AN ECONOMIC EVALUATION OF CALCIUM AND VITAMIN D VERSUS HORMONE REPLACEMENT THERAPY, FOR THE PREVENTION OF HIP FRACTURES IN CANADIAN POSTMENOPAUSAL WOMEN

By

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Graduate Department of Nutritional Sciences
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An economic evaluation of calcium and vitamin D versus hormone replacement therapy, for the prevention of hip fractures in Canadian postmenopausal women.

Doctor of Philosophy, 1999
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ABSTRACT

Osteoporosis is a major health problem. As average life expectancy increases, the incidence of hip and other fractures in postmenopausal women (PMW) also increases. The number of hip fractures (HF) and health care resources required to manage them are expected to quadruple in the next 40 years, under a No Intervention (NI) scenario, as the Canadian population ages. Consequently, implementation of effective preventative interventions are necessary in PMW to avoid future HFs. The hypothesis of the thesis is that population supplementation with Calcium and vitamin D (CaVD) will result in fewer HFs, lower healthcare cost, and life years gained (LYG) compared to NI, if therapy is initiated in PMW at either age 50 (CaVD50), or age 65 (CaVD65), and continued until age 90 or death. In an economic evaluation, the intervention under study must be compared to the current gold standard of care. Currently hormone replacement therapy (HRT) is that standard. The evaluation was initiated to determine the incremental cost-effectiveness of CaVD or HRT versus NI. A forty-year Markov economic model was developed to conduct the evaluation. Canadian-specific probabilities and cost of events, needed for the model, were generated by manipulation of medical databases and literature reviews; efficacy of CaVD in osteoporosis prevention was evaluated via the conduct of a meta-analysis. The model was run under the base case assumptions (CaVD and HRT had 20%, and 50% reduction in HF risk respectively, versus NI) and 3% rate of discounting. CaVD65 strategy was considered weakly dominant (resulted in fewer HFs and lower cost than NI) under the base
case assumptions. HRT strategy initiated at age 65 was dominant over all strategies evaluated. HRT initiated at age 50 was cost-effective ($10,969/LYG; fewer HFs, but cost more than NI), while CaVD50 was not ($94,843/LYG). The model results were sensitive to the cost of CaVD, HRT, long-term care, hip fracture repair, and to treatment efficacy assumptions, however use of acceptable cost ranges for these parameters did not alter the rank-ordering of the interventions.

In conclusion, CaVD65 is a cost-effective alternative for those women who choose not to take HRT for the prevention of HFs.
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I can do all things through Christ who strengthens me.

Philippians 4:13
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Appendix A
Supplement A
LIST OF ABBREVIATIONS

1,25 (OH)_{2} D_{3}: 1.25 dihydroxyvitamin D_{3} Vitamin D

AI: Adequate Intake

BMD: Bone Mineral Density

BrCA: Breast Cancer

CaMos: Canadian Multicentre Osteoporosis Study

CaVD: Calcium and vitamin D therapy

CaVD50: Calcium and vitamin D therapy initiated at age 50 years.

CaVD65: Calcium and vitamin D therapy initiated at age 50 years.

CHD: Coronary Heart Disease

CI: 95% Confidence Interval

CIHI: Canadian Institute for Health Information

CMG: Case Mix Group

DRG: Diagnosis Related Group

EAR: Estimated Average Requirement

FNB: Food and Nutrition Board

HC: Home Care

HDL: High Density Lipoprotein

HRT: Hormone Replacement Therapy

HRT50: HRT initiated at age 50 years

HRT65: HRT initiated at age 65 years

IU: International Unit
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>LDL</td>
<td>Low Density Lipoprotein</td>
</tr>
<tr>
<td>LOS</td>
<td>Length of Stay</td>
</tr>
<tr>
<td>LYG</td>
<td>Life Years Gained</td>
</tr>
<tr>
<td>LYL</td>
<td>Life Years Lost</td>
</tr>
<tr>
<td>LTC</td>
<td>Long-Term Care</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td>MRD</td>
<td>Most Responsible Diagnosis</td>
</tr>
<tr>
<td>NI</td>
<td>No Intervention</td>
</tr>
<tr>
<td>OCCP</td>
<td>Ontario Case Cost Project</td>
</tr>
<tr>
<td>OHT</td>
<td>Ovarian Hormonal Therapy</td>
</tr>
<tr>
<td>OSC</td>
<td>Osteoporosis Society of Canada</td>
</tr>
<tr>
<td>PMW</td>
<td>Post Menopausal Woman</td>
</tr>
<tr>
<td>RC</td>
<td>Rehabilitation Care</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
</tr>
<tr>
<td>RDA</td>
<td>Recommended Dietary Allowance</td>
</tr>
<tr>
<td>RNI</td>
<td>Recommended Nutrient Intake</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>WMD</td>
<td>Weighted Mean Difference</td>
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1. INTRODUCTION

Osteoporosis is currently a major health problem with estimated costs of treatment in Canada exceeding $1.3 billion annually (Goeree et al, 1996). Unfortunately, the projected combination of population growth and increased life expectancy is anticipated to place an approximate four-fold increase on these health resources by the year 2050; thereby highlighting the need to develop and promote the use of effective preventive interventions. The greatest burden of illness and costs of osteoporosis are attributed to fracture of the hip; where greater than 90% of hip fractures in older postmenopausal women are attributable to the disease process (Melton et al, 1992). As a consequence, this thesis provides a focused examination of hip fracture incidence and costs in postmenopausal women with the perspective that the majority of hip fracture events captured represent fractures secondary to osteoporosis, but, with the understanding that a smaller percentage of fractures can be attributed to other causes.

A number of approaches have been studied in the past 10 years to evaluate their efficacy in preventing osteoporosis. For example, hormone replacement therapy (HRT) has been shown to be effective at maintaining bone mass (Christiansen et al, 1980), and is considered to be the current gold standard for the treatment of osteoporosis. Concerns over the potential increased risk of breast cancer with HRT, however, have prevented a significant proportion of the postmenopausal population from using this therapy. Another strategy that has been recommended for the prevention of osteoporosis is calcium and vitamin D (CaVD) supplementation. This therapy does not offer any protective effects against cardiovascular disease, as is the case for HRT, however it is considered not to increase the risk of breast cancer.
Significant changes are occurring in the utilization of pharmaceuticals and healthcare interventions in Canada. Firstly, there is the acute question of cost containment, and secondly the quest for enhancement of quality of care. Worldwide, guidelines are being implemented that include health economics evaluation as one of the three tiers in the licensing of pharmaceuticals. To demonstrate the utility of any therapy, analyses are conducted relative to the current gold standard; in this instance, HRT. These analyses are necessary to support the application process for the attainment of reimbursement from a number of Canadian provinces. Despite this advancement within the pharmaceutical domain, the adoption of health economic evaluations into other health care disciplines is currently in its infancy. Indeed, this approach has yet to be applied to the use of nutritional supplements for the prevention of age-related diseases, including osteoporosis.

This thesis therefore provides a unique contribution in that it employs current health economic techniques to evaluate the benefits of CaVD supplementation for the prevention of hip fractures in postmenopausal women. Not only does it demonstrate the usefulness of this approach in the evaluation of CaVD, but more broadly opens the potential for economic evaluations to be included in nutritional programme evaluations for developed countries, particularly as they relate to diseases of aging.

The conduct of economic evaluations involves the collection of data on clinical outcomes and associated costs of intervention and treatment. Ideally the time horizon of the economic evaluation should match the time period over which the clinical trial data were collected. Unfortunately, clinical trials evaluating therapies requiring long-term administration for the prevention of outcomes, such as hip fracture, at five or more years post initiation are lacking. Typically these trials evaluate surrogate marker changes, e.g.
changes in bone mineral density, and use these markers to predict risk reduction of actual outcomes (hip fracture) in later years. The economic evaluations of preventative therapies under these circumstances are conducted via use of economic models, such as the Markov model employed in this thesis, which allows for the longitudinal assessment of cost/benefits based on projected risk reduction.

Recently, considerable discussion has surrounded the age at which HRT initiation should occur (at menopause versus 65 years of age) for the prevention of hip fractures (Barrett-Connor, 1998). The median age of women at the age of the cessation of menstrual bleeding and initiation of the menopause is 50 years (Carr et al, 1987). Comparable arguments can be applied to all treatment strategies for hip fracture prevention. Decisions surrounding the age at which osteoporosis preventative strategies should be initiated have been implicated as important in providing the greatest benefit to risk ratio for interventions, and assuring efficient use of health care resources. As a consequence, the current evaluation compares the impact of initiating therapy at menopause (50 years of age) versus a 15 year delay (65 years of age) prior to initiation. Thus, the hypothesis under examination in this thesis is that supplementation with CaVD or treatment with HRT in Canadian postmenopausal community-dwelling women at the time of study initiation, will result in fewer medical events and lower overall healthcare cost than no intervention if therapy is initiated shortly after menopause. The secondary hypothesis is that delay of supplementation (by 15 years) beyond the initiation of the menopause, in women which were community-dwelling at 50 years of age, will result in more medical events and additional costs than supplementation initiated shortly after menopause.
2. REVIEW OF THE LITERATURE

2.1 Epidemiology of Fractures

Osteoporosis is a growing epidemic primarily in women in whom a 15% lifetime risk exists for a hip fracture (Clark et al, 1992), and at least 40% of Caucasian women over the age of 50 will suffer a fracture of the spine, hip and distal radius (Melton et al, 1992). Annually, 1.2 to 1.5 million fractures a year occur in the United States in women and men that are attributed to osteoporosis (Rudy, 1989). The estimated lifetime risk of fracture in Caucasian 50 year-old women is 17.5% at the hip, 15.6% at the vertebra, and 16.0% at the distal forearm (Melton et al, 1992). The incidence of hip fracture is of the greatest interest and importance due to the complications that result from this type of fracture, and its lifetime occurrence in one-third of women and one-sixth of men over the age of 65 (Owen et al, 1982).

Osteoporosis is a term that has been used to describe the clinical outcome (fracture) and the process that gives rise to fractures (Kanis, 1990). In 1991 a consensus development conference defined osteoporosis as (Consensus development conference, 1991):

"A disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk."

2.1.1 Hip Fractures

Fracture rates of the femoral neck have been increasing over the past decade in Canada, principally from the rise in the median age of the population (Jaglal et al, 1996).
Martin et al (1991), in reviewing the incidence of hip fractures over a twelve year period in Manitoba and Saskatchewan, noted that the number of fractures exceeded the percent increase in the population.

Canadian data on the incidence and demography of osteoporosis, and hip fractures specifically, are available from Statistics Canada, although limitations exist with respect to the accuracy of these data (Narod et al, 1986). Fractures of the femoral neck can be estimated with the greatest accuracy since they require a surgical procedure which is tracked nationally. Measures of the incidence of fractures of the spine and the radius/humerus based upon the number of surgical procedures tend to underestimate frequency since they often do not require hospitalization, or in the case of vertebral fractures can occur and not be recognized as such by the patient.

The annual incidence of hip fractures in Canada in 1981 was estimated to be (Narod et al, 1986): Male 32.7/100 000 Female 89.8/100 000

This rate is somewhat lower than the rates from the United States - Rochester, Minnesota (Gallagher et al, 1980): Male 42.9/100 000 Female 124.5/100 000

The discrepancy in rates reported by Gallagher et al, and by Narod et al are surprising since the populations of both Canada and Rochester are both predominantly Caucasian, and of northern European descent. Narod et al (1986) suggest that the variability may be due to a sampling error since this estimate assumes that Rochester is typical of the United States. Alternatively the Narod et al (1986) projections may have under-estimated fracture incidence, since as will be discussed later, an incomplete database was used.
The total number of hip fractures in the United States in 1986 was 238,000 (Hughes et al, 1988). The total number of hip fractures in Canada in 1987 was 18,903 (Statistics Canada, 1989). It appears from these data that the incidence of hip fractures in Canada is approximately one-tenth that of the United States, corresponding to population size, but as with the Narod et al (1986) data could be suggestive of a somewhat lower incidence in Canada.

2.1.2 Vertebral Fractures

Vertebral fractures, although more frequent than hip fractures, are more difficult to determine due to subjective variables in their diagnosis from radiographs. A number of algorithms have been proposed that utilize vertebral body dimensions to classify this type of fracture (Eastell et al, 1991; Black et al, 1991). Estimates of vertebral fracture prevalence increase from 3% at age 50 to 40% at age 80 (Melton, 1989). Kelsey's et al (1987) estimate of vertebral fractures, of approximately 500,000 per year, is an underestimate according to Melton (1989) indicating that the majority of these fractures are undiagnosed (Cooper et al, 1992).

2.1.3 Fractures of the Forearm

Location of fracture has been correlated with age, with forearm fractures increasing in the 50s until age 65 and then plateauing (Wasnich, 1996). A number of researchers have suggested that the plateau is a result of the inability of the elderly to extend their arm in a protective reflex with increasing age (Cummings et al, 1989).
Seasonal differences are noted with an increased rate of distal arm fractures (Colles fractures) in the winter months where the potential for falls on slippery surfaces exist.

2.2 Pathogenesis of Fractures

In order for a fragility fracture to occur two elements are required, namely bone fragility (low bone mineral density) and some degree of trauma. A number of models have been constructed to explain the interrelationship between fracture and the pathogenic factors (Riggs 1988). As individuals age a decrease in bone mass is observed. Although, on average, women who sustain fractures have lower bone densities than do women without fractures, there is considerable overlap. Therefore, density alone cannot explain the propensity to fracture. Falls occur more frequently as we age and are more common in women than men. One third of all elderly experience at least one fall per year (Cummings et al, 1989). Falls may be the result of environmental hazards, are iatrogenic, or due to deficits intrinsic to the elderly. Although the incidence of hip fractures increases 30 fold between ages 50 and 80, this is far exceeded by the increase in falls between these ages. Attention has been focused on the mechanics of falling since only 1% of falls in the elderly will result in hip fracture (Hayes et al, 1991). A number of protective devices have thus been developed and have demonstrated a reduced frequency of hip fracture (Lauritzen et al, 1993).

Examination of Statistics Canada figures demonstrate the exponential rise of hip fracture rate with increasing age in both men and women (Statistics Canada, 1989). Similarly examination of the fracture rate data from this source indicate that 80% of all
hip fractures occur in individuals over age 45, and 80% of these occur in women. Similar rates are also seen in the U.S. (Melton, 1986).

Hips fracture rates correlate seasonally, with an increase during the winter months (Jacobsen et al, 1991). This may be due to a number of factors including tripping that can occur indoors during the darker winter months, similarly the elderly do not venture outside in inclement weather resulting in reduced exposure to sunlight resulting in decreased levels of dihydroxylated vitamin D since vitamin D is not synthesized in winter months in Canada.

Racial differences appear to influence fracture rates with the lowest rate seen in Blacks, intermediate rates in Asians and the highest rates in Caucasians (Cummings et al, 1985).

With advancing age, changes in the calcitropic hormones contribute significantly to the pathogenesis of osteoporosis. Albright et al (1941) proposed that osteoporosis pathogenesis consists of two separate paradigms, one that is related to the loss of estrogen at the menopause, and the other that is age related. This concept has been classified into the following categories: Type I and Type II osteoporosis (Riggs 1985). Type I osteoporosis, postmenopausal osteoporosis, is generally defined as affecting women within 15 to 20 years of menopause with the main clinical manifestation being vertebral fractures. Estrogen deficiency is felt to underlie this form of osteoporosis and as a result the skeleton becomes more sensitive to parathyroid hormone (PTH) resulting in increased calcium resorption from bone. In these patients a reduced level of serum PTH causes a decrease in serum 1,25-dihydroxyvitamin D₃ production and malabsorption of calcium (Gallagher, 1990).
Type II osteoporosis, senile osteoporosis, is seen in both men and women over the age of 75 and is manifested mainly by hip and vertebral fractures (Ullrich, 1991). Decreased bone formation and a decline in 1 alpha-hydroxylase activity in the kidney results in a decline in serum 1,25-dihydroxyvitamin D$_3$, which leads to malabsorption of calcium and secondary hyperparathyroidism. In some Type II patients there may also be a decline in the function or number of the vitamin D-binding receptors in the gut (Gallagher, 1990). Treatment of patients with vitamin D analogues may normalize calcium absorption and improve calcium balance.

In both types of osteoporosis, bone mass decreases because bone resorption exceeds bone formation. Estrogen deficiency and decreased renal capacity to synthesize 1,25-dihydroxyvitamin D$_3$ affect all elderly women, resulting in increased risk for the development of osteoporosis.

2.3 Role of Bone Tissue

Bone is an active tissue composed of both organic and inorganic components. The organic component is produced by the osteoblasts and consists of 95% type I collagen and 5% noncollagenous proteins, e.g., osteocalcin, osteonectin, bone morphogenic protein, proteoglycans, and sialoproteins (Baron, 1996), however the functions of the noncollagenous proteins are not well understood. Osteocalcin (bone gla protein) comprises 20-40% of the noncollagenous proteins, is produced by the osteoblasts and is thought to be involved in the mineralization of osteoid to form bone. Its production is stimulated by 1,25-dihydroxyvitamin D. Elevated levels of osteocalcin can act as a predictor of a therapeutic response to calcitonin. Osteonectin comprises 20% of
the noncollagenous proteins. The osteonectin-collagen complex potentiates the deposition of calcium phosphate salts onto the matrix.

The inorganic component makes up 70% of the bone mass and consists primarily of an insoluble crystal, hydroxyapatite. The mineral is initially deposited on the organic matrix as calcium phosphate salts and later transformed into apatite crystals. Bone apatite is a heterogeneous mixture mostly consisting of calcium and phosphate but also containing varying amounts of carbonate, magnesium, fluoride, sodium, and potassium.

The skeleton is comprised of two types of bone, namely trabecular (cancellous) bone and cortical (compact) bone. Trabecular bone is found primarily in vertebrae and the ends of long bones. Cortical bone, on the other hand, is found in the shafts of long bones. Although the majority of bone in the skeleton is cortical, alterations in bone turnover are usually noted in the trabecular component because of its higher metabolic activity, where 80% of bone remodelling occurs (Gennant et al, 1983).

2.3.1 Bone Remodeling

Skeletal growth and development continues from in utero until the end of the third decade of life. Peak trabecular bone mass is reached by the end of the 2nd decade, while peak cortical mass is attained by the end of the 3rd decade (Heaney, 1996). Bone is a non-static tissue metabolically, and continuously remodels itself. The factors controlling bone resorption and formation under normal remodelling situations are not well understood, however, under normal circumstances bone resorption and formation are balanced. A disturbance in this remodelling process will result in bone loss (negative bone balance) (Dempster, 1995).
The remodelling process is responsible for replacing the old bone matrix with the new at an annual turnover rate of 25% in trabecular bone and 2-3% in cortical bone (Dempster et al, 1993). This remodelling sequence proceeds in the following order (Dempster, 1995):

1) **initiation**, the generation of an impulse that alters the status of a resting bone surface, lowering its threshold for activation;

2) **activation**, the provocation of the earliest cellular responses to the initiating stimulus;

3) **resorption**, the removal of organic and inorganic components of bone by osteoclasts;

4) **reversal**, the termination of resorption and initiation of formation; and

5) **formation**, osteoblastic repair of the resorption cavity.

This sequence of events prior to menopause ensures that bone mass is preserved. However, once menopausal age is reached bone mass preservation becomes compromised. This long-term, progressive loss in bone mass is the summation of short-term losses (failure of formation to equal resorption) at the individual remodelling loci. Bone loss can be accelerated by excessive resorption or diminished formation. The cells that mediate these processes are the osteoclast (resorption) and the osteoblast (formation). Osteoblast and osteoclast functions are controlled by hormones, and also by substances produced by the bone cells themselves.
2.3.2 The Osteoclast

The osteoclast is a multinucleated cell that resorbs bone. The active osteoclast is characterized by a ruffled border at the site where the cell attaches to bone. Tartrate resistant acid phosphatase (TRAP) is an enzyme that is produced by the osteoclast and reflects osteoclastic activity. The ruffled border is the site where resorption occurs. Although the exact mechanism is unclear, $\text{H}^+$ secretion by the osteoclast promotes hydroxyapatite dissolution. The osteoclast also causes the breakdown of the organic component of bone (collagen) by releasing proteases. It is currently postulated that an important protease produced by the osteoclasts is cathepsin B. Inhibitors of this protease block PTH-induced bone resorption \textit{in vitro} and indices of bone resorption \textit{in vivo}.

The osteoclast is derived from a haematopoietic stem cell by fusion. Conflicting evidence exists both in favour of and against the hypothesis that cells of the monocyte-macrophage series are the preosteoclasts. Therefore, at present, the identity of this stem cell is unknown (Jilka et al, 1994).

A number of drugs and hormones have been implicated in affecting the function of osteoclasts. Glucocorticoids cause bone loss by increasing the resorption activity of osteoclasts (Mitchell et al, 1990). Estrogen therapy on the other hand reduces or halts osteoclastic resorption and preserves bone mass (Alden, 1989). Congenital absence of carbonic anhydrase II (CA II) in children results in a syndrome that includes osteopetrosis because osteoclasts are unable to resorb bone in the absence of CA II.
2.3.3 The Osteoblast

The osteoblast is a cuboidal cell that lines bone surfaces. The principal protein produced by osteoblasts is type I collagen, the predominant collagen of bone. In addition to collagen, the osteoblast synthesizes a variety of noncollagenous proteins, including osteocalcin and osteonectin (Jilka et al, 1994).

Exercise and anabolic hormones, including progesterone, stimulate osteoblastic activity leading to bone formation (Alden, 1989). Evidence now exists that the osteoblast plays a key role in the activation of bone remodelling. Osteoblasts, not osteoclasts, have receptors for PTH and 1,25-dihydroxyvitamin D$_3$ (DeLuca, 1990). PTH and 1,25-dihydroxyvitamin D$_3$ cause changes in osteoblast function, but not directly that of osteoclasts. Osteoblasts are required for the hormonal induction of bone resorption by osteoclasts, and isolated osteoclasts alone will not resorb bone (Gennari et al, 1990a). Glucocorticoid use has also been associated with suppressed osteoblast function and decreased bone formation (Hodgson, 1990).

2.3.4 Growth Factors

Recent studies indicate that factors produced by the bone cells themselves modulate the remodelling process. PTH has been shown to regulate the production of insulin-like growth factor 1 (IGF1) by osteoblasts. IGF1 in turn increases bone formation. This may partly explain the anabolic effects of PTH. In addition, PTH induces the release of granulocyte-macrophage stimulating factor (GM-CSF) and macrophage stimulating factor (M-CSF) from osteoblasts. Both substances appear to enhance the recruitment of osteoclasts from precursors. Finally, transforming growth
factor beta (TGFβ) appears to be released from the organic matrix of bone during osteoclastic resorption (Fujita et al, 1990). TGFβ itself stimulates osteoblastic activity and bone formation and enhances osteoclast apoptosis (Parfitt et al, 1996).

Bone remodelling is maintained by the activity of osteoclasts and osteoblasts, and is under the control of a number of systemic factors. These factors include PTH, calcitonin (CT), and 1,25-dihydroxyvitamin D3. Fine tuning of this balance and amplification appear to be regulated by local factors including cytokines and growth factors such as IL-1, IL-2, IL-6, TNF alpha, TGF beta, IFN alpha, and IFN gamma. Sub-optimal functioning of these control mechanisms may lead to an imbalance between osteoclastic bone resorption and osteoblastic bone formation which could cause osteoporosis. Conditions associated with immune dysfunction such as aging, corticosteroid therapy, and rheumatoid arthritis are associated with osteoporosis, which are also more common in females, like most of the autoimmune-collagen diseases (Fujita et al, 1990).

In both postmenopausal (Type I) and senile (Type II) osteoporosis, it is common to find reduced levels of serum 1,25-dihydroxyvitamin D3 and malabsorption of calcium. In Type I patients a reduced level of serum PTH causes a real decrease in serum 1,25-dihydroxyvitamin D3 production and malabsorption of calcium.

2.4 Predisposition Characteristics to Disease

Osteoporosis is characterized by a decrease in bone mass. Both the organic matrix (collagen) and mineral component (hydroxyapatite crystal) are diminished in the osteoporotic patient (Termine et al, 1996). The literature has classified a number of risk
factors for developing the disease in women and includes: Northern-European heritage, petite, a smoker, sedentary, family history of osteoporosis (particularly maternal), history of low dietary calcium intake, and early menopause or premenopausal oophorectomy (Sowers, 1993). Men are less likely to develop osteoporosis because of greater initial bone mass and slower rate of bone loss with age than women (Jackson et al, 1990).

Osteoporosis is manifested by a decrease in bone mineral density (BMD) and strength. The resulting diminution of bone tissue is expressed as reduced BMD. In the earliest stage, the patient is asymptomatic. However, as bone density decreases, spontaneous or fragility low trauma fracture occurs. The morbidity and mortality associated with osteoporosis are most evident in the relation to hip fractures. Women who suffer hip fractures have a 12 to 20% greater risk of dying within the first year after the fracture (Josse, 1989). Vertebral fractures occur in 400,000 women in the United States each year causing loss of height, pain, and, if recurrent, deformity (Dowager's Hump).

A number of models have been proposed to predict change in bone mass with respect to the risk factors listed above. These models additionally consider the peak bone mass attained by menopause and the rate of bone loss as a function of age as risk factors which need to be considered. Peak bone mass at menopause is critical since individuals with lower densities are more likely to cross the fracture threshold at an earlier age. The loss in ovarian function, as a result of menopause or oophorectomy, results in a 3-5% per annum loss in BMD during the first five to ten years of menopause. Following this period of rapid BMD change, annual rates of loss are on the order of 0.5%. The
individual with the lower initial bone density will cross the threshold of a normally low density at an earlier age and be more prone to fracture (Cummings et al, 1993).

The peak bone density reached in young adulthood depends on many factors including physical activity and calcium intake (Prince et al, 1991). Physical activity appears to be important for maintaining and increasing normal bone mass. The exercise modality that optimally maintains or increases axial bone density has yet to be determined. However, a positive correlation has been reported between bone mass and a variety of fitness and physical activity measurements, including maximal oxygen uptake, muscular strength, and lifetime physical activity (Snow-Harter et al 1992). Similarly, a positive correlation between calcium intake and bone density has been noted in young women. This correlation is independent of physical activity (Recker et al, 1992a). Likewise, calcium intake (1-1.5 g elemental calcium/day) in premenopausal women appears to reduce the rate of age-related bone loss during this time period (Matkovic et al, 1994). Thus, prior to menopause, physical activity and diet are important determinants of bone health. In addition immobilization following a fracture results in a lack of weight bearing activity which results in greater bone loss.

2.5 Diagnosis of Osteoporosis

Diagnosis of advanced or severe osteoporosis can usually be made by routine x-rays of the spine or femur, however detection by this method is only possible once a 25-30% loss in BMD occurs. Characteristic x-ray features of the osteoporotic skeleton prior to fracture include cod-fish vertebrae, and accentuation of the trabecular pattern in the
femoral neck. Diagnosis by routine radiography is unreliable since the disease has usually progressed substantially before detection.

A number of non-invasive techniques currently exist which can quantify bone mass \textit{in vivo}. These techniques provide a numerical evaluation of bone mass. This advance in technology allows the clinician to obtain the BMD, in $\text{gm/cm}^2$, for the spine and hip. This information is critical since a decrease in BMD has been linked to an increased incidence of fracture (discussed below, section 2.6).

A number of techniques are currently utilized to quantify bone mass. These methods include: dual xray absorptiometry, and quantitative computed tomography. Digital radiography, a new variation of dual xray absorptiometry, has the advantage of speed (five minutes for each scan), low radiation exposure (1-1.5 rem), and reproducibility (a coefficient for variation of 1 \%) (Kimmel et al, 1994).

These \textit{in vivo} techniques offer a number of advantages in the treatment of osteoporosis. The literature (Melton et al, 1989) has established that approximately 95\% of vertebral fractures occur in the elderly with lumbar densities below 1.0 $\text{gm/cm}^2$. Similarly 95\% of hip fractures in the elderly occur in those who have femoral densities below 0.7 $\text{gm/cm}^2$. These techniques allow the clinician to identify patients at risk of fracture, and to monitor the efficacy of treatment regimens by performing periodic determinations of BMD (Cummings et al, 1990b).

An additional advantage to this technology is its use as a screening tool with which BMDs can be performed on perimenopausal women who may be at high risk for osteoporosis, and if BMDs are below the "normal" range for that age then the clinician
can initiate therapy to minimize bone loss. Screening however is currently not endorsed by the Osteoporosis Society of Canada (OSC, 1996).

2.5.1 Differential Diagnosis and Classification

Idiopathic postmenopausal osteoporosis is a diagnosis of exclusion. Secondary causes such as osteomalacia, multiple myeloma, hyperparathyroidism, hyperthyroidism, carcinoma, and hypercortisolism must be considered. In the male, osteoporosis may be a manifestation of testicular failure, and in the young female, a feature of Turner's syndrome (Sklarin et al, 1996). Osteomalacia is a defect in collagen matrix mineralization. Because milk is supplemented with vitamin D in North America, nutritional deficiency of the vitamin is rare provided milk is consumed. Osteomalacia due to abnormality in vitamin D metabolism however may occur in renal failure resulting in decreased 1,25-dihydroxyvitamin D₃ production by the kidney. Other conditions such as steatorrhoea (loss of fat-soluble vitamins through the intestinal tract), or vitamin D dependent rickets, characterized by decreased 1 alpha-hydroxylase activity in renal mitochondria, can also lead to a defect in vitamin D metabolism (Holick, 1996). Bone mineralization defects can also occur in the severely hypophosphatemic patient (typically the result of excess ingestion of phosphate binding antacid).

Multiple myeloma, hyperthyroidism, hyperparathyroidism, and carcinoma can all present as osteopenia (Khosla et al, 1995). Plasma cells are capable of producing a variety of substances termed osteoclast activating factors that induce bone resorption. Similarly, PTH and thyroid hormone in excess induce bone resorption. Recent studies suggest that chronic administration of suppressive doses of thyroid hormone is associated
with decreased bone mass. Finally, certain tumours are capable of inducing bone resorption resulting in hypercalcemia.

Drug-induced osteoporosis can occur if the patient is exposed to excess glucocorticoids (Lukert, 1996). Under these conditions, intestinal calcium absorption is inhibited leading to decreased calcium availability for bone formation. In an attempt to maintain calcium homeostasis under conditions of low calcium absorption, bone resorption is often increased leading to a loss in BMD.

Although idiopathic postmenopausal osteoporosis is the most common form of the disease that will be encountered, other causes of diminished bone density need to be considered. Consequently, evaluation of these patients should include serum calcium, phosphorus, and alkaline phosphatase levels, a complete blood count, serum or urine protein electrophoresis, thyroid function tests, PTH and serum cortisol levels, and 24-hour urinary calcium excretion. Although these routine laboratory parameters when obtained in normal and osteoporotic patients cannot predict the affected woman, they help to define secondary causes. The combination of urinary calcium and hydroxyproline, serum alkaline phosphatase, and other newer serum and urine markers of bone resorption may help to identify "fast bone losers" in the perimenopausal period (Hansen et al, 1991). Theoretically, these women are at greatest risk for rapid progression of osteoporosis.

Bone gla protein (osteocalcin) is the most abundant noncollagenous protein in adult bone. Osteocalcin is a marker for bone formation and elevated values may indicate high bone turnover.

Likewise, the pyridinoline-specific markers of bone resorption reflects bone breakdown due to increased osteoclastic activity (Delmas, 1995). The urinary levels of
the pyridinolines increase in postmenopausal women and women on suppressive doses of thyroid hormone, while estrogen treatment reduces levels to premenopausal values.

2.6 Bone Mineral Density Loss With Age And Propensity To Fracture

A number of models have been proposed in the literature to relate BMD to fracture risk (OTA, 1995a). This modelling process involves two steps, namely predicting BMD over time and relating BMD to fracture risk. Inherent in these models are a number of constraints including the site of BMD determination, and the technique used for the assessment (Marshall et al, 1996).

Characteristics of BMDs by age have been described using a number of U.S. studies in a Office of Technology (OTA) report (OTA, 1995b). These studies evaluated the age-specific shape, the means, and standard deviation of the BMD distribution in Caucasian women.

Melton et al (1986) evaluated the BMD of the proximal femur, in a number of women in Rochester, Minnesota, using dual photon absorptiometry (DPA). BMD was measured at two sites of the proximal femur, at the cervical and the intertrochanteric regions, of 300 women from an age-stratified sample. The most important reason cited for refusal of participation in the study was poor health especially in those women aged ≥ 70 years, consequently the distribution of this group may be biased toward higher values. BMD (gm/cm²) at each site was related to age through a multiple regression model for each of six ages corresponding to the midpoints of six age strata (ie 35-44,..., ≥85years). The data were used to obtain smoothed BMD distributions for each of the six age strata. Multiplication of these distributions by the number of residents in each of the age strata
and subsequent summation across all age groups resulted in the total number of Rochester women expected to be in each of the BMD intervals.

In the Study of Osteoporotic Fractures (SOF) (Cummings et al, 1993), the largest cross-sectional study of bone mass, 9,704 healthy women over the age of 65 were screened and measured by Single Photon Absorptiometry (SPA) at the proximal radius, distal radius and calcaneous (Cummings et al, 1990c). The Framingham Osteoporosis Study (FOS) (Hannan et al, 1992), another large cross-sectional study in which the BMD was obtained in 708 women over the age of 68, was also used in the OTA analysis. An analysis of the distribution of the observed BMD at the proximal radius for age groups 65-89 demonstrated a normal distribution (OTA, 1995b). Most studies showed a slightly higher rate of bone loss just after the menopause which slowed after the age of 55 or 60 (OTA 1995b).

The associations between BMD and age in the literature are generally based on case-control, and cross-sectional studies since large longitudinal studies are lacking. There are a number of issues relating to the use of cross-sectional data to estimate longitudinal changes in BMD. The possibility of bias in the selection of subjects is one consideration. Secondly the sample size in each age stratum must be large enough to allow for sufficient precision. Lastly, cross-sectional estimates of BMD changes may differ from longitudinal studies if cohort effects such as nutritional factors or medication use vary with age. Two large case-controlled studies in which the possibility of these methodological issues were minimized were used by OTA (1995a) to characterize the change in BMD with age (Cummings et al, 1990a). Using the SOF and FOS studies, OTA developed a base case distribution of BMD with age in postmenopausal women. In two
other distributions, OTA also identified fast and slow BMD losers. In the OTA
evaluation the base-case annual BMD loss in untreated postmenopausal women was
estimated as 1.8%, 1.3%, 1.0% and 0.9% for 50-54, 55-59, 60-64 and ≥65 year-olds
respectively. In the fast-loser group BMD loses were estimated as 2.0%, 1.5%, and 1.2%
for 50-54, 55-59, and ≥60 year-olds respectively. Slow-loser rates were presented as
1.6%, 1.2%, and 0.9% and 0.8% for 50-54, 55-59, 60-64 and ≥65 year-olds respectively
(OTA, 1995b). The existence of “fast bone losers” after the menopause has been
observed, and it has been demonstrated that genetic, environmental, and lifestyle factors
can impact on the rate of bone loss (Christiansen et al, 1987).

Optimally age-specific BMDs could be determined by following a large cohort of
women over their lifetime (longitudinal study). Unfortunately as indicated above
longitudinal studies in which a large number of women are followed for a number of
years are lacking. Currently a prospective 5 year study (Canadian Multicentre
Osteoporosis Study (CaMos)) is in progress in Canada (Kreiger et al, 1998). The
objective of this study is to evaluate the changes in BMD, diet and disease incidence in a
random Canadian population sample of both genders. The baseline BMD data from this
study for Canadian men and women ≥50 years will be available in late 1998.

The next step in this process is to establish the relationship between hip fracture
optimal model is one that can predict the probability of hip fracture for a woman at any
age, based on her current BMD. The estimation of a standardized relative risk involves
the calculation of a ratio of the risk of fracture for a person whose bone mass is one
standard deviation below the mean to the risk of a person whose bone mass is at the
mean. The SOF dataset, due to its large sample size, has published this type of information relating bone mass to relative risk of fracture. The data from this study suggest that a logistic relationship exists between BMD and hip fracture risk (Cummings et al, 1993). The conclusion of the analysis was that each standard deviation (SD) decrease in femoral neck density increased the age-adjusted risk of hip fracture 2.6 times (95% CI 1.9, 3.6).

2.7 Osteoporosis Prevention/Treatment Interventions

There are currently a number of effective treatments for the prevention and treatment of osteoporosis. These treatment strategies include the antiresorptive agents and the anabolics. Ovarian hormone therapy products (i.e. hormone replacement therapy (HRT)), the bisphosphonates, calcitonin and calcium and vitamin D being examples of the antiresorptive class of drugs. Fluoride and parathyroid hormone (PTH) are examples of the anabolic agents. The focus of the thesis is on calcium, vitamin D, and HRT, consequently the material in this section focuses primarily on these agents.

2.7.1 Calcium

Calcium is an essential nutrient since obligatory body losses through sweat, skin, hair, nails, as well as urine and feces, must be replaced. In the event that calcium is not available through the diet, then serum calcium levels are maintained at the expense of skeletal calcium. Thus, adequate calcium intake is an essential component in any osteoporosis treatment regimen (Heaney et al, 1983). Calcium intake is one of many factors that has been associated with the growth, maintenance, and prevention of loss of
bone from the skeleton. These studies have examined the effect of calcium on bone mass during the developmental stage, menopausal stage and postmenopausal state of women. Elegant calcium balance studies have been conducted in the last decade yielding considerable information on the impact of dietary calcium on bone development (Heaney et al, 1986). This has resulted in good cross-sectional data, but as with other aspects of osteoporosis good longitudinal information is lacking. Unfortunately few longitudinal studies have been conducted evaluating the role of calcium supplementation and its effects on BMD. Information on the factors that influence bone mass has been collected from studies in which bone mass or BMD is measured directly. Studies using the currently available densitometry equipment have allowed for the examination of the impact of an intervention on BMD, at various skeletal sites.

2.7.1.1 Calcium Intake and Peak Bone Mass

Studies examining the relationship between calcium intake and bone mass can be divided somewhat arbitrarily in the attainment of maximal bone mass during skeletal growth and maturation, and those focusing on maintenance of bone once peak bone mass has been attained. Peak bone mass is influenced by a combination of endogenous (genetic, hormonal; probably most important) and environmental factors (nutrition, exercise) (Johnson et al, 1992). Evidence suggesting that increasing calcium intake during the pre-menopausal years results in increased peak bone mass generally comes from cross-sectional and retrospective studies. A number of studies on the impact of calcium supplementation in boys and girls have been conducted, demonstrating that bone mass can be enhanced with calcium supplementation for example. Johnson et al (1992)
evaluated the impact of a three-year, 1000 mg calcium supplementation in 10 year-old male and female monozygotic twins, in whom dietary intake was estimated at 900 mg per day. Their study concluded that a mean increase in BMD occurred in the six sites monitored, averaging 1.4% increase over those treated with placebo, with the greatest increase seen in the pre-pubertal stage. This finding was also supported in a calcium trial in adolescent twins, where it was found that the BMD of the spine and hip was augmented at one year by 6% versus 4% with 1000 mg calcium supplement or placebo respectively (Nowson et al, 1995).

Other evidence suggesting a relationship between calcium intake and bone mass comes from an ecological study of two districts of Yugoslavia. Young adult men and women in the district with higher calcium intakes (1087 mg per day) had greater metacarpal bone density at age 30 than those in the lower intake district (812 mg per day) (Matkovic et al, 1979). The differences in BMD of the two groups declined with age, suggesting that calcium intake has a greater impact on the development of peak bone mass, than on subsequent bone loss. Similarly, estimated calcium intake in early adulthood has been positively correlated with bone density of the radius and spine of premenopausal women (Nieves et al, 1995), via a retrospective review of the current and adolescent dietary habits of sixty-six 30-39 year-old women.

A number of studies have been conducted in which young women have been exposed to levels above and below the recommended RDA for this age group (Matkovic et al, 1990, Lloyd et al, 1993, Nowson et al, 1995). Andon et al (1994) evaluated the impact on BMD in young female teenagers in which they either consumed 1200 mg,
1500 mg, or 850 mg calcium a day via the diet and use of supplements. The highest gain in whole body bone mineral content was in the group with the highest intake, followed by those teenagers with the calcium intake closest to the current RDA, and the lowest accretion was observed in the 850 mg calcium-consuming group.

The relationship between BMD and exercise has also been examined in a number of prospective, retrospective and cross-sectional studies with conflicting results. A Finnish prospective population study was conducted between 1980 and 1986 in 3,596 boys and girls aged 3 to 18 years in whom diet, exercise and smoking data were collected (Lamberg-Allardt et al, 1995). Six years later, 264 of the participants (of a randomly selected subgroup) had BMD determination of the femoral neck and spine. The data indicated a positive correlation between exercise and BMD in this young cohort of men and women. Nevertheless less compelling data for the benefits of exercise on BMD is also available (Snow-Harter et al, 1992).

The bulk of the evidence demonstrates that BMD increases with calcium intakes in adolescents, however none of these studies were able to establish a level of calcium intake above which no further increase in bone mass would be attained. Nevertheless, the results from these studies were compelling enough to warrant an increase in the calcium recommendation during adolescent years (FNB, 1997).

Increasing evidence that bone mass continues to build for several years beyond the attainment of full height (approximately 18 years), has resulted in an increase in the recommended dietary allowance (RDA) for calcium for young adults ages 18 through 24 years (calcium intake raised from 800 to 1200 mg per day) (FNB, 1997).
2.7.1.2 Calcium Intake and Bone Loss in Pre- and Postmenopausal Women

The importance of adequate calcium intake (1,200mg/day) in young adulthood in women has been well documented. Clear cut evidence for intakes exceeding RNI are lacking since most studies initiate subjects on calcium at a level that meets the RNI. In perimenopausal women, however, the rate of bone loss is rapid (3-5% per year) during the first five years of the menopause. One of the problems in estimating calcium needs in this age group is that calcium intakes are below the RNI and RDA standards. Consequently, clear evidence that increased intake (to at least the current requirement levels) is beneficial in minimizing bone losses during this critical period of negative bone balance is lacking. Consequently, as with adolescents the level of calcium intake necessary to maintain BMD has not been well established.

A number of prospective studies have shown that increasing calcium intake via dietary sources from 900 to 1500 mg per day can prevent bone loss from the spine in premenopausal adult women. In a cross-sectional study Picard et al (1988) evaluated the BMD of the spine in 183 pre-menopausal women between the ages of 40-50 years. They found that women who consumed >1,000 mg of calcium per day had a higher BMD at the spine than those women whose calcium intake was <500 mg/day. A recent review of 31 cross-sectional studies on the impact of calcium supplementation on bone mass in mostly premenopausal women, resulted in either a positive correlation between mass and supplementation, or neutral effects (Ott, 1994). Recker et al (1992b, 1995) also conducted a study to evaluate the change in bone mass in women immediately before the menopause for a period of two years. Annual assessment of calcium intake by 7-day diet
diary demonstrated intakes in these 75 women to be representative of the US population (651 mg/day); no calcium supplements were provided. The analysis indicated that there was no significant change in BMD at the sites monitored (forearm, spine and total body) during the two years of study, thereby questioning whether low calcium intakes lead to premature bone loss during this age period.

Loss of BMD is accelerated in women entering into menopause, hence a number of investigators have questioned whether calcium supplementation can help offset this menopausally-related bone loss. Unfortunately results from these studies have not yielded compelling data. That is, cross-sectional studies conducted on women who enter the menopause (49-55 years) have shown that supplementation during this time period did not have a significant impact on bone loss in comparison to placebo treated patients (Johnell et al, 1984; Nilas et al, 1984; Lukert et al, 1987). Similar results were also seen in a number of longitudinal studies in these perimenopausal and early-menopausal women. Slemenda et al (1987), conducted a three year longitudinal study in which the BMD of 84 women (42-58 years), was measured and dietary calcium monitored. They concluded that dietary calcium is not related to bone loss.

Furthermore, a number of randomized clinical trials, in which supplementation with calcium ranged from 500 mg to 2 grams, did not show a significant difference in BMD from control in early menopausal women (Dawson-Hughes et al, 1990; Ettinger et al, 1987; Riis et al, 1987). During this period, despite calcium supplementation, women continued to lose bone at a rate of 2-5% per annum. Thus the current bulk of evidence would suggest that calcium supplementation during these early few years into menopause
cannot blunt the BMD losses associated with the loss of endogenous estrogen production (Ettinger et al, 1987).

In contrast to the menopausal years, many studies conducted to evaluate the impact of calcium supplementation in older postmenopausal women (5 or more years postmenopausal) have shown significant effects on slowing bone loss. Postmenopausal women, generally 55 years of age and older, are increasingly at higher risk of calcium deficiency, since their ability to absorb calcium declines due to lower levels of 1,25-dihydroxyvitamin D3 (stimulates calcium absorption from the gut) and intakes often do not meet recommended levels.

Not surprisingly, evidence exists that low calcium intakes are associated with increased bone loss in post-menopausal women. In a large two-year double-blind, placebo controlled trial, women with low usual calcium intakes were recruited (half under 400 mg and half 400-650 mg) and treated with placebo or 500 mg of elemental calcium. It was found that in women with usual intakes under 400 mg daily, supplementation prevented bone loss from the spine, hip, and forearm. The higher intake group had a lower bone loss overall, however the impact of supplementation was not statistically significant (Dawson-Hughes et al, 1990). This finding suggests that supplementation to increase total intake to 800 mg of calcium daily, can reduce bone loss and risk of osteoporotic fracture. However, considerable controversy exists on the additional benefit of calcium intake above 800 mg per day (Riis et al, 1987).

Recently, Shea at al (1998) conducted a meta-analysis using the Cochrane Collaborative process (Chalmers et al, 1995). In this analysis all randomized clinical controlled trials (RCTs) were sought in which one intervention in the study was calcium
alone in postmenopausal women. There were 15 studies that met the search criteria in the calcium vs placebo meta analysis, 5 of which evaluated BMD changes at the femoral neck (Shea et al, 1998). The analysis found a modest, yet non-statistically significant, reduction in femoral neck bone loss.

The five studies in the calcium vs placebo analysis are listed in the left column of Table 2.1. The results from these studies, as well as their confidence intervals are presented as weighted mean differences (WMDs), which is a measure of the difference between the change elicited, in the outcome of interest, between the active and control regimens under a number of studies. The magnitude of change in this outcome over a number of studies is then “weighted” based on the number of subjects in each study (Bracken, 1992). The studies used in this meta analysis are briefly described in Table 2.2.

The five studies used by Shea et al (1998), evaluated the impact of calcium on BMD at the femoral neck. These studies demonstrated that the impact of calcium supplementation on BMD at the femoral neck was variable. These variable effects may be a result of the various supplementation levels, the age of the subjects, environmental factors, and calcium intake through the diet.

Chevalley et al (1994) evaluated the impact of supplementation with 800 mg calcium on retirement home residing subjects (72.1± 0.6 years), with and without a fracture history, and found that the regimen prevented femoral BMD decreases. A study by Lau et al (1992) in Hong Kong on community residing women 62-92 years of age supplemented with 800 mg calcium demonstrated a non significant change in BMD from
Table 2.1: WMD at Femoral Neck for Calcium vs placebo intervention

<table>
<thead>
<tr>
<th>Study</th>
<th>WMD</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lau et al, (1992)</td>
<td>-2.40</td>
<td>[-10.72, 5.94]</td>
</tr>
<tr>
<td>Dawson-Hughes et al, (1990)</td>
<td>1.23</td>
<td>[-0.56, 3.02]</td>
</tr>
<tr>
<td>Dawson-Hughes et al, (1990)</td>
<td>-0.22</td>
<td>[-3.59, 3.15]</td>
</tr>
<tr>
<td>Lamke et al, (1978)</td>
<td>4.50</td>
<td>[-1.79, 10.79]</td>
</tr>
<tr>
<td>Overall</td>
<td>1.22</td>
<td>[-0.17, 2.61]</td>
</tr>
</tbody>
</table>

*EM: early menopausal 54.5 years  LM: late menopausal 59.9 years
Table 2.2 Studies used in the calcium versus placebo meta-analysis using the Cochrane Collaborative methodology (Shea, 1998)

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention (Active/Control)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chevalley et al, 1994</td>
<td>Retirement home residents; mean age 72.4 years; placebo controlled RCT</td>
<td>800 mgs calcium daily x 18 months; (26 treatment/25 control)</td>
<td>BMD - DPA at femoral neck, mid-femoral shaft and lumbar spine</td>
</tr>
<tr>
<td>Lau et al, 1992</td>
<td>Community (hostel for the elderly); mean age 77 years; placebo controlled RCT</td>
<td>800 mgs calcium daily x 10 months; (12 treatment/12 control)</td>
<td>BMD - DEXA at femoral neck, femoral shaft and lumbar spine</td>
</tr>
<tr>
<td>Dawson Hughes et al, 1990 LM</td>
<td>Community; mean age 59.9; placebo controlled RCT</td>
<td>500 mgs calcium daily x 2 years; (54 treatment/71 control)</td>
<td>BMD - DEXA at femoral neck and lumbar spine</td>
</tr>
<tr>
<td>Dawson-Hughes et al, 1990 EM</td>
<td>Community; mean age 54.5; placebo controlled RCT</td>
<td>500 mgs calcium daily x 2 years; (23 treatment/11 control)</td>
<td>BMD - DEXA at femoral neck and lumbar spine</td>
</tr>
<tr>
<td>Lamke et al, 1978</td>
<td>Community; mean age 60 years; placebo controlled RCT</td>
<td>1000 mgs calcium daily x 1 year; (19 treatment/17 control)</td>
<td>BMC at femoral neck, and femoral shaft</td>
</tr>
</tbody>
</table>
baseline after 10 months of treatment. Healthy community-dwelling postmenopausal women with a mean age of 60 years were supplemented with 1,000 mg daily (Lamke et al, 1978). The study found a significant increase in BMD at the femoral neck after one year of treatment.

The two studies by Dawson Hughes et al (1990), were reported in the same paper on two groups of menopausal women. The early menopausal group (EM) had a mean age of 54.5, and a second group late menopausal (LM) which were 59.9 years of age. A WMD of 1.23 (-0.56, 3.02) was seen for the LM subjects whereas the EM group had a WMD of -0.22 (-3.59, 3.15). This finding is suggestive that calcium supplementation in the LM subjects had a greater impact on BMD than the EM subjects. The meta-analysis of RCTs covering postmenopausal subjects supplemented with calcium showed a BMD weighted mean difference (WMD) at the femoral neck of 1.22%, with a confidence interval of -0.17 and 2.61 (Shea et al, 1998). Although the overall WMD is not significantly different from placebo treatment, due to the confidence interval values, the data suggested that a modestly beneficial effect of calcium exists. Nonetheless, a review of the studies included in the calcium versus placebo meta-analysis suggested a minimum of 1,000 mg of calcium, based on the total calcium intake used in the studies from both dietary and supplement sources (Shea et al, 1998). The results from Shea’s meta-analysis indicated that there are insufficient data to discriminate a variable response of calcium supplementation with age, (except perhaps within the first five years of menopause), consequently for the thesis model it will be assumed that the impact of calcium combined with vitamin D on femoral neck BMD is comparable across all age groups.
A number of confounders may have influenced the results including poor vitamin D status. In section 2.7.2, vitamin D and its impact on BMD changes will be discussed.

2.7.1.3 **Calcium Intake Recommendations**

Currently Health and Welfare Canada’s Recommended Nutrient Intakes for calcium in women ≥ 50 years of age is 800mg. Recently a report was produced by the Food and Nutrition Board (FNB) with the primary objective of “the establishment of a set of reference values to replace the Recommended Dietary Allowances (RDAs) for the United States”, with the secondary objective to establish “one set of reference values for the United States and Canada” (FNB, 1997). The FNB solicited input from Canadian experts in this field in deriving these new values.

The Adequate Intake (AI) value suggested by the FNB for calcium in women ≥ 50 years is 1,200 mg. AI is based on “observed or experimental determinations of the average nutrient intake, by a defined population or subgroup, that appears to sustain nutritional state, such as normal circulating nutrient values or growth” (FNB, 1997). AIs are used when sufficient scientific evidence is not available to calculate an estimated average requirement (EAR).

Based on these most recent recommendations, as well as the published consensus statements from the Scientific Advisory Board of the Osteoporosis Society of Canada (OSC, 1996), which recommend 1000-1500 mg of calcium as the nutrient intake for women ≥50 years of age, we have decided to base the thesis on a target of 1200 mg calcium coming from both dietary and supplement sources. This level of supplementation via the tablet dosage form would ensure that the “typical” Canadian
woman would just exceed the newly recommended AI for calcium of 1,200 mg. The mounting evidence suggesting that higher levels of calcium intake are required in older Canadian women has prompted the thesis evaluation to consider 1,200 mg of calcium intake as the minimum intake by postmenopausal women. The decision to follow the FNB recommendations in the thesis for calcium intake is also supported by the position taken by the Osteoporosis Society of Canada (OSC, 1996).

2.7.1.4 Current Calcium Intakes In The Population

Issues surrounding calcium status include low intake, upper safety limits and the appropriate level of supplementation for the population. Intake levels for calcium by a population typical of Canadians is necessary for use in the economic model, since the level of calcium supplementation that will be provided for in the economic analysis will be based on the current level of intake. A number of population surveys have been conducted to determine current calcium intake. These studies have typically demonstrated that intakes are lower, especially in the 50+ age groups, than the recommended intakes.

Current calcium consumption in the diet of Americans has been ascertained from a number of United States Department of Agriculture (USDA) surveys (January????, 1996). The results from the most recent survey are not complete, however the data presented are from the first wave of the USDA Continuing Survey of Food Intakes (CSFI) 1994-96; survey data are still being collected. The reported calcium intakes probably represent an underestimate of actual intakes due to under-reporting of food uses. Sampling (for the total survey) was designed to be representative of the U.S. population
and took into account geographic location, degree of urbanization, and socioeconomic characteristics. One third of the planned sample was to be recruited in each of three years during which the survey would be conducted. The reported data are from the first year.

While the data should have been sampled on a representative basis, cell sizes are only about one third of expected final sizes and precision of estimates suffers from low sample size. Unlike several older USDA surveys, the success in recruitment and retention of subjects in this survey was high, consequently bias in the data was reduced. The collection of dietary data were based on two one day interviews via 24 hour recall.

The calcium intakes, for this sample of the survey participants (720 men and 720 women in the survey - aged 50-79 years), was 750mg ± 376 (mean ± SD) in males and 571mg ± 286 in females (Table 2.3). The median intakes were 670 mg and 516mg in males and females respectively. It should be noted that calcium intakes are skewed.

The preliminary intake data from this survey by 5-year age groups is presented in Table 2.4. The table also includes the percentage of individuals who are using calcium and vitamin D supplements to complement their diet. The preliminary survey results suggest that close to half of the women under the age of 80 years use calcium supplements. While this percentage declines precipitously in women over the age of 80 years; this may simply be reflective of the small “n” in these older age groups. Importantly, while many females are using calcium supplements, few combine this with vitamin D. Smaller population surveys have been conducted in Canada, but for most provinces results are not currently available. Results from the Quebec arm of this initiative are available (Bertrand, 1995). The survey was based on a 24-hour recall and the summary data are presented in Table 2.5. The Canadian calcium intake data via the
<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>720</td>
<td>720</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>750 ± 376</td>
<td>571 ± 286</td>
</tr>
<tr>
<td>Median</td>
<td>670</td>
<td>516</td>
</tr>
<tr>
<td>5^{th}-95^{th} centiles</td>
<td>273-1449</td>
<td>210-1104</td>
</tr>
<tr>
<td>Skewness</td>
<td>1.3344</td>
<td>1.8830</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>3.819</td>
<td>2.5710</td>
</tr>
<tr>
<td>RDA</td>
<td>800</td>
<td>800</td>
</tr>
</tbody>
</table>
Table 2.4 Estimated Calcium and Energy Intakes and Usage of Supplements by Age and Gender, US, 1994 Based on 1994 data of the CSFII 1994-96 survey as released by USDA on CD ROM, (January 1996).

<table>
<thead>
<tr>
<th>GROUP</th>
<th>N</th>
<th>Dietary calcium median (mg)</th>
<th>Dietary calcium mean (mg)</th>
<th>Supplemental calcium (% of sample)</th>
<th>Supplemental vitamin D (% of sample)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-54</td>
<td>145</td>
<td>696</td>
<td>758</td>
<td>28.1</td>
<td>6.3</td>
</tr>
<tr>
<td>55-59</td>
<td>110</td>
<td>660</td>
<td>714</td>
<td>24.0</td>
<td>4.0</td>
</tr>
<tr>
<td>60-64</td>
<td>127</td>
<td>707</td>
<td>745</td>
<td>5.9</td>
<td>0</td>
</tr>
<tr>
<td>65-69</td>
<td>104</td>
<td>665</td>
<td>777</td>
<td>13.6</td>
<td>0.7</td>
</tr>
<tr>
<td>70-74</td>
<td>86</td>
<td>720</td>
<td>769</td>
<td>35.3</td>
<td>0</td>
</tr>
<tr>
<td>75-79</td>
<td>72</td>
<td>748</td>
<td>763</td>
<td>20.0</td>
<td>13.3</td>
</tr>
<tr>
<td>80-84</td>
<td>50</td>
<td>699</td>
<td>733</td>
<td>28.6</td>
<td>0</td>
</tr>
<tr>
<td>85-89</td>
<td>26</td>
<td>731</td>
<td>712</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>WOMEN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-54</td>
<td>144</td>
<td>517</td>
<td>560</td>
<td>59.5</td>
<td>11.9</td>
</tr>
<tr>
<td>55-59</td>
<td>128</td>
<td>543</td>
<td>587</td>
<td>42.9</td>
<td>8.6</td>
</tr>
<tr>
<td>60-64</td>
<td>115</td>
<td>485</td>
<td>563</td>
<td>46.9</td>
<td>9.4</td>
</tr>
<tr>
<td>65-69</td>
<td>117</td>
<td>560</td>
<td>601</td>
<td>43.3</td>
<td>0</td>
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<tr>
<td>70-74</td>
<td>92</td>
<td>542</td>
<td>579</td>
<td>42.3</td>
<td>15.4</td>
</tr>
<tr>
<td>75-79</td>
<td>55</td>
<td>509</td>
<td>534</td>
<td>55.6</td>
<td>0</td>
</tr>
<tr>
<td>80-84</td>
<td>40</td>
<td>495</td>
<td>585</td>
<td>11.1</td>
<td>11.1</td>
</tr>
<tr>
<td>85-89</td>
<td>29</td>
<td>458</td>
<td>499</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 2.5 Mean calcium intakes in women in Quebec based on 24 hour recall.

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of subjects</th>
<th>Calcium (mean, mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-34</td>
<td>593</td>
<td>788</td>
</tr>
<tr>
<td>35-49</td>
<td>209</td>
<td>658</td>
</tr>
<tr>
<td>50-64</td>
<td>114</td>
<td>622</td>
</tr>
<tr>
<td>65-74</td>
<td>166</td>
<td>574</td>
</tr>
</tbody>
</table>
diet do not appear to be appreciably different from the larger USDA survey. The mean intakes are consistently below both the current RNI of 800 mg per day as well as the target of 1,200 mg in line with the OSC recommendations (OSC, 1996). This is the likely target for calcium of Canadian women if the FNB report is adopted (FNB, 1997).

A poster was presented recently with calcium intake data from the Canadian Multicentre Osteoporosis Study (CaMos) by age and sex at the 16th International Congress of Nutrition (Poliquin et al., 1997). This dataset reports calcium intakes greater than previous Canadian estimates by 100 to 400 mg. The reason for this discrepancy in data is not yet readily apparent and until the report is published cannot be evaluated. Nevertheless, the CaMos data is based on food frequency estimates of calcium intake rather than 24 hour recall. It is likely that the different approaches in attempting to estimate calcium exposure, in part, account for the differences reported.

It should be noted that primary food sources of calcium are obtained from dairy products such as milk (whole milk 307 mg/250 ml serving) cheeses, ice cream, and yogurt. Secondary food sources of calcium include meat, fish, poultry and alternates. The major nutrients in the meat, fish, poultry and alternates group are protein, iron, niacin and thiamine. Examples include canned salmon and sardines provided the bones are eaten. Other examples include beans (95 mg calcium per 250 ml serving), almonds (175 mg calcium per 125 ml serving), and tofu (processed with calcium sulfate: 145 mg per 125 mL serving).

In the economic model we assumed that on average female subjects 50 years and older are obtaining on average 575 mg of calcium through their diet. For the purpose of the thesis, estimates of calcium intake based on the larger 24 hour recall population
surveys in the US and Canada were used. Thus it was assumed that mean intakes in women ≥50 years of age was 575mg. To reach the target of 1200 mg, an additional 625 mg of calcium would be needed. To accomplish this level of supplementation in the model it was decided that 750 mg of elemental calcium, with one 500 mg and one 250 mg tablet as the calcium carbonate salt would be used; since a 625 mg calcium tablet was not available.

2.7.2 Vitamin D

Research over the last two decades has revealed new insights into the role of vitamin D in regulating calcium and bone metabolism. Vitamin D can either be synthesized in the skin or ingested via the diet. Both routes require vitamin D to undergo hydroxylations in the liver and kidney on carbons 25 and 1, respectively, to form 1,25-dihydroxyvitamin D$_3$ (1,25-(OH)$_2$D$_3$). 1,25-(OH)$_2$ D$_3$ is considered to be the biologically active form of vitamin D which is responsible for controlling calcium metabolism by regulating intestinal calcium transport and the functions of bone cells (i.e. osteoblasts possess nuclear receptors for 1,25-(OH)$_2$ D$_3$ and respond to the hormone by inducing osteocalcin synthesis) (Eyre, 1996).

2.7.2.1 Vitamin D Intake And Its Role In Bone Mass

Vitamin D has long been recognized as being an essential fat soluble substance responsible for the growth and development of healthy bones in children. However, vitamin D is also essential for the maintenance of skeletal health throughout life. There are a variety of factors that affect an individual’s vitamin D status. Since milk is the only
significant dietary source of vitamin D, casual exposure to sunlight or consumption of a vitamin D supplement for most adults are their only alternatives to meet vitamin D requirement if they do not consume milk. Aging, sunscreen use, changes in season, latitude, and melanin pigmentation however can significantly decrease the cutaneous synthesis of vitamin D. It has historically been assumed that vitamin D-deficiency in the elderly is not a significant health problem in North America since food is fortified with this vitamin. In the previous section however, it was evident that calcium consumed via the diet were below the recommended intakes, consequently it was assumed that vitamin D intakes would also be below the recommended intakes since the calcium data imply that seniors are not consuming large quantities of milk.

The fact that vitamin D status may not be optimal in postmenopausal women has been borne out in recent literature. Mounting evidence has indicated that as many as 60% of free living healthy elderly residing in a Boston nursing home suffer from vitamin D-deficiency by the end of the winter (Holick et al, 1992). The low levels of vitamin D intake appear to be physiologically relevant since there is evidence that up to 40% of patients with hip fractures may be vitamin D-deficient (Holick, 1996). In addition, vitamin D-deficiency can result in osteomalacia; a mineralization defect in bone.

Vitamin D is biologically inactive, however full biological activity as discussed previously is produced endogenously via hydroxylation at the 25 position (in the liver), and then at the 1 position (in the mitochondria of the renal tubule cells). Consequently, liver and/or kidney disease can adversely affect the metabolism of vitamin D. 1,25 (OH)2D3, the hormonally active form of the vitamin, increases intestinal calcium absorption, enhances renal tubular calcium reabsorption, stimulates osteoblast synthesis
of osteocalcin, but in different cell systems and in higher concentrations decreases osteoblast synthesis of collagen, and augments bone resorption. In postmenopausal osteoporotic women decreased calcium absorption and reduced circulating levels of 1,25 (OH)₂D₃ in patients have prompted the use of this activated hormone in the treatment of this disease (Reichel et al, 1989). 1,25 (OH)₂D₃, however has a narrow therapeutic window. This disadvantage requires careful dosing to prevent the toxic sequelae of hypercalciuria and hypercalcemia (Aloia et al, 1988).

The combination of decreased production of the activated vitamin and reduced intake of vitamin D via the diet can result in accelerated bone loss in the elderly.

2.7.2.2 Intake Of Vitamin D And Its Analogues, And Their Impact On Bone Loss In Postmenopausal Women

Interest in studying the effects of vitamin D using the randomized controlled clinical trial (RCT) approach has been seen in the last twenty years. These studies typically however, have studied the impact of vitamin D on the skeletal system with either augmented calcium intake via the diet or with supplements. Calcium intakes reported in these studies via the diet were typically below the RDA and the researchers encouraged increased calcium intakes during these trials (Cummings et al, 1987). Consequently, studies in which vitamin D has been administered alone without any form of calcium supplementation are lacking. Similarly research using the RCT approach has been conducted primarily on the 1,25 (OH)₂D₃ analogue of vitamin D since sponsors of this research have funded studies of these newer analogues. The following review of the clinical studies on vitamin D discuss the impact of these analogues on the skeletal system.
The discussion will initially discuss the studies in which vitamin D was used and then be followed by those RCTs in which the vitamin D analogues were evaluated for the prevention of osteoporosis.

A large randomized study in which vitamin D (800 IU) and calcium (1.2 grams) supplementation was implemented in 3,270 mobile elderly women (mean age 84 (SD 6) years) residing in nursing homes. The study found that following supplementation for 18 months that a 43% reduction (p=0.043) in hip fractures occurred (Chapuy et al, 1992). The occurrence of hip fracture was also monitored over a three year period (Chapuy et al, 1994). The study found after a three year supplementation in this group that a 29% reduction in risk of hip fracture was observed.

Ooms et al (1995) studied the effect of 400 IU of vitamin D on bone loss on 177 women 70 years and older over a two year period. The outcome measures were BMD of the femoral neck, trochanter, and the distal radius. Calcium intake in the active and control group (n=171), was maintained between 800 and 1000 mg via manipulation of the diet. The study demonstrated that significant increases in BMD at the femoral neck occurred in the vitamin D/calcium arm over the control group.

Another study, in which annual intramuscular injections of vitamin D$_2$ (150,000 IU/year) were administered to 341 older Finnish women (mean age 86 years), resulted in a significant reduction (25%) of all fractures, and a non-significant reduction of 22% at the neck of the femur (Heikinhimo et al, 1992). Supplemental calcium was not administered in this study.

Aloia et al (1988) showed that a mean administration of 0.8 μg of 1,25 (OH)$_2$D$_3$ and supplementation of 1g or less of calcium to 17 postmenopausal women, over a two
year period, increased calcium absorption and bone density of the spine and radius. The study also demonstrated a decreased fracture rate, from 333/1 000 patient-years in the controls to 250/1 000 patient-years in the treated patients, by decreasing bone resorption. Hypercalciuria however, occurred in all subjects, and hypercalcemia occurred in 89% of the treated subjects. In a subsequent study (Gallagher et al, 1990), the dose of 1,25 (OH)₂D₃ was adjusted (mean, 0.62 μg/day), and was supplemented with less than 1 g of calcium, to maintain serum calcium less than 11 mg/dl in 25 postmenopausal women. In this 2-year prospective study of patients with vertebral fractures, 1,25 OH₂D₃ increased spine density by 2% compared to a 3% loss in the controls. There were no differences in vertebral fracture rates during the study and urine calcium increased from 144 mg/d to 256 mg/d, although there were no changes in renal function. Most recently the hormone at a dose of 0.5 micrograms/day administered to 314 postmenopausal women has been reported to decrease fracture rate after 2 years of therapy (Tilyard et al, 1992). In contrast, in a double-blind randomized 2-year trial, no significant differences between control and treated groups in spine density or fracture rate were seen. The 43 subjects in the treated group were administered 0.43 μg /day of 1,25 (OH)₂D₃, and supplemented with 1 gram or less of calcium despite twofold increments in urine calcium (Ott et al, 1989).

The effects of 1-α(OH) vitamin D₃ were studied recently in an RCT by Orimo et al (1994) over a one year period in eighty Japanese postmenopausal women (71.9 ± 7.3 years). These women were randomized to either 1 μg of 1-α(OH) vitamin D₃ plus 300mg of elemental calcium, or 300mg of calcium. The outcomes evaluated in this study were changes in BMD at a number of femoral sites, and the spine. Significant increases in
lumbar and femoral BMD were observed. The study also demonstrated a significantly lower rate of vertebral fracture in the active group (75/1000 patient years), than the control group (277/1000).

Considerable controversy exists with the use of both calcium and vitamin D, since the studies conducted to-date have used different salts and analogues of calcium and different metabolites of vitamin D. The outcomes typically have been changes in BMD from baseline for a one to two year period. The efficacy of these two “nutritional” approaches to osteoporosis management require further evaluation of the literature to demonstrate a reduction in hip fracture risk.

The studies suggest a benefit of combined calcium and vitamin D administration. In order to validate this finding a meta-analysis was conducted in the thesis to evaluate the impact of calcium and vitamin D on BMD in postmenopausal women. The meta-analysis was conducted using the Cochrane Collaborative approach and is described in detail in Chapter 6 of the thesis.

It is clear that calcium absorption and 1,25 OH₂D₃ production decreases with age, consequently the use of these agents has the potential to have a positive impact on the clinical management of osteoporosis.

2.7.2.3 Current Vitamin D Intakes In The Population

Dietary intakes of vitamin D are variable between individuals consequently there is less confidence on the estimates of vitamin D consumption than for calcium (McKenna, 1992). Estimating the population’s current level of intake through diet is difficult due to the lack of surveys that collect this type of information for vitamin D
Similarly the level of fortification in foods, and specifically in milk was recently evaluated by Chen et al (1993). Milk, irrespective of its fat content, in Canada and the United States is fortified with 10µg of vitamin D per quart. A recent survey of Canadian and United States milk revealed that up to 70% of milk sampled did not contain vitamin D in the range of 8-12 µg (Chen et al, 1993). Consequently, it is anticipated that highly variable intakes of vitamin D will be observed, since dietary sources of this vitamin is derived predominantly from milk, hence vitamin D intakes will vary in parallel to milk consumption. Hence there are two sources of variation: whether people consume milk and degree of fortification of the milk consumed. Unfortunately, most databases used for surveys will be based on assumption that vitamin D level in milk is at recommended fortification levels, probably overestimating intakes.

The basis for vitamin D intake estimation is the use of food consumption data. Analysis of the National Health and Nutrition Examination Survey (NHANES) II, revealed that median intake by younger women was 2.9µg (114 IU) per day. A number of clinical studies in which vitamin D intakes were estimated in older women suggest that these women have comparable intakes. Krall et al (1989) in their study of postmenopausal women in the eastern United States found a similarly low intake of 2.3µg (90 IU) in these subjects. Murphy et al (1986) evaluated vitamin D intake from the NHANES II study. They found a range of vitamin D intake from the subjects survey to be 0-49µg (0-1960 IU)/day.

As highlighted in the introduction section of the thesis, decreased sunlight exposure in the winter months (especially in institutionalized women), compounded by the low levels of vitamin D intake, and potentially poor metabolism of this vitamin by
older women to its active form, can lead to deficiency. The recently published FNB report recommends AIs for women 51 through 70 years to be 10μg (400 IU) of vitamin D per day, and 15μg (600 IU) in women over the age of 70 (1997). Justification for these adequate intake recommendations were based on a few RCTs which demonstrated the benefits of vitamin D supplementation on BMD and highlighted the low intakes in the general population. The recommendations in escalating vitamin D requirements in women over the age of 70 were due to the reduced exposure of these women to sunlight, and to decreased ability to hydroxylate the vitamin by the liver and kidney (FNB, 1997).

In the model we assume that a 400 IU tablet of vitamin D is sufficient to cover these women. This level is at the recommendation for women less than 70 years of age, but would result in an estimated shortfall of 100 IU in women over the age of 70 years, nevertheless some of this shortfall would be met by dietary intake. The choice of vitamin D for the economic evaluation and not the 1,25 (OH)2D3 analogue, were two fold: issues surrounding the potential safety of the activated analogue, and cost. The clinical data suggest that the use of the 1,25 (OH)2D3 analogue is more effective than the unhydroxylated form of vitamin D in the elderly due to their reduced ability to hydroxylate this vitamin. The studies also suggest that supplementation of this analogue has been associated with hypercalcemia and hypercalciuria in some subjects. In the economic evaluation treatment is initiated with vitamin D at either age 50 or 65 years. At these younger ages the use of the activated form of vitamin D may be unsafe since these women presumably have reasonable kidney function. Consequently in the evaluation we used the unactivated form of vitamin D. The cost of the activated versus the non-
activated forms of vitamin D was also a consideration since the differences between them varied by a factor of 10 (Drug Trading, 1998).

Currently there are a limited number of marketed dosages of oral vitamin D; these are either in tablets of 400 IU and 1,000 IU, or in a marketed combination calcium/vitamin D products which typically contain 125 IU of vitamin D and 500 mg of elemental calcium. Supplements with a combination of calcium and vitamin D (125 IU vitamin D) do not contain sufficient quantities of vitamin D. Multivitamin supplements marketed in Canada contain 400 IU of vitamin D. These combination products (with 400 IU) are generally in the form of a multivitamin and contain other supplements which may not be necessary, and are expensive in comparison to generically available calcium and vitamin D. Similarly these tablets are large and may be difficult to swallow. Supplementation with 1,000 IU of vitamin D was not desirable due to the possible toxicity in certain individuals if the therapy is applied universally to postmenopausal women. In order to simplify the tablet taking process for the patient, and encourage maximal compliance, we assumed in our model that a 400 IU vitamin D tablet would be used to supplement postmenopausal women of all ages.

2.7.3 **Hormone Replacement Therapy**

In the 1940s Fuller and Albright (1941) found that estrogen deficiency was linked to postmenopausal osteoporosis and that estrogen replacement reduced urinary calcium excretion. Estrogen replacement, they hypothesized, may be effective for prevention of fractures. The use of HRT, however, was not studied extensively until the 1970s when investigators such as Lindsay, Nachtigall, Christiansen, and others, demonstrated through
RCTs that estrogen treatment prevented postmenopausal bone loss, spine fractures, and may have an effect on hip fracture incidence. Over the last twenty years extensive studies have demonstrated the positive impact of estrogen on BMD of the spine, forearm, hip, and other sites. A smaller number of longitudinal studies have followed patients for longer periods of time and have shown a reduction of hip and vertebral fractures in patients on HRT. Similarly, the positive effects of estrogen on the cardiovascular system have also been observed. In the last ten years, studies have been conducted to evaluate the effects of estrogen on the bone remodeling cycle, the influence of the progesterone, and the potential association of estrogen therapy with breast cancer.

Clearly HRT is more effective in preventing postmenopausal reduction in bone loss than calcium and calcium/vitamin D supplementation. Similarly longer-term studies have been conducted in which changes in BMD as well as fracture reduction data at the femoral neck have been demonstrated.

In type I osteoporosis, the reduction in endogenous estrogen production has been associated with suppressed PTH release, increased urinary calcium excretion, impaired calcium absorption in the gut, and increased urine deoxypyridinoline (a marker indicating bone resorption). A number of studies have been conducted to evaluate the impact of estrogen replacement in Type I osteoporotic women. These studies have shown that supplementation resulted in increased PTH production (Prince et al, 1991), increased 1,25-dihydroxyvitamin D₃ (Prince et al, 1991), increased intestinal responsiveness to 1,25 (OH)₂D₃ (Gennari et al, 1990b), and decreased urinary deoxypyridinoline and calcium excretion (Stock et al, 1985). These results would suggest a decreased risk of fractures associated with HRT usage.
2.7.3.1 **HRT And Hip Fracture Risk Reduction**

The efficacy of HRT in reducing hip fractures has been documented through a number of either retrospective or prospective cohort, and case-control studies of generally one to ten years duration (Weiss et al, 1980; Kiel et al, 1987; Cauley et al, 1995). RCTs in which women at the menopause are treated with HRT and followed until the age when hip fractures are prevalent (ie to age 75-85 years) are lacking. Consequently, reliance on the efficacy of HRT in reducing the actual risk of fracture are based on these weaker types of study design. In contrast a large number of RCTs have been conducted in women at the menopause using HRT over a shorter duration of treatment (1-3 years), but the endpoint of these studies is a surrogate marker of fracture reduction. The primary surrogate marker used is BMD change.

There are a number of case-control studies in which fracture risk reduction for HRT users was determined usually via retrospective review. Weiss et al (1980) conducted a population-based case-control study in which 327 fracture patients (34% estrogen users) admitted to orthopedic clinics in the Seattle, Washington area were interviewed about estrogen use, fracture history, and osteoporosis risk factors. They also interviewed 576 controls from the community (52% estrogen users). A decreased risk of hip fracture was seen only in users with 5 years or more of HRT use. Analysis of the hip fracture data yielded that current users of estrogen had a relative risk (RR) of 0.42 (and 95% confidence interval (CI) of 0.30 to 0.63 versus controls. Long-term estrogen users (>10 years) had a hip fracture RR of 0.46 (CI, 0.30 to 0.69) versus controls.
In another population-based case-control study, Kanis et al (1992) found that in southern European women (50 years of age and older) who suffered a hip fracture, that a RR of 0.45 (CI, 0.30 to 0.67) existed in HRT ever users versus never users. Controls were of the same age as the fracture patients, and were neighbours of the cases or were sampled from population registers. Only 1.9% of cases, and 3.5% of controls had ever used estrogen, indicating the lower utilization rates of HRT in Europe versus North America.

Cauley et al (1995) conducted a prospective cohort study with internal controls in which 9,704 nonblack women, 65 years or older, were followed for a period of up to 6.5 years collecting information every four months on current HRT use and fracture incidence. They found that in current HRT users who initiated therapy within 5 years of menopause, and used this intervention for more than 10 years, this cohort had the smallest number of hip fractures (relative risk (RR), 0.29; CI, 0.09 to 0.92), when compared to women who never used estrogen. The relative risk for hip fracture tended to be lower among current users (in any duration of HRT use) than never users (RR, 0.60; CI 0.36 to 1.02). Cauley et al (1995) concluded that HRT should be initiated soon after the menopause and continued indefinitely.

A meta analysis was conducted by Grady et al (1992) in which they pooled eleven epidemiological studies (case-control and cohort) on risk reduction of hip fracture among estrogen users and non-users. The pooled estimate of the RR of hip fracture for ever-users of estrogen to never-users was found to be 0.75 (0.68 to 0.84). This estimate of RR of hip fracture, however, included ever user data with current user data, consequently the
RR values underestimate the impact of HRT on hip fracture in women who use HRT long-term.

In summary the studies suggest that the use of HRT decreases the risk of hip fracture in postmenopausal women. In order for the therapy to be effective for the prevention of hip fracture prolonged use is necessary, with a minimum of 5 years of exposure being suggested as most beneficial although effects have been seen in RCTs of shorter duration.

2.7.3.1.1 HRT and Hip Fracture Risk Reduction used in the Model

In the thesis the RR of hip fracture data from Weiss et al (1980) were used as the basis for the efficacy of HRT, since this was the largest study which examined current use and incorporated the duration of treatment into its estimate of RR (ie RR 0.46; CI, 0.30 to 0.69) for hip fracture versus controls. The assumption is made in the thesis that women will be treated with an intervention (i.e. HRT) for a period exceeding ten years, consequently the data from the Weiss et al (1980) study is the most appropriate. The base case reduction in hip fractures with use of HRT in the thesis was 50%, with sensitivity analysis conducted based on the 95% confidence intervals from the Weiss study (1980) at a low of 31% risk reduction (CI 0.69) versus controls, and maximal hip fracture reduction of 70% (CI 0.30) versus controls.

Similar RR assumptions have been used in a number of cost-effectiveness analyses in which HRT has been used for 10 years or more. The Office of Technology Assessment (1995) cost-effectiveness analysis used a 59% risk reduction in hip fractures in women who were treated with HRT. Goddard (1992) assumed that the RR of hip
fracture was 0.5 for estrogen users. Similarly Tosteson et al (1991), and Roche et al (1990) assumed a reduction in hip fractures of 60% (i.e. RR=0.4). Geelhoed et al (1994) assumed that life-long use of HRT would offer a 69% reduction in hip fractures (i.e. RR=0.31). This is at the optimistic end of the range for this therapy in preventing hip fractures.

A number of studies have demonstrated that duration of treatment with HRT for a minimum of 5 years or more resulted in significant risk reduction in hip fractures (Weiss et al, 1980), consequently in the thesis the impact of HRT on reducing hip fracture incidence will not take effect until the fifth year of treatment (i.e. treatment between initiation and 5th year results in no reduction in fracture risk). This delay assumption is similar to that used by others in cost-effectiveness evaluations (Tosteson et al, 1991; Roche et al, 1990; Daly et al, 1992; Geelhoed et al, 1994).

One of the issues that needs to be addressed when evaluating the effectiveness of a therapy over a twenty-five to forty year period is its efficacy with age. The question involved is: "Is the impact of HRT the same from a bone impact perspective on a 50 year-old the same as a 70 year-old woman?" Studies on the effects of estrogen in various postmenopausal ages have shown that similar effects on bone turnover and mass are seen at all ages at least up to the eighth decade (Lindsay, 1995). Consequently in the model it was assumed that the impact of HRT on BMD was the same independent of age of initiation of therapy (i.e. 50 or 65 years of age).
2.7.3.2 **Coronary Heart Disease and HRT**

A number of prospective longitudinal studies have shown that women who were exposed to HRT had a lower incidence of cardiovascular events (Gordon et al, 1978; Willett et al, 1983). Investigation of the Framingham population by researchers have resulted in the identification of a number of risk factors associated with coronary heart disease (CHD) (Gordon et al, 1978). These findings have prompted a number of randomized clinical studies that evaluated the effect of HRT on a number of these surrogate markers of CHD.

Lind et al (1979) randomized 56 women to a control group or HRT. They noted no change in blood pressure in women placed on oral estrogen. In another study by Luotola (1983) 20 hypertensive and 20 normotensive women were placed on estrogen therapy in a cross over design study. The study showed a significant reduction in blood pressure in both groups which rose again with placebo. In a large study by Wren et al (1981) 184 women were on oral estrogen therapy, and 144 women served as controls. The study showed a decrease in both systolic and diastolic pressures in the estrogen treated women, whereas no change was seen in the placebo group.

Considerable effort has been expended on studying the impact of estrogen therapy on lipoproteins and lipid metabolism. The majority of this work was initiated in studies on oral contraceptive preparations. Oral estrogens have been shown to increase high density lipoprotein (HDL), and decrease low density lipoprotein (LDL). These effects are probably dose related with a 1-26% increase in HDL, 4-19% decrease in LDL (Bush,
In studies where the impact of 0.625mg conjugated equine estrogens were used, a 10% increase in HDL, and a 4% decrease in LDL was seen. Wren (1992) reviewed over 100 articles to evaluate the present state of knowledge regarding the effect of estrogen on the female cardiovascular system (i.e. atherosclerosis, myocardial infarction, hypertension and thrombosis). The evidence from this literature review supported the concept that estrogen reduced the risk of atherosclerosis and myocardial infarction. It also confirmed that postmenopausal estrogen is a vasodilating agent which will lead to a fall in blood pressure and an improvement in blood flow and the pulsatility index. The consensus of the published data was that estrogen conveyed a highly protective effect on the cardiovascular system of postmenopausal women. There was a reduction of up to 50% in myocardial infarction and stroke, a reduction in the incidence of hypertension and an improvement in blood flow.

Grady et al (1992) performed a meta-analysis on 32 epidemiological studies which evaluated the relationship between non-contraceptive use of estrogen and CHD. The studies in the meta-analysis were primarily a combination of case-control, and cohort studies. Their pooled estimate of the RR for CHD in women who had ever used estrogen versus never users was 0.65 (CI, 0.59 to 0.71).

Stampfer et al (1991) followed 48,470 women, 30 to 63 years old, who were participants in the Nurses' Health Study, and who did not have a history of cancer or cardiovascular disease at base line. During up to 10 years of follow-up, they documented the incidence of strokes, major coronary disease (nonfatal myocardial infarctions or deaths from coronary causes), and deaths from all causes. They also adjusted for age and other risk factors, and the overall RR of major coronary disease in women currently
taking estrogen was 0.56 (CI, 0.40 to 0.80). Current estrogen use was associated with a reduction in the incidence of coronary heart disease as well as in mortality from cardiovascular disease.

Recently study data were presented in which 15 years of follow-up on a large number of HRT users were followed. Grodstein et al (1996) evaluated the impact of HRT on cardiovascular disease using up to 16 years of follow-up in 59,337 women from the Nurses' Health Study, who were 30 to 55 years of age at baseline. Using this database they documented cases of myocardial infarction or death from coronary disease in this group. The analysis showed a marked decrease in the risk of major coronary heart disease among women who took estrogen with progestin (multivariate adjusted RR, 0.39; 95 percent confidence interval, 0.19 to 0.78) or estrogen alone (RR, 0.60; CI, 0.43 to 0.83), as compared with women who did not use hormones. They also found that treatment for less than two years with HRT treatment demonstrated the same benefits as longer duration of therapy, hence HRTs impact on CHD is considered to have immediate impact. There was no significant association between stroke and use of combined hormones (multivariate adjusted RR 1.09 (CI, 0.66 to 1.80) or estrogen alone (RR, 1.27; CI, 0.95 to 1.69). They concluded that the addition of progestin does not appear to attenuate the cardioprotective effects of postmenopausal estrogen therapy.

2.7.3.2.1 HRT and Coronary Heart Disease Risk Reduction Used in the Model

In the thesis the most recent data from the Nurse's study (Grodstein et al, 1996) will be used with RR= 0.60 (CI, 0.43 to 0.83). Thus a 40% reduction (RR = 0.60) in CHD events was used in the base case analysis versus controls. Sensitivity analysis was
conducted to evaluate the impact of varying the efficacy of HRT on CHD using the upper and lower confidence intervals from the Nurse’s study of 17% reduction (CI = 0.83) to a 57% reduction (CI = 0.43) in CHD events versus controls. The protective effects of HRT on CHD were assumed to occur immediately upon initiation of therapy as supported by the literature and described in the section above.

A recent analysis of the impact of HRT on CHD events and life expectancy (Col et al, 1997) used the same risk reduction values in their analysis. Similar reductions in risk of CHD have been assumed with HRT usage in a number of cost-effectiveness analyses and have been summarized in the OTA report on HRT (OTA, 1995b).

2.7.3.3 Breast Cancer and HRT

One of the more important risk factors for developing breast cancer is a woman’s lifelong exposure to endogenous estrogen. Factors influencing this relationship include early menstruation, late menopause, late first pregnancy, or nulliparity increasing this risk (Gail et al, 1989). Obese postmenopausal women are also at an increased risk due to the increased serum concentrations of endogenous estrogen (Cauley et al, 1996). The contribution of HRT in postmenopausal women to the risk of breast cancer has created debate around the decision to use this therapy. Recently a number of researchers in Ottawa created a clinical outcome-based decision aid with the purpose of allowing women to be educated on the benefits and risks of HRT (Robinson, 1997). This instrument objectively weighs the woman’s personal risk factors and allows for a more informed decision to be made on the use of HRT.
HRT regimens are potentially of three types: 1) unopposed estrogen, 2) estrogen plus cyclic progestin, and 3) estrogen plus continuous progestin (Grady et al, 1992). The duration of therapy is dependent on the primary reason for treatment initiation. The suggested duration can range from a few months to a lifetime based on the purpose of treatment initiation. Long-term treatment is often necessary for urogenital atrophy, osteoporosis and cardiovascular disease which is why there is concern about the relationship to breast cancer. Some data suggests that the cardioprotective effect may be lost within three years of discontinuing treatment, reinforcing the need for long term therapy (Witt et al, 1997). Unfortunately, a longer duration of estrogen therapy correlates with an increased incidence of breast cancer (Zhang et al, 1997). It has been suggested that the addition of progestin to the estrogen regimen (in order to minimize the incidence of endometrial cancer), may cause a decrease in any benefits to coronary heart disease, and may have no effect or result in a higher risk of breast cancer in comparison to unopposed estrogen (Witt et al, 1997).

Mills et al (1989) evaluated the incidence of breast cancer in HRT users versus non-users over a six year period in white Seventh-Day Adventist women residing in California. The data was adjusted for age, ages at menarche, first birth and menopause and a RR of 1.39 (CI, 1.00 to 1.94) was seen.

Grady et al (1992) estimated the RR of breast cancer based on a meta-analysis of 39 epidemiological studies of primarily case-control and cohort design. The analysis found that no increased risk for breast cancer in women who ever took estrogen for ≤ 5 years. Nevertheless, in users of estrogen of 8 years or more a RR of 1.25 (CI, 1.04 to 1.51) was found.
The Nurses’ Health Study cohort was broadened from the use of oral contraceptives, cigarette smoking and risk of major illnesses in women to include estrogen replacement therapy (Colditz et al, 1995). This study found that women currently taking HRT had an increased risk of breast cancer. The greatest risk was in women who had been taking estrogen or estrogen plus progestin for five or more years, with a 46% increase in breast cancer (RR 1.46 CI, 1.20 to 1.76). The increase was most pronounced among women over the age of fifty-five. Women aged 65-69 had a sixty-nine percent increase in breast cancer risk among women who were current HRT users consistent with an escalating risk with prolonged use. Former HRT users had no significant increase in risk when compared with women who had never used hormone therapy; this was true even for women who had taken hormones for five or more years in the past. Women who stopped taking hormones after five or more years of use, were still at increased risk of breast cancer for up to two years after stopping therapy. After two years the risk was comparable to that of women who had never taken HRT. A shorter duration (under five years) of use was not consistently related to the risk of breast cancer (Colditz et al, 1995).

The Framingham study evaluated the relationship between bone mass and breast cancer incidence. The basis for this relationship is that estrogen status is an important determinant of BMD, where the greater the bone mass the higher the level of estrogen present. This cohort was divided into four quartiles with quartile number one containing those with the lowest bone mass and by association lower estrogen levels, up to quartile number four with the highest bone mass and therefore the highest planned estrogen levels. The incidence of breast cancer was greater among the women in the fourth
quartile who had the highest bone mass. The incidence of breast cancer for quartile two to four ranged from 1.3 to 3.5 when compared to the first quartile. Thus these data are consistent with previous studies suggesting an increased risk of breast cancer associated with HRT use.

Progestins have been added to estrogen replacement therapy in the treatment of menopausal and post menopausal women to reduce the incidence of endometrial cancer. The addition of the progestin to estrogen therapy has raised the issue of the potential impact on breast cancer incidence. Some of the more recent studies where women took estrogen plus progestin have shown an increased risk of breast cancer, while in others no increase was seen. The protective effects of progestins against endometrial cancer, have not been shown to be present against breast cancer. However, some concern exists regarding the combined effect of progestin with conjugated estrogen, since there is evidence that progestins may act synergistically with estradiol to enhance cellular proliferation rates in breast tissue of premenopausal women.

The Nurses Cohort (Colditz et al, 1995) showed similar RRs for estrogen alone and estrogen plus progestin. A population-based case-controlled study by Stanford et al (1995) did not find any increase in the risk of breast cancer with the use of estrogen plus progestin in either current or long term users when compared to community controls. These conflicting results have resulted in controversy amongst researchers and confusion to menopausal women contemplating the use of HRT.

In summary, a number of studies have demonstrated a significant increase in breast cancer incidence in women who have taken HRT for five or more years (Col et al, 1997). It is for these women, who were candidates for long-term HRT, that alternative
treatment strategies be made available beyond their first 5 years of treatment with HRT. Before women initiate HRT the risk/benefit ratio must be evaluated. Caution needs to be exercised in administering HRT to those women with a family history of breast cancer or benign breast disease (Witt et al, 1997). Regularly scheduled mammography, and routine examinations of the breast must be done due to the relationship between prolonged estrogen exposure and breast cancer.

### 2.7.3.3.1 HRT and Breast Cancer Risk Used in the Model

A 46% increase in breast cancer risk will be assumed for HRT users in the base case assumptions of the thesis evaluation based on the large prospective Nurse’s study (Colditz et al, 1995). Sensitivity analysis will also be conducted to determine the impact of the lower (1.20) and upper (1.76) confidence intervals about the base case (RR of 1.46 found in the Nurse’s study), on the intervention’s cost and outcomes results. The impact of HRT on breast cancer was assumed to occur only at the tenth consecutive year of HRT use in the thesis model, based on a number of publications that support HRT’s limited impact on breast cancer until after a ten year duration of treatment.

### 2.7.3.4 Summary Of The Base Case, Optimistic, And Pessimistic Scenarios For HRT

The clinical impact of the HRT strategy that were discussed in the previous sections and based on the literature are summarized in Table 2.6. The base case scenario was defined using the relative risk values of HRT’s impact on hip fractures, breast cancer
and CHD. The impact of the intervention for the optimistic and pessimistic scenarios were derived from the lower and upper 95% confidence intervals.

2.8 Integrating The Impact Of Calcium/Vitamin D And HRT On Osteoporosis

The review of the literature on osteoporosis supports the role of calcium, vitamin D and HRT in the management of this disease. Uncertainty about the precise clinical impact of each of these clinical strategies makes the economic evaluation of these interventions on osteoporosis challenging. It is evident from the literature that HRT is the more effective regimen in the prevention of osteoporosis compared to calcium, vitamin D and the do nothing (no intervention) approach. HRT has additional benefits in its cardioprotective impact, however this intervention has been implicated in increasing the risk of breast cancer development. An economic evaluation of these prevention strategies in Canadian postmenopausal women requires the identification of all costs and consequences related to this disease and the potential events (i.e., breast cancer, myocardial infarcts) resulting from these interventions. The incidence of these events as well as their associated costs can be addressed in economic evaluations through the use of economic models.

2.8.1 Economic Models

Clinical decision analysis has been used extensively over the past twenty years to analyze and inform clinical decisions under uncertainty. The use of its conceptual framework - the "decision tree", allows for the therapeutic management problem to be disaggregated into a number of manageable units. Each unit allows for a decision to be
Table 2.6 The impact of hormone replacement therapy on hip fractures, coronary heart disease and breast cancer based on the review of the literature.

<table>
<thead>
<tr>
<th></th>
<th>Base case scenario</th>
<th>Optimistic scenario</th>
<th>Pessimistic scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRT- hip fracture</td>
<td>- 50% (5 year delay)</td>
<td>- 70%</td>
<td>- 31%</td>
</tr>
<tr>
<td>HRT - CHD</td>
<td>- 40% (immediate)</td>
<td>- 57%</td>
<td>- 17%</td>
</tr>
<tr>
<td>HRT - breast</td>
<td>+ 46% (10 year delay)</td>
<td>+ 20%</td>
<td>+ 76%</td>
</tr>
</tbody>
</table>

- : indicates a reduction in relative risk  
+ : indicates an increase in relative risk
made, and each choice is generally associated with a probability of an event's occurrence (Beck et al, 1983).

For chance events that occur over a short period of time (ie the results of a surgical procedure), the decision-tree approach works adequately. In the case of more complex medical processes where the natural history of the disease involves events that occur repeatedly (such as hemorrhage with anticoagulation therapy), or over a prolonged period of time (ie. myocardial infarction following coronary artery bypass surgery), or when the timing of events is important, the resultant decision tree becomes extremely complicated and "bushy". Under these circumstances the Markov model of prognosis is an excellent alternative (Sonnenberg et al, 1993). The economic model of this thesis, uses the Markov modelling approach.

2.8.1.1 The Markov Model Approach

In Markov models, we assume that a patient is always in one of a finite number of discrete health states, called Markov states. An example of a simple model in which three states exist, is diagrammed below:

\[
\begin{align*}
\text{WELL} & \quad \mathbb{P}_{wi} \rightarrow \text{ILL} & \mathbb{P}_{id} \rightarrow \text{DEAD} \\
\end{align*}
\]

These three states are referred to as the states of health. At any time "t" the patient can be in only one of these three states. Changes in the patients state are allowed and are
referred to as transitions. Transition from one state to the other is allowed at each cycle. Cycle length can vary from a few hours to years, and generally cycle length is defined as a single value in a model. Transitions among the states occur instantaneously upon switch from one cycle to the next (Figure 2.1). In each model there are a number of rules governing through which states one is allowed to move to and fro. In this example we have three simple states, and we have not placed any implicit restrictions on the movement between states. One state however (the DEAD state) is referred to as an absorbing state, since once a patient moves into this state they can no longer move out of it into another state on the subsequent cycle.

A unique feature about these models is the Markovian assumption; the absence of memory in the process (Beck et al, 1983). In other words, all patients in a given state have the same prognosis, no matter how they got to the present state.

2.8.1.2 Markov Processes and Chains

There are two types of Markov models, the Markov chain and the Markov process. In a Markov chains model, the transition probabilities (P_{wi}, P_{ww}, etc) are constant. This feature of constant transition probabilities are realistic only for diseases with a short time horizon. In chronic diseases, Markov processes are used in order to adjust for the annual mortality and increased likelihood of developing diseases (morbidity) as one ages. In Markov process type of models with a long time horizon, population mortality needs to be incorporated into the model. In Markov processes the probability of entering each stage generally changes with age.
Figure 2.1: A three-state Markov Model
2.8.2 The Construction of a Markov Model

There are a number of key steps that are required for the development of a Markov model:

Step 1: Listing of all of the states of health that the patient could potentially encounter, as well as a good definition of each of these states.

Step 2: Next the definition of the allowable state transitions are presented. This means that the ground rules are set to clarify which are the allowed transitions from each of the states. For example one may decide that one can only go from WELL to ILL and then to the DEAD state, however the transition from WELL to DEAD may not be permitted.

Step 3: Finally transition probabilities are assigned. These probabilities are sometimes expressed as rates. If transition information is provided as a rate, $r$, and the event is occurring over a time interval $t$ then the transition probability $p(t)$ can be defined as follows:

$$p(t) = 1 - e^{-r}.$$

In summary all events are represented as transitions from one state to another. In order to calculate life expectancy, as it is needed in this thesis for osteoporotic hip fracture patients, there are three methods by which a Markov model may be evaluated:
i) as a Monte Carlo simulation, ii) as a cohort simulation, or iii) by matrix algebra.

i) Monte Carlo simulation

In the Monte Carlo approach patients traverse a Markov process one by one, and a random generator determines what happens to the individual patient at each process (Beck et al, 1983). As each patient begins at the well stage they proceed to be assigned at each subsequent cycle to their next state as dictated by the transition probabilities. The patient proceeds through each of the random states until the defined number of cycles or until they reach the absorbing state (DEAD), which ever comes first. The time until the patient reaches the DEAD state is the life expectancy for that individual.

After the first individual has completed the simulation (ie is now DEAD), the next patient is simulated through the process, and this continues until a sufficient number of patients are run "through". The number of subjects going through the process are generally in the order of 1,000 or more. The accuracy of the Monte Carlo simulation approach is dependent on: i) the number of patients simulated through the model, ii) the quality of the random generator used and iii) knowledge of the initial health state and the associated transition probability distributions for the disease state. This modelling method requires substantial computing time, however with faster computers and more recent software developments in this area, this modelling approach is more efficient than it was five years ago.
ii) **Markov Cohort**

In contrast to the "individual subject" approach in a Monte Carlo simulation, the *cohort* method follows a *large number of patients at the same time* (Sonnenberg et al, 1993). The cohort begins in the well state (at age 50 in our case), and at each of the cycles the cohort is distributed to the different states based on the transition probabilities (Table 2.7).

The model begins at cycle zero (Table 2.7) in which all 1,000 individuals are in the WELL state. Typically the model is allowed to run until the individuals in the cohort run through the non-absorbing states (WELL and ILL), or the defined number of states, and the model stops when all of the patients reach the absorbing state (DEAD). As the number of cycles increase with time, it is observed that the cohort is moving from the WELL to the ILL and ultimately accumulating at the DEAD state.

At cycle 0, all the individuals are in the WELL state. In the example presented in Table 2.7 the transition probabilities from WELL to WELL were set to 0.30 for cycles 0 to 2, and this probability decreases to 0.20 for the rest of the cycles. The transition probabilities from WELL to ILL on the other hand remain constant at 0.50 for all cycles. The number of individuals who are in the DEAD state at the end of each cycle is the residual of those subjects in the non-absorbing states of WELL and ILL (ie DEAD = 1,000 - (WELL + ILL)).
Table 2.7 Markov Cohort simulation - tabular representation

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>WELL</th>
<th>ILL</th>
<th>DEAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1000</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>300</td>
<td>500</td>
<td>200</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
<td>150</td>
<td>760</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>45</td>
<td>928</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>9</td>
<td>988</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>2</td>
<td>998</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0</td>
<td>1000</td>
</tr>
<tr>
<td>Sum</td>
<td>1411</td>
<td>706</td>
<td></td>
</tr>
</tbody>
</table>

Average Cycles (Sum/1,000)  

|               | 1.41 | .71 |

Life Expectancy  

\[ 1.41 + 0.71 = 2.12 \]
At the end of the process the total number of patient-cycles at each state is divided by the size of the original cohort, which yields the expected time that each individual member will spend in each state. The life expectancy can then be determined by summing the expected values from each of the non-absorbing death states. In this example the life expectancy of the patients described in this cohort Markov model is 2.12 years. This approach also allows for time-dependent probabilities and utilities to be incorporated into the analysis.

The model in this thesis will be of the Markov cohort type. The approach taken and the construction of the model to address the objectives of the thesis are described in detail in chapter 4.

iii) Fundamental Matrix Solution

This approach requires constant transition probabilities and consequently is appropriate for Markov chain type of processes. This process has not been considered for this thesis. The difference between a cohort simulation and the fundamental matrix solution may be thought of as analogous to the difference between determining the area under a curve by dividing it into blocks and summing their areas versus calculating the area by solving the integral of the function describing the curve (Beck et al, 1983). The fundamental matrix solution is exact, however conceptually is difficult to apply.
2.9 Summary

The assembly of all the required data (probability of event occurrence, and event cost), and the efficacy of the interventions used in the prevention of osteoporosis, are necessary for the economic evaluation of these regimens in Canadian postmenopausal women. The construction of the hip fracture prevention economic model will allow us to complete the evaluation of these interventions from a Canadian health system perspective, to discuss potential prevention strategies for this disease, and the avoidance of the debilitating hip fracture event.
3. HYPOTHESIS/OBJECTIVES

3.1 Hypotheses

The primary hypothesis of this thesis is that supplementation with calcium and vitamin D or treatment with hormone replacement therapy in Canadian postmenopausal women will result in fewer medical events and lower overall healthcare cost than no intervention if therapy is initiated shortly after menopause. The secondary hypothesis is that delay of supplementation (by 15 years) beyond the initiation of the menopause will result in more medical events and additional costs than supplementation initiated shortly after menopause.

3.2 Objectives

*Overall Objective: Conduct of an economic evaluation to compare the cost-effectiveness of calcium/vitamin D versus hormone replacement therapy in reducing the risk of hip fractures, coronary heart disease and breast cancer, associated with osteoporosis treatment in early postmenopausal Canadian women.*

The specific objectives are:

3.2.1 *Objective #1*

To create an economic evaluation model, that is reflective of the incidence and management of osteoporotic hip fractures, cardiovascular disease and breast cancer in Canadian postmenopausal women. This model will be used to evaluate the costs and outcomes of no intervention versus the preventative interventions with calcium/vitamin D or hormone replacement therapy supplementation.
3.2.2 Objective #2

To assemble from the literature and administrative database sources Canada-specific probabilities for the rates of hip fractures, coronary heart disease, breast cancer and associated costs of managing those events.

3.2.3 Objective #3

To evaluate the costs and outcomes of the two active interventions versus no intervention in preventing hip fractures, coronary heart disease, and breast cancer, from a Canadian health system perspective, in postmenopausal women who either delay this therapy by 15 years or initiate it shortly after menopause.
4. HIP FRACTURE