5.1: Radiation Treatment and Time to Hip Fracture in Cohort 1. Curative Radiation and Surgery Cohort

The Curative Radiation and Surgery cohort was assembled to analyze the effect of radiation treatment (Yes or No) on the time to hip fracture for men treated with curative radiation and surgery. There were 14,912 subjects in this cohort, of whom 9,604 received radiation, 6,031 received surgery, and 723 received both. There were 245 hip fracture events in this cohort, 32 amongst the men who received surgery and 213 amongst the men who received radiation. All variables except Income Quintile were significant in the univariate analysis, and the hazard ratio for radiation treatment was 3.29 (95% CI 2.27-4.78), Table 5.1.

Table 5.1: Univariate Analysis for Time to Hip Fracture in Cohort 1. Curative Radiation and Surgery Cohort

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Hazard Ratio 95% C.I.	
Curative Surgery					1.00		
Curative Radiation	1.19	0.19	39.50	<.001	3.29	2.27	4.78
Age at Diagnosis	0.13	0.01	144.91	<.001	1.14	1.12	1.17
Duration of ADT (Years)	0.22	0.04	26.82	<.0001	1.24	1.15	1.35
Income Quintile	-0.06	0.04	1.73	0.18	0.94	0.87	1.03
Charlson Score	0.19	0.08	6.17	0.01	1.21	1.04	1.41
Diagnosis Year	-0.41	0.13	10.21	<0.01	0.66	0.52	0.85

The risk of hip fracture in men exposed to radiation treatment was 60% higher than in men not exposed to radiation treatment in the multivariate analysis, with a hazard ratio of 1.60 (95% CI 1.07-2.37), Table 5.2.

Table 5.2: Multivariate Analysis for Time to Hip Fracture Cohort 1. Curative Radiation and Surgery Cohort, including all Variables

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Hazard Ratio 95% C.I.	
Curative Surgery					1.00		
Curative Radiation	0.47	0.20	5.34	0.02	1.60	1.07	2.37
Age at Diagnosis	0.12	0.01	101.11	<.0001	1.13	1.10	1.15

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Hazard Ratio 95% C.I.	
Duration of ADT (Years)	0.17	0.04	16.11	<.0001	1.19	1.09	1.30
Income Quintile = 1					1.00		
Income Quintile = 2	0.01	0.20	0.00	0.96	1.01	0.69	1.48
Income Quintile = 3	0.17	0.19	0.73	0.39	1.18	0.81	1.73
Income Quintile = 4	0.09	0.20	0.19	0.66	1.09	0.74	1.62
Income Quintile = 5	-0.05	0.20	0.07	0.79	0.95	0.64	1.40
Charlson Score = 0					1.00		
Charlson Score = 1	0.28	0.22	1.57	0.21	1.32	0.86	2.05
Charlson Score = 2	0.63	0.28	5.15	0.02	1.88	1.09	3.25
Charlson Score = 3	0.71	0.34	4.51	0.03	2.04	1.06	3.93
Charlson Missing	0.15	0.22	0.48	0.49	1.17	0.76	1.80
Diagnosis Year = 86-92					1.00		
Diagnosis Year = 93-96	-0.27	0.17	2.48	0.12	0.76	0.54	1.07
Diagnosis Year = 97-00	-0.51	0.33	2.34	0.13	0.60	0.32	1.15

To determine the most parsimonious model, variables were removed from the model if removing the variable caused the estimate for Radiation Treatment to change by less than 10%. After removing a second or subsequent variable, the other variables that had been removed were added back into the model to confirm that their continued exclusion caused the estimate for Radiation Treatment to change by less than 10%. Income Quintile, Charlson Score and Year of Diagnosis were not included in the parsimonious model, Table 5.3. The risk of hip fracture was 1.59 times greater in those subjects who received radiation compared to those who did not receive radiation (95% CI 1.07-2.35).

Table 5.3: Parsimonious Multivariate Model for Time to Hip Fracture in Cohort 1. Curative Radiation and Surgery Cohort

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Hazard Ratio 95% Confidence Limits	
Curative Surgery					1.00		
Curative Radiation	0.46	0.20	5.26	0.02	1.59	1.07	2.35
Age at Diagnosis	0.12	0.01	103.80	<.0001	1.13	1.10	1.15
Duration of ADT (Years)	0.19	0.04	19.10	<.0001	1.21	1.11	1.31

5.2: Radiation dose to the Hip-bone and Time to Hip Fracture in Cohort 2. Hip-bone Radiation Dose Cohort

The Hip-bone Radiation Dose cohort was assembled to determine the threshold dose and the dose-response relationship between radiation dose to the hip-bone and the risk of hip fracture in men who had received curative radiation treatment for prostate cancer. There were 5,424 subjects and 60 hip fracture events in this cohort. Radiation dose was analyzed as a continuous variable for doses above the threshold dose of 55 Gy BED. There were no hip fractures at doses less than 55 Gy BED, and the percentage of subjects with hip fracture was less at the highest radiation doses, Table 5.4.

Table 5.4: Radiation Dose to the Hip-bone and Number of Hip Fractures in Cohort 2. Hip-bone Radiation Dose Cohort

	Subjects		Hip Fractures	
Radiation Dose to Hip-bone (Gy BED)	N	(%)	N	(%)
40-54	32	1	0	0
55-65	1340	25	24	40
66	2523	47	27	45
67-81	1529	28	9	15
Total	5424	100	60	100

Age at Diagnosis and Duration of ADT were significant in the univariate analysis, Table 5.5. There were only 4 fractures in subjects with a Charlson Score greater than zero, therefore subjects with Charlson Scores greater than zero were collapsed into one category.

Table 5.5: Univariate Models for Time to Hip Fracture for Cohort 2. Hip-bone Radiation Dose Cohort

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Hazard Ratio 95% C.I.	
Hip-bone Radiation Dose (Gy BED)	-0.05	0.04	2.17	0.14	0.95	0.88	1.02
Age at Diagnosis	0.10	0.02	18.27	<.0001	1.11	1.06	1.16
Duration of ADT (Years)	0.32	0.12	6.71	0.01	1.37	1.08	1.75
Income Quintile	0.08	0.09	0.85	0.36	1.09	0.91	1.29
Charlson Score	-0.36	0.21	2.96	0.09	0.69	0.46	1.05
Diagnosis Year	0.08	0.23	0.12	0.73	1.08	0.70	1.69

Age at Diagnosis and Duration of ADT were significant in the multivariate model, and the confidence limits of the hazard ratios include 1.00 for all of the other variables including Radiation Dose to the Hip-bone, Table 5.6.

Table 5.6: Multivariate Model for Time to Hip Fracture for Cohort 2. Hip-bone Radiation Dose Cohort

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Hazard Ratio 95% C.I.	
Hip-bone Radiation Dose (Gy BED)	-0.06	0.04	2.34	0.13	0.94	0.88	1.02
Age at Diagnosis	0.10	0.02	17.84	<.0001	1.10	1.05	1.16
Duration of ADT (Years)	0.33	0.13	6.35	0.01	1.39	1.08	1.79
Income Quintile = 1					1.00		
Income Quintile = 2	-0.02	0.45	0.00	0.96	0.98	0.40	2.37
Income Quintile = 3	0.50	0.40	1.56	0.21	1.65	0.75	3.61
Income Quintile = 4	0.29	0.43	0.46	0.50	1.34	0.58	3.09
Income Quintile = 5	0.29	0.41	0.51	0.47	1.34	0.60	2.96
Charlson Score = 0					1.00		
Charlson Score > 0	-0.32	0.53	0.37	0.54	0.73	0.26	2.04
Charlson Missing	0.40	0.31	1.66	0.20	1.49	0.81	2.73
Diagnosis Year = 86-92					1.00		
Diagnosis Year = 93-96	0.15	0.33	0.22	0.64	1.17	0.61	2.23
Diagnosis Year = 97-00	0.14	0.50	0.09	0.77	1.16	0.44	3.05

The risk of hip fracture fell by 6% with each one Gy increase in radiation dose between 55 and 81 Gy Biological Equivalent Dose to the hip-bone.

Table 5.7: Parsimonious Multivariate Model for Time to Hip Fracture for Cohort 2. Hip-bone Radiation Dose Cohort

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Hazard Ratio 95% C.I.	
Hip-bone Radiation Dose (Gy BED)	-0.06	0.04	2.60	0.11	0.94	0.87	1.01
Diagnosis Year = 86-92					1.00		
Diagnosis Year = 93-96	0.17	0.32	0.28	0.60	1.19	0.63	2.24

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Hazard Ratio 95% C.I.	
Diagnosis Year = 97-00	0.34	0.48	0.50	0.48	1.40	0.55	3.60

5.2.1: The Effect of Changing the Threshold Dose on the Dose-Response Relationship

There was no difference in the Radiation Dose-response for a threshold dose of 50 Gy BED compared to the threshold dose of 55 Gy BED that was used in Table 5.7. With a threshold of 60 Gy BED, the risk of hip fracture fell by 3% for the 21 Gy BED increase in radiation dose between 60 and 81 Gy BED (HR 0.97, 95% CI 0.81-1.14), therefore on average, for each one Gy BED increase in radiation dose to the hip-bone between 60 and 81 Gy BED, the risk of hip fracture decreased by 0.14%.

5.3: The Effect of ADT Category on the Time to Hip Fracture in Cohort 3. ADT Category Cohort

The ADT cohort was assembled to determine if ADT administered for curative, relapsed or palliative treatment of prostate cancer had a different effect on the risk hip fracture. There were 10,186 subjects in this cohort, of whom 2,138 received curative ADT and experienced 7 hip fractures (0.3%); 2,544 received relapsed ADT and experienced 72 fractures (2.8%); and 5,504 received palliative ADT and experienced 172 fractures (3.1%). ADT Category was modeled as a time-dependent variable.

The risk of hip fracture for subjects in the Relapsed, and Palliative ADT Categories are both significant compared to subjects in the Curative Category in the univariate models, Table 5.8.

Table 5.8: Univariate Models for Time to Hip Fracture for Cohort 3. ADT Category Cohort

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Hazard Ratio 95% C.I.	
Curative ADT					1.00		
Relapsed ADT	1.89	0.51	13.97	<.001	6.64	2.46	17.93
Palliative ADT	2.28	0.46	24.67	<.0001	9.74	3.97	23.90
Duration of ADT (Years)	0.24	0.04	43.39	<.0001	1.28	1.19	1.37
Age at Diagnosis	0.12	0.01	173.05	<.0001	1.13	1.11	1.15
Curative Surgery					1.00		
Curative Radiation	-0.88	0.14	39.27	<.0001	0.41	0.31	0.55

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Hazard Ratio 95% C.I.	
Income Quintile	-0.01	0.04	0.07	0.80	0.99	0.91	1.08
Charlson Score	0.29	0.05	32.15	<0.001	1.34	1.21	1.48
Diagnosis Year	-0.02	0.10	0.03	0.85	0.98	0.81	1.20

Subjects in the Relapsed and Palliative ADT Categories have a significantly higher risk of hip fracture in the multivariate model, Table 5.9.

Table 5.9: Multivariate Model for Time to Hip Fracture for Cohort 3. ADT Category Cohort

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Hazard Ratio 95% C.I.	
Curative ADT					1.00		
Relapsed ADT	1.62	0.53	9.35	<.01	5.06	1.79	14.30
Palliative ADT	1.77	0.72	5.96	0.01	5.84	1.42	24.13
Duration of ADT (Years)	0.08	0.10	0.59	0.44	1.08	0.89	1.31
Age at Diagnosis	0.10	0.01	59.54	<.0001	1.10	1.07	1.13
Curative Surgery					1.00		
Curative Radiation	0.54	0.59	0.84	0.36	1.72	0.54	5.53
Income Quintile = 1					1.00		
Income Quintile = 2	0.44	0.23	3.61	0.06	1.56	0.99	2.46
Income Quintile = 3	0.27	0.25	1.16	0.28	1.31	0.80	2.13
Income Quintile = 4	0.50	0.25	4.06	0.04	1.66	1.01	2.70
Income Quintile = 5	0.24	0.27	0.83	0.36	1.27	0.76	2.14
Charlson Missing					1.00		
Charlson Score = 0	0.32	0.39	0.66	0.42	1.37	0.64	2.94
Charlson Score = 1	0.44	0.45	0.97	0.33	1.55	0.65	3.73
Charlson Score = 2	0.97	0.46	4.48	0.03	2.65	1.08	6.52
Charlson Score = 3	0.94	0.42	5.03	0.02	2.57	1.08	5.86
Diagnosis Year = 86-92					1.00		
Diagnosis Year = 93-96	-0.21	0.20	1.04	0.31	0.81	0.54	1.21
Diagnosis Year = 97-00	0.06	0.27	0.05	0.82	1.06	0.63	1.79

The risk of hip fracture for men treated with relapsed compared to curative ADT was 5.77 (95% CI 2.11-15.79) and for palliative compared to curative ADT was 5.98 (95% CI 1.49-24.0) in the parsimonious model, Table 5.10.

Table 5.10: Parsimonious Multivariate Model for Time to Hip Fracture in Cohort 3. ADT Category Cohort

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Hazard Ratio 95% C.I.	
Curative ADT					1.00		
Relapsed ADT	1.75	0.51	11.65	<.001	5.77	2.11	15.79
Palliative ADT	1.79	0.71	6.36	0.01	5.98	1.49	24.00
Duration of ADT (Years)	0.10	0.10	1.10	0.29	1.11	0.91	1.35
Age at Diagnosis	0.09	0.01	57.15	<.0001	1.10	1.07	1.12
Radiation Treatment	0.37	0.59	0.38	0.54	1.44	0.45	4.62

5.4: Exploring the Influence of Intermittent LHRH Injections on the Time to Hip Fracture in the ADT Category Cohort

LHRH injections are administered continuously or intermittently. Testosterone will recover towards normal when LHRH injections are stopped. As testosterone recovers, the loss of bone mineral density associated with ADT will be reduced, and may cease. Ultimately, bone mineral density may return to normal. The rate at which the effect of accumulated LHRH exposure reduces after stopping LHRH injections was explored by varying the rate of reduction of the accumulated duration of LHRH injections in the months after LHRH injections stopped and exploring the impact of this variation on the estimate of the effect of ADT duration on the risk of hip fracture, after adjustment for age at diagnosis, radiation treatment, income quintile, Charlson score and year of diagnosis. The rate of reduction of the accumulated duration of LHRH injections was varied from 0.5 months per month, to one month per month, to two months per month, for each month after LHRH injections were stopped.

Increasing the rate of reduction from 0.5 months per month to 2 months per month increased the rate of hip fracture from 1.102 to 1.104 per year of ADT Exposure, Table 5.11.

Table 5.11: The Impact of Varying the Rate of Decline of Net Duration of LHRH Injections on the Effect of ADT Exposure on Time to Hip Fracture in Cohort 3. ADT Category Cohort

Rate of Reduction of LHRH Duration	Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Hazard Ratio 95% Confidence Limits	
0.5 Months per Month	ADT Duration (Years)	0.09721	0.03895	6.2285	0.0126	1.102	1.021	1.190
1.0 Month per Month	ADT Duration (Years)	0.09842	0.03891	6.3980	0.0114	1.103	1.022	1.191
2.0 Months per Month	ADT Duration (Years)	0.9899	0.03889	6.4808	0.0109	1.104	1.023	1.191

5.5: Exploring the Interval between Starting ADT and Increased Risk of Hip Fracture

The risk of hip fracture from ADT exposure starts when there is sufficient reduction in bone mineral density to reduce the strength of the hip-bone below the threshold where a low-trauma fracture can occur. Therefore, there is an interval after starting ADT before this threshold is reached. During this interval, a subject should be assigned to the non-exposed group for risk of hip fracture. The impact of varying this interval on the effect size of ADT exposure on the risk of hip fracture was explored. Hip fractures that occurred before the interval were attributed to no ADT exposure, and hip fractures after the interval were attributed to the duration of ADT exposure at the time of the hip fracture.

The change in the effect size of duration of ADT Exposure on the rate of hip fracture was less than 2% as the interval was increased from 0.5, to one, to two years, after adjustment for age at diagnosis, radiation treatment, income quintile, Charlson score and year of diagnosis, Table 5.12.

Table 5.12: The Impact of Varying the Interval between Onset of ADT Exposure and Attributing Hip Fracture to the Effect of ADT Exposure on Time to Hip Fracture in Cohort 3. ADT Category Cohort

Interval from Onset of ADT Exposure to Attributing Hip Fracture	Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Hazard Ratio 95% Confidence Limits	
0.5 years	ADT Duration (Years)	0.11	0.03	9.05	0.002	1.11	1.04	1.19
1 year	ADT Duration (Years)	0.10	0.04	6.40	0.01	1.10	1.02	1.19
2 Years	ADT Duration (Years)	0.08	0.04	3.51	0.06	1.09	0.996	1.18

5.6: Including Subjects with Pathological Fractures

Subjects with any pathological fracture recorded in the Hospital Separation Abstracts were excluded from the study cohorts. This was the most conservative way of accounting for the possibility that a hip fracture may have been a pathological fracture. To test the impact of this exclusion, the multivariate analyses for time to hip fracture in Cohort 1. Curative Radiation and Surgery were repeated after including subjects who had a pathological fracture.

The number of hip fracture events increased from 245 to 260, and the hazard ratio for Radiation Treatment for time to hip fracture declined from 1.59 (95% CI 1.07-2.35) to 1.40 (95% CI 0.97-2.02) after subjects with any pathological fracture were included, Tables 5.3 and 5.13.

Table 5.13: Multivariate Analysis of Time to Hip Fracture in Cohort 1. Curative Radiation and Surgery Cohort, including Pathological Fractures

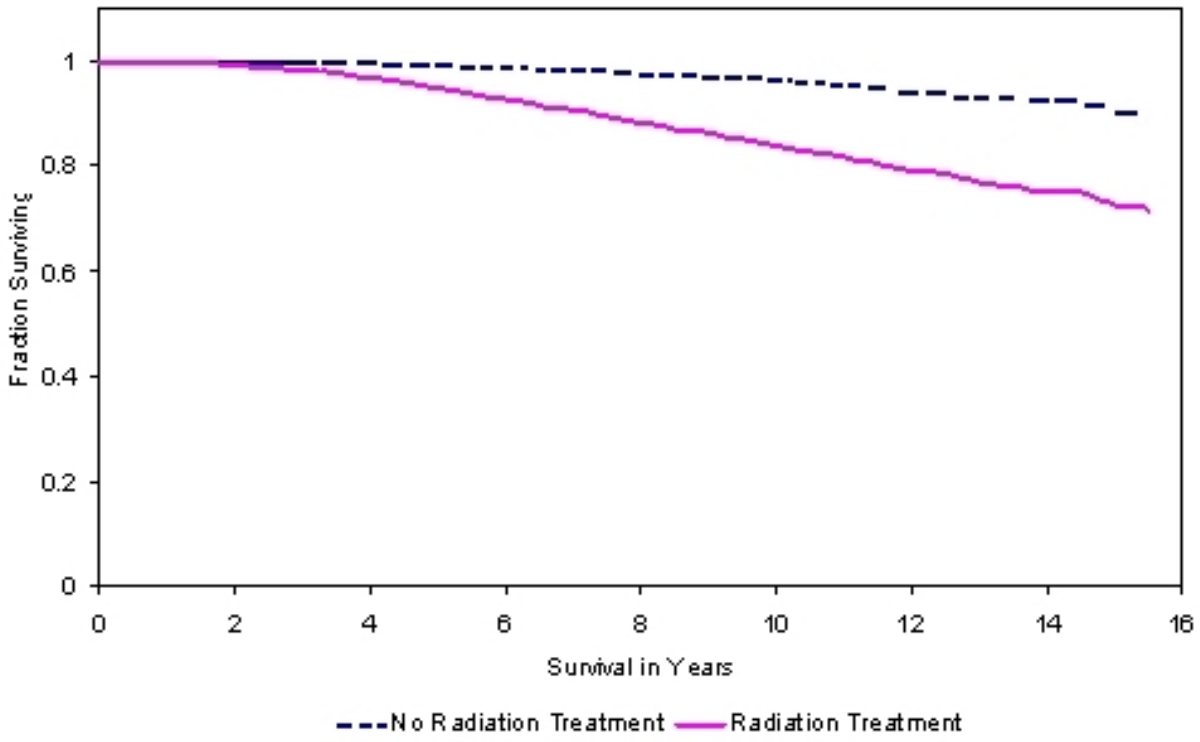
Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Hazard Ratio 95% Confidence Limits	
Radiation Treatment	1	0.34	0.19	3.20	0.07	1.40	0.97	2.02
Age at Diagnosis	1	0.12	0.01	108.36	<.0001	1.13	1.10	1.15
Duration of ADT	1	0.18	0.04	17.66	<.0001	1.20	1.10	1.30

5.7: All-cause Survival for Study Cohorts

Informative censoring may occur if subjects who are censored have a different probability of a hip fracture than subjects who are not censored. Subjects at risk of hip fracture

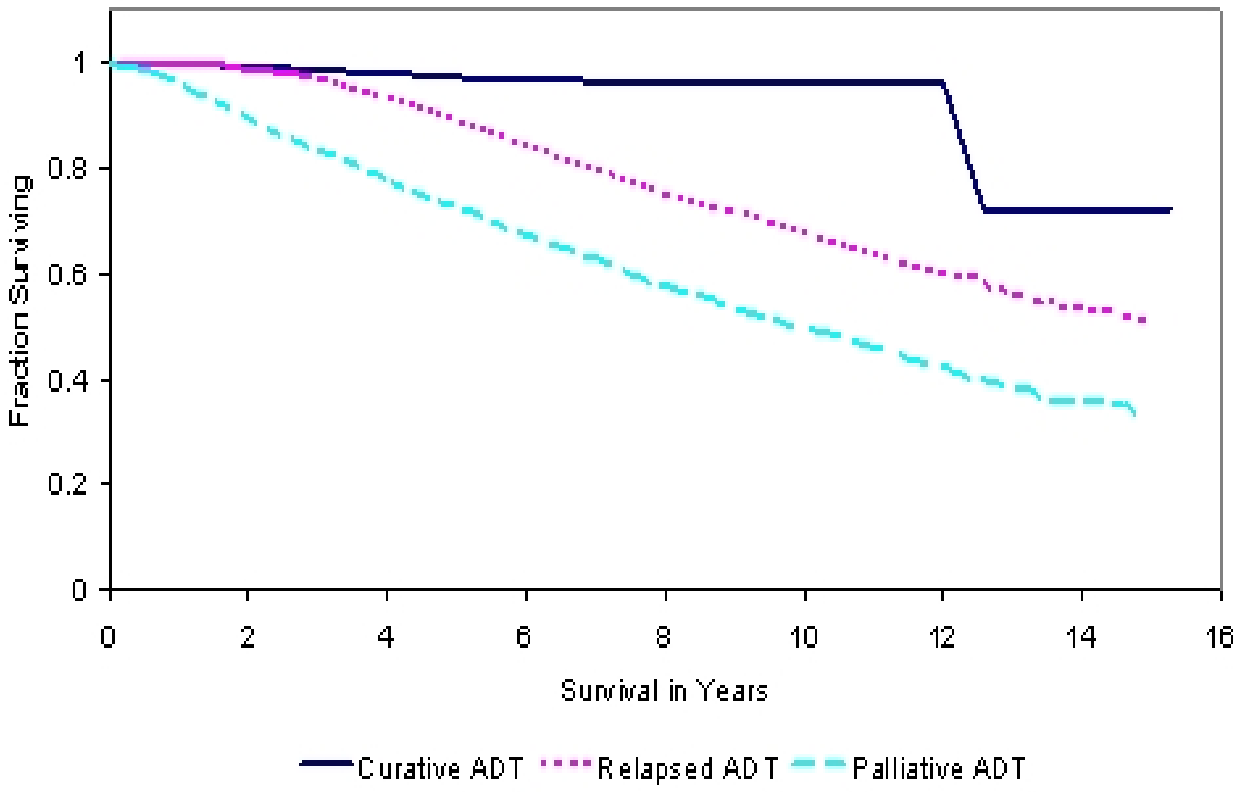
were censored because of death, or survival after the end of the study without a hip fracture. For the subjects exposed and not exposed to radiation in the Curative Radiation and Surgery cohort, the all-cause survival was shorter for the exposed subjects, Figures 5-1, which reduces the probability that differences in survival may have increased the effect of radiation treatment on the risk of hip fracture.

Figure 5-1: All-Cause Survival with and without Curative Radiation Treatment for Cohort 1. Curative Radiation and Surgery Cohort



In the ADT treatment cohort, survival was shortest for the Palliative ADT category, and longest for the curative ADT category, Figure 5-2. This may have affected the estimate of the effect of palliative ADT on the risk of hip fracture, because subjects in the palliative category had less opportunity to experience a hip fracture associated with ADT exposure.

Figure 5-2: All-Cause Survival for ADT Categories in Cohort 3. ADT Category Cohort



5.8: Summary of Results of Analyses

The risk of hip fracture was 1.59 times greater in subjects who received curative radiation treatment for prostate cancer compared to those who received curative surgery (HR 1.59, 95% CI 1.07-2.35) after adjustment for age at diagnosis, income quintile, Charlson score, year of diagnosis, and ADT duration, Table 5.3.

For men treated with curative radiation whose radiation dose to the hip-bone could be estimated from the administrative data, the risk of hip fracture fell by 6% with each one Gy increase in radiation dose between 55 and 81 Gy Biological Equivalent Dose to the hip-bone, after adjustment for age at diagnosis, income quintile, Charlson score, year of diagnosis, and ADT duration, Table 5.7. With a threshold of 60 Gy BED, the risk of hip fracture decreased by 3% with each one Gy increase in radiation dose between 60 and 81 Gy BED (HR 0.97, 95% CI 0.81-1.14).

The risk of hip fracture for men treated with relapsed ADT compared to curative ADT was 5.77 (95% CI 2.11-15.79) and for palliative ADT compared to curative ADT was 5.98 (95% CI 1.49-24.0), after adjustment for radiation treatment, age at diagnosis, income quintile, Charlson score, year of diagnosis, and ADT duration, Table 5.10. There were only seven hip fractures in the 2,138 subjects who received curative ADT, which contributed to the wide confidence intervals for these estimates.

To explore the rate of recovery of testosterone in the setting of intermittent LHRH injections, the value of the rate of reduction of the cumulative ADT exposure after stopping LHRH injections was varied from 0.5 months per month, to one month per month, to two months per month. With the increase in these values, the effect of ADT exposure on the rate of hip fracture increased from 1.102 (95% CI 1.021-1.190) to 1.103 (95% CI 1.022-1.191) to 1.104 (95% CI 1.023-1.191) per year of ADT Exposure after adjustment for age at diagnosis, radiation treatment, income quintile, Charlson score, and year of diagnosis, Table 5.11.

To explore the delay between starting ADT and the increase in fracture risk from loss of bone mineral at the hip-bone, the value of this delay was varied from 0.5 years, to one year, to two years. With the increase in these values, the effect of ADT exposure on the rate of hip fracture decreased from 1.11 (95% CI 1.04-1.19) to 1.10 (95% CI 1.02-1.19) to 1.09 (95% CI 0.996-1.18) per year of ADT Exposure after adjustment for age at diagnosis, radiation treatment, income quintile, Charlson score, and year of diagnosis, Table 5.12.

The hazard ratio for Radiation Treatment for time to hip fracture in Cohort 1. Curative Radiation and Surgery declined from 1.59 (95% CI 1.07-2.35) to 1.40 (95% CI 0.97-2.02) when subjects with any pathological fracture were included in the cohort, Tables 5.3 and 5.13.

Chapter 6: Discussion

In this chapter, the findings of the study are discussed in the context of existing knowledge, the strengths and limitations of the study are examined, and the implications of the findings for policy and future research are explored.

6.1: The Effect of Radiation Treatment on the Risk of Hip Fracture

This is the first population-based study that has reported on the risk of hip fracture in men treated with radiation for prostate cancer. Previous reports of hip fracture associated with radiation treatment for prostate cancer were in men who had medical conditions predisposing them to radiation side effects, such as Csuka and colleagues who reported bilateral hip damage from radiation treatment in a man with chronic rheumatoid arthritis (43).

The risk of hip fracture was 59% higher in men who received curative radiation compared to men who received curative surgery for prostate cancer (HR 1.59, 95% CI 1.07-2.35). This finding was consistent with the study from Baxter et al. that used population-based administrative data to examine the risk of pelvic fractures after radiotherapy (48) and reported a pelvic fracture hazard rate of 3.16 for anal cancers, 1.66 for cervical cancers, and 1.65 for rectal cancers in irradiated versus non-irradiated women after controlling for race, age, and cancer stage. Baxter's study did not report specifically on the risk of hip fracture, but 90% of the pelvic fractures in her study were hip fractures. The higher rate of fractures in women with anal cancers may be due to the radiation treatment that is routinely administered to the groin lymph nodes in these patients. The groin lymph nodes lie just in front of the hip-bone, therefore radiation treatment to the groin for anal cancer results in a higher radiation dose to the hip. The groin lymph nodes are not usually irradiated in the treatment of cancers of the rectum or cervix. The radiation treatment techniques for prostate cancer are similar to the techniques that are used for cervical and rectal cancer, and the hip fracture risk from radiation treatment to prostate cancer was similar to the risk in cervical and rectal cancers in Baxter's study.

There are no previous dose-response estimates of radiation dose to the hip and the risk of hip fracture. The only other dose-response data for hip fracture is from Emami and colleagues (50). Emami's estimate is based on the work of Shimanovskaya and Shiman, who published an extensive review of the literature relating to radiation bone injury, together with their own experience, which was gathered in Leningrad between 1929 and 1974 (85). However, all of the data available to Shimanovskaya and Shiman was from case reports and case series and none of

these patients were treated with radiation techniques that are comparable to the techniques used for treating prostate patients in BC since 1986.

The risk of hip fracture fell by 6% for each one Gy increase in radiation dose between 55 and 81 Gy (HR 0.94, 95% CI 0.87-1.01). After conversion into equivalent units, Emami's estimate of the dose risk response for hip fracture for each one Gy increase between 87 and 110 Gy BED was 1.36% (50). The range of doses received by the hip-bone in this present study was 40 – 81 Gy BED, and the range described by Emami's data was 87 - 110 Gy BED. None of the subjects in this present study received radiation doses to the hip in the range described by Emami and colleagues, so it is possible that the dose-response relationship in the dose range of this study is different from the relationship in the range of doses in Emami's report.

The sigmoid-shaped dose-response curve is widely used for predicting the relationship between radiation dose and the resulting biological effect of radiation, although the exact mathematical function that defines this shape is still being explored (49). The dose-response curve is relatively flat up to the threshold dose, and then rises up to a saturation dose. Above the saturation dose, the dose-response curve becomes flat again. Although the concept of a threshold dose is debated with respect to radiation-induced cancers (86), it remains useful for setting dose restraints and estimating dose-response relationships for normal tissue tolerance in clinical radiotherapy. There were no hip fractures in this study at doses less than 55 Gy BED, therefore this dose was used initially as the threshold dose to estimate the dose-response for hip fracture. However, the absence of hip fractures below 55 Gy BED may be due to insufficient study subjects or to insufficient follow-up. With a threshold of 60 Gy BED, the risk of hip fracture fell by 3% for each one Gy increase between 60 and 81 Gy BED (HR 0.97, 95% CI 0.81-1.14). However, the distribution of radiation dose to the hip-bone was not uniform, with 79% of the subjects and 41% of the hip fractures, receiving between 60 and 69 Gy BED, Table 4.3, which means that the dose-response data was distributed unevenly over a small dose range, which further decreases the reliability of the dose-response estimates.

The protective effect of increasing radiation dose for hip fracture found in this study may be from residual confounding, in that healthier patients tend to be selected for longer courses and higher doses of radiation treatment. In addition, there has been a gradual increase in curative radiation doses administered to the prostate over the years of this study, which means that subjects treated with the higher doses were treated more recently, and will have had shorter follow-up, and therefore less opportunity to experience a hip fracture. Residual confounding

may also influence the increased risk of hip fracture associated with radiation treatment compared to surgical treatment because patients selected for surgery tend to be healthier than patients treated with radiation.

The ICD coding for pathological fracture is not specific for the site of fracture. Hanna and colleagues in Kingston, Ontario reviewed 64 charts of approximately 3000 cases that they identified as having a pathological hip fracture from administrative health data (87). Upon chart review, they found that 22 of these 64 cases (34%) did not have a pathological hip fracture.

Coleman reported a 75% incidence of bone metastases in men with advanced prostate cancer, and 25% of these men experienced a pathological bone fracture, including vertebral fractures (88). After subjects with an ICD-9 coding for a pathological fractures were included in this present study, the number of hip fracture events increased from 245 to 260, and the risk of hip fracture after radiation treatment declined from 1.59 (95% CI 1.07-2.35) to 1.40 (95% CI 0.97-2.02). Given the difficulty of identifying pathological hip fractures in administrative data, and the different etiology of pathological hip fracture compared to hip fracture resulting from osteoporosis, the most conservative approach was to exclude all subjects who were diagnosed with any pathological fracture. However, it is probable that some of the excluded subjects did experience a non-pathological hip fracture, and that the risk of hip fracture associated with radiation treatment in the population in this study lies between 1.59 and 1.40.

In summary, this study found an increased risk of hip fracture associated with radiation treatment for prostate cancer that is similar to the risk found after radiation treatment of pelvic cancers in women. However, the radiation dose-response estimate is inconsistent with previous estimates, although previous estimates are based on radiation treatment techniques that are not consistent with current practice.

6.2: The Influence of ADT Indication on ADT Duration and the Risk of Hip Fracture

Although there is an extensive literature reporting on the increased risk of hip fracture in men with prostate cancer treated with ADT, none of the existing studies have examined whether the hip fracture risk differs according to the indications for androgen deprivation therapy (ADT). The primary objective of this component of the study was to determine whether the risk of hip fracture risk differed for men who received ADT for different indications. For this reason, men were categorized as having received ADT for curative intent, for relapsed cancer after curative treatment, or for palliative intent. There were only seven hip fractures in the 2,138 men who received ADT for curative intent (0.3%), whereas there were 72 fractures in the 2,544 men who

received ADT after relapse (2.8%), and 172 in the 5,504 men who received palliative ADT (3.1%). The risk of hip fracture in the Curative category was very low, and this may have contributed to the wide confidence intervals in the comparisons between the rate of hip fracture in the palliative and relapsed ADT Categories.

The increased risk of hip fracture in men exposed to ADT has been reported in three studies using administrative health data. Dickman et al. looked at men who received orchiectomy within 6 months of diagnosis of prostate cancer and reported a 1.6 times higher rate of hip fracture between diagnosis and death compared to men in the same community who did not have an orchiectomy (54). Melton and colleagues reported a Standardized Incidence Rate of 1.91 for hip fracture in men treated by orchiectomy compared to the general population (55). Shahinian et al. found a hip fracture rate of 4.06% from 12 to 60 months after prostate cancer diagnosis in men exposed to LHRH injections or orchiectomy within six months of diagnosis, compared to 2.06% in men who were not exposed to ADT (56). However, in none of these studies were men categorized by indication for ADT.

The overall prognosis for men in these treatment categories was not the same, with 23% of the subjects in the Palliative Category having a Charlson comorbidity score of 3 or 4, compared to 7% and 5% in the Relapsed and Curative categories respectively, Table 4.14, and the ten year all-cause survival was approximately 50%, 70%, and 95%, for men in the Palliative, Relapsed, and Curative, categories respectively, Figure 5-2. The difference in the hip fracture risk from ADT exposure in the different ADT categories may also be influenced by the competing cause of death, with men in the Palliative Category having the highest death rate, and therefore less opportunity to experience a hip fracture.

LHRH injections can be administered continuously or intermittently (i.e. stopped and restarted). Testosterone will recover after LHRH injections are stopped, and using intermittent LHRH injections as opposed to continuous therapy may reduce the risk of hip fracture, but this has not been reported previously. In this study there were 51 subjects who experienced a hip fracture after exposure to LHRH injections without orchiectomy. The recovery of testosterone after stopping LHRH injections was modeled by reducing the total LHRH exposure by 0.5, 1 or 2 months for each month after the LHRH injections were stopped. Reducing the total LHRH exposure by 0.5, 1, or 2 months for each month after the LHRH injections were stopped increased the risk of hip fracture respectively by 1.102, 1.103, and 1.104 for each year of ADT. This was a paradoxical finding in that a faster reduction in LHRH exposure might be expected to

reduce the risk of hip fracture. However, this finding can result from attributing each hip fracture in the exposed population to a shorter duration of LHRH exposure. This may lead to an increase in the number of fractures at shorter durations of LHRH exposure. This may cause an increase in the effect of duration of LHRH exposure on the risk of hip fracture.

For most biological exposures, there is a delay before the effect of the exposure is observed. After ADT starts, there is a delay of a few days before testosterone levels fall. There is a further delay before a reduction is observed in bone mineral density (BMD). Hip fractures that occur during the delay between starting ADT exposure and a reduction in BMD should be attributed to the non-exposed population. In a meta-analysis of twenty-one studies published between 1998 and 2002, the BMD loss during the first year of ADT treatment was 2% at the hip, which is at the limits of sensitivity of the methods that are available to measure BMD (89). For this study, the delay was taken to be one year, but a range of values was explored for 0.5, 1 and 2 years. These delays represent a difference in the time to experience an increased risk of hip fracture after starting ADT. The risk of hip fracture for each year of ADT exposure was 1.11, 1.10 and 1.09 respectively for these three values, which suggests a protective effect for hip fracture when the onset of hip fracture risk is delayed.

In conclusion, this study found that the risk of hip fracture varied by different categories of ADT treatment, and that the risk of hip fracture was sensitive to the rate of recovery from the ADT effect with intermittent ADT, and sensitive to the rate of onset of the ADT effect.

6.3: Strengths and Limitations of the Study

The major strength of this study was the availability of comprehensive population-based data derived from universal health coverage. The only men not covered by the provincial health insurance plan are serving members of the military and the Royal Canadian Mounted Police, but these men comprise a small proportion of the provincial population, and they are younger than the age at which most men are diagnosed with prostate cancer, so the proportion of these men diagnosed with prostate cancer was also likely to be small.

A concern of this study was that the investigator did not control the process of data collection. Administrative data are collected to manage the health care system. Many different people in numerous places collect these data over numbers of years. The data used in this study were collected throughout the province of BC by coding staff working in hospitals and cancer clinics between 1985 and 2002. Most of the coding staff and their supervisors who collected the data have now moved to other tasks or retired, so it was difficult to confirm the policies and

procedures under which the data was collected. Most of the data used in this study has not been verified. Despite this limitation, verification studies have shown a high degree of accuracy in Canadian health care administrative data (90), and the verification of LHRH prescriptions that was performed as part of this present study showed an excellent rate of agreement between administrative and clinical data.

The data from the BC Cancer Agency was assembled by health records staff who were not supervised by the investigator. The investigator submitted identifiers to the BC Ministry of Health but had no influence over the processes and procedures used by the Ministry for matching the identifiers to the records of the Medical Services Plan. The Ministry of Health sent anonymised identifiers to the Center for Health Services Policy and Research (CHSPR) who assembled the files for the investigator. Once again, the investigator had no part in this process, and there were no opportunities to confirm the validity of the data after anonymization. It is expected that most errors are randomly distributed throughout the data, but this is a difficult assumption to verify. However, the comparison that was made in this study between the hospital abstracts and the physician billing records showed an acceptable rate of agreement for hip fracture events, after allowing for the limitations in ICD coding in the physician billing records.

The investigator created two hundred and eight SAS programs during the process of linking the files, creating the variables, and analyzing the data. It is inevitable that there will be programming errors in a project of this size. Despite extensive checking and rechecking, some of these errors may have influenced the results of the analysis.

As stated by Pilote and Abrahamowicz and colleagues in a recent publication (91), "The robustness of results from observational studies is highly dependent on the nature of the analysis." The analysis in this study was complicated by the use of time-dependent variables. It was necessary to analyze each LHRH prescription and create look-up arrays of LHRH exposure by time period. The SAS implementation of time-dependent variables in Cox regression models was difficult to verify, especially with files containing large numbers of observations..

This study was limited by the small numbers of events in some of the subset analyses. Despite using population data from a 16-year period, there were insufficient events to achieve statistical significance for several analyses. Most investigators in this area have used Medicare data linked to the SEER cancer registry. The SEER cancer registry includes approximately ten percent of the US population, so the SEER population is almost seven times the population of BC. SEER data also includes cancer stage and tumour grade, whereas stage and grade are only

present in the BC Cancer Registry for subjects who are seen at the Cancer Agency. Cancer stage and grade are important prognostic indicators, and men with more advanced stage and higher grade cancer are more likely to receive radiation treatment than surgery. This study was unable to include cancer stage and grade as confounding variables in the analysis. These variables are important in order to control for differences in disease severity and prognosis between treatment groups and changes in disease severity over time. Their inclusion may have weakened the associations found in this study between radiation treatment and hip fracture but strengthened the association between radiation dose and hip fracture..

This study attempted to control for comorbidity and socioeconomic status using the Charlson Index and the Income Quintiles respectively. Charlson Index was missing for subjects that did not have a hospital admission in the 6 months before or after their prostate cancer diagnosis date. Missing subjects were assigned a missing category in the Charlson Index indicator variable. This allowed the inclusion of these subjects in the multivariate analysis, but may have weakened the association between comorbidity and hip fracture.

Income Quintile was obtained from census area estimates by Statistics Canada. Area level indicators may not accurately indicate the socioeconomic status of individuals in the area, which may introduce an aggregation bias into the analysis.

In attempting to examine the effects of intermittent ADT and the interval between starting ADT and measuring hip fracture, this study embarked on areas where there is, at present, little supporting biomedical research, therefore it is difficult to substantiate some of the assumptions made in the analysis.

6.4: Implications of the Findings for Policy and Future Research

The most significant policy concern in prostate cancer is over-treatment, and the complications that follow from unnecessary treatment. The numbers of men diagnosed with prostate cancer in Canada increased from 7,000 in 1981 to 18,500 in 2000, and the number of hospital separations for radical prostatectomy increased from 182 to 4,561 per year in the same period. (92). Long-term follow up data, from Cancer Registries in Scandinavia and Connecticut, suggest that the majority of men diagnosed with prostate cancer, but without curative treatment, do not die of prostate cancer (5, 93), while other researchers have shown that elderly men subjected to radical prostatectomy or radiation treatment will only gain a few months of additional survival (94). It is likely that part of the dramatic increase in treatment is driven by unrealistic fear of prostate cancer and a lack of appreciation of the side effects of treatment. This

study should contribute to the understanding of the complications related to radiation treatment and androgen deprivation. This study extends existing knowledge of the effects of androgen deprivation therapy (ADT) and hip fracture by demonstrating that men who receive ADT as part of curative treatment experience very few hip fractures, but the hazard rate for fracture was greatest for men who receive ADT for palliation compared to men who receive for ADT together with curative treatment. The risk is of hip fracture is important because of the increasing number of asymptomatic men who are treated with ADT at diagnosis. Shahinian et al. reported that the use of ADT in men older than 80 years with localized disease increased from 3.75 in 1991 to 30.9% in 1999, despite the lack of evidence for benefit (13). Men whose cancer relapses after radical treatment survive longer than men treated for palliation. At present, there is insufficient data to guide physicians on the risks and benefits of early versus late treatment in asymptomatic men with PSA relapse after curative radiation or surgery.

The implications of this study are that men who receive ADT together with curative treatment experience few hip fractures, but that fracture risk is greatest in men who receive ADT for palliation of prostate cancer. Studies are now underway examining the risks and benefits of following men without treatment for low-risk prostate cancer. These are not randomized studies, but they are likely to yield useful information to guide physicians in advising patients with low-risk prostate cancer. Future research in prostate cancer should examine which cancers are likely to progress and which can likely be followed lifelong without treatment. If this was better understood, patients and their physicians would be reassured that non-intervention was not putting lives at risk.

The study findings also have implications for reducing the toxicity of prostate cancer treatment. The number of hip fractures was increased with men who receive radiation treatment, and there was no clear relationship between radiation dose and hip facture risk. The implication is that the radiation dose to the hip-bone should be kept as low as possible. Several new approaches to radiation treatment are being explored which reduce the dose to the hip-bones, and to the bladder and rectum, which are adjacent to the prostate and are sensitive to radiation side effects.

Further research is needed to examine the risks and benefits of intermittent versus continuous ADT. Conti and colleagues recently published a meta-analysis of existing studies and found that the majority of the studies were too small to yield comparative information, and none of the studies have reported on survival outcomes for intermittent compared with

continuous ADT (95). Randomised studies of intermittent versus continuous ADT have recently been completed for men who have relapsed after curative therapy and men diagnosed with advanced disease, but the results of these studies will not be known for several years.

Research using administrative health data will continue to yield timely data on treatment outcomes and side effects. However, prospective cohort studies are better able to identify and control for the many biases that affect treatment choices and outcome measurement. There is a lack of population-based information on the side effects of treatment and on whether treatment improves or worsens health-related quality of life. It is increasingly important to link prognosis and health outcomes with biological information from tumour and normal tissue, in order to tailor treatment to men who will benefit, to reduce toxicity in men who are susceptible to side-effects, and to spare from treatment those whose tumours are not a risk to their health. With increasing use of the Internet and other electronic technologies, it may be possible to collect prospective data on representative samples of men at acceptable cost (96).

6.5: Conclusions

This is the first study to report an increased risk of hip fracture in men treated with radiation compared to surgical treatment for prostate cancer. The increased risk is similar to that reported in women who received radiation treatment for rectal and cervical cancer. This is also the first study to attempt to estimate the dose-response relationship between radiation dose to the hip-bone and hip fracture. The finding of a non-significant protective effect for increasing radiation dose is likely due to both residual confounding and insufficient hip fracture events. This study confirms the findings of previous studies that have shown an increased risk of hip fracture associated with ADT, and extends previous findings in showing that the risk of hip fracture is much greater in men who receive ADT for relapsed or palliative treatment of prostate cancer compared to those who receive ADT together with curative radiation or surgery.

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Appendix A: Tumour, Node and Metastasis (TNM) Stage and Gleason Score

TNM Definitions (97)

Primary tumor (T)

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

T1: Clinically inapparent tumor not palpable nor visible by imaging

- T1a: Tumor incidental histologic finding in 5% or less of tissue resected
- T1b: Tumor incidental histologic finding in more than 5% of tissue resected
- T1c: Tumor identified by needle biopsy (e.g., because of elevated PSA)

T2: Tumor confined within prostate

- T2a: Tumor involves 50% or less of one lobe
- T2b: Tumor involves more than 50% of one lobe but not both lobes
- T2c: Tumor involves both lobes

T3: Tumor extends through the prostate capsule

- T3a: Extracapsular extension (unilateral or bilateral)
- T3b: Tumor invades seminal vesicle(s)

T4: Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

Regional lymph nodes (N)

Regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries. They include the following groups (laterality does not affect the N classification): pelvic (not otherwise specified [NOS]), hypogastric, obturator, iliac (i.e., internal, external, or NOS), and sacral (lateral, presacral, promontory [e.g.,

Gerota], or NOS). Distant lymph nodes are outside the confines of the true pelvis. They can be imaged using ultrasound, CT, MRI, or lymphangiography and include: aortic (para-aortic, periaortic, or lumbar), common iliac, inguinal (deep), superficial inguinal (femoral), supraclavicular, cervical, scalene, and retroperitoneal (NOS) nodes. Although enlarged lymph nodes can occasionally be visualized, because of a stage migration associated with PSA screening, very few patients will be found to have nodal disease, so false-positive and false-negative results are common when imaging tests are employed. In lieu of imaging, risk tables are generally used to determine individual patient risk of nodal involvement. Involvement of distant lymph nodes is classified as M1a.

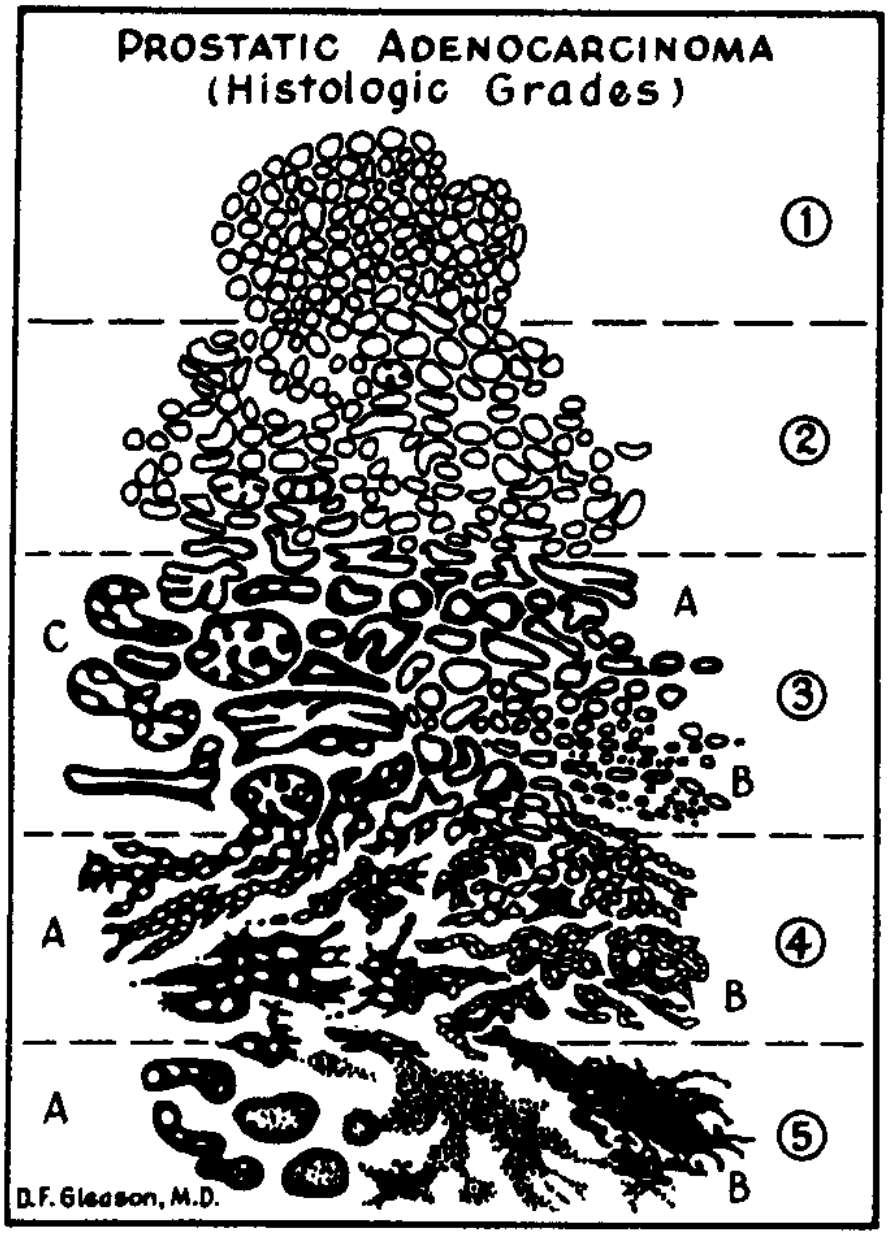
NX: Regional lymph nodes were not assessed
N0: No regional lymph node metastasis
N1: Metastasis in regional lymph node(s)

Distant metastasis (M)

MX: Distant metastasis cannot be assessed (not evaluated by any modality)
M0: No distant metastasis
M1: Distant metastasis
- M1a: Nonregional lymph node(s)
- M1b: Bone(s)
- M1c: Other site(s) with or without bone disease

Gleason Score

The cancer histology is graded according to the appearance of the prostate cancer under the microscope. Low grade (grade 1 and 2) cancers are well differentiated, i.e. resemble normal prostate tissue, and intermediate (grade 3) and high grade (grade 4 and 5) cancers are progressively less well differentiated. The Gleason score is the sum of the grade of the predominant tumour, and the second largest area of tumour. Therefore the Gleason score has two numbers that sum between 2 and 10 (from 1+1 to 5+5) (98).



Appendix B: BC Cancer Agency Drug Identification Numbers and Drug Names for LHRH Injections

This table lists the BCCA Drug Identification Numbers and drug names that were present in the BCCA Pharmacy File for LHRH injections.

BCCA Drug Identification Number	BCCA Drug Name
00727695	LEUPROLIDE INJ 5 MG/ML
00836273	LEUPROLIDE ACETATE 7.5 MG KIT
00857599	-GOSERELIN PFS 3.6 MG*
00884502	LEUPROLIDE 3.75 MG DEPOT
02049325	GOSERELIN 3.6 MG SYR
02225905	GOSERELIN 10.8 MG SYR
02228955	BUSERELIN 6.3 MG IMPLANT
02230248	LEUPROLIDE ACETATE 22.5 MG DEPOT
02239833	LEUPROLIDE ACETATE 30 MG DEPOT
02240749	BUSERELIN 9.45 MG IMPLANT
1225905	GOSERELIN ACETATE 10.8MG
2225905	GOSERELIN ACETATE 10.8MG
2228955	BUSERELIN ACETATE 6.3MG (
2230248	LEUPROLIDE 22.5 MG SR (LU
591000000	GOSERELIN PFS 3.6 MG
727695	LEUPROLIDE INJ 5 MG/ML
836273	LEUPROLIDE DEPOT 7.5MG/VI
857599	GOSERELIN ACETATE 3.6 MG
GUOTT13	GOSERELIN ACETATE 3.6 MG (GUOTT)
GUOTT13FREE	GOSERELIN ACETATE 3.6 MG (GUOTT)
GUOTT48	GOSERELIN ACETATE 3.6 MG (GUOTT)

BCCA Drug Identification Number	BCCA Drug Name
GUOTT95/	GOSERELIN ACETATE 3.6 MG
GUPH	GOSERELIN ACETATE 3.6 MG

Appendix C: Income per Person Equivalent Calculation

The Income Per-Person Equivalent (IPPE) is calculated from census data by Statistics Canada using the Total Household Income in the Enumeration Area (EA) and the number of multi-person households, as follows (76):

IPPE = Total Household Income in EA / Person Equivalents.

Where Person Equivalents =

1.00 * (number of one-person households in EA) +
1.36 * (number of two-person households in EA) +
1.72 * (number of three-person households in EA) +
1.98 * (number of four-person households in EA) +
2.30 * (number of five- or more person households in EA)

Appendix D: Charlson Comorbidity Index

Calculation of the Charlson Comorbidity Index (CCI) (78).

The Charlson Comorbidity Index is the sum of scores for the following conditions:

Score for each condition	Condition
1	Myocardial infarct
1	Congestive heart failure
1	Peripheral vascular disease
1	Cerebrovascular disease
1	Dementia
1	Chronic pulmonary disease
1	Connective tissue disease
1	Ulcer disease
1	Mild liver disease
1	Diabetes
2	Hemiplegia
2	Moderate or severe renal disease
2	Diabetes with end organ damage
2	Any tumor
2	Leukemia
2	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
6	Acquired immunodeficiency syndrome

Assignment of the Charlson Score from the Charlson Comorbidity Index:

Charlson Comorbidity Index	Charlson Score
0	0
1	1
2	2
Greater or equal to 3	3

Appendix E: UBC Research Ethics Board Certificate of Approval

The University of British Columbia
Office of Research Services
Behavioural Research Ethics Board
Suite 102, 6190 Agronomy Road,
Vancouver, B.C. V6T 1Z3

CERTIFICATE OF APPROVAL- MINIMAL RISK RENEWAL

PRINCIPAL INVESTIGATOR:	DEPARTMENT:	UBC BREB NUMBER:
Charlyn Black	UBC/College of Health Disciplines	H04-80912

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
BC Cancer Agency	Vancouver Island BCCA

Other locations where the research will be conducted:
N/A

CO-INVESTIGATOR(S):
Paul Blood

SPONSORING AGENCIES:
N/A

PROJECT TITLE:
A Population-Based Analysis of the Risk of Hip Fracture in Men With Prostate Cancer Exposed to Androgen Deprivation Therapy in BC Using Anonymised Linked Administrative Data

EXPIRY DATE OF THIS APPROVAL: February 29, 2009

APPROVAL DATE: February 29, 2008

The Annual Renewal for Study have been reviewed and the procedures were found to be acceptable on ethical grounds for research involving human subjects.

Approval is issued on behalf of the Behavioural Research Ethics Board

Dr. M. Judith Lynam, Chair
Dr. Ken Craig, Chair
Dr. Jim Rupert, Associate Chair
Dr. Laurie Ford, Associate Chair
Dr. Daniel Salhani, Associate Chair
Dr. Anita Ho, Associate Chair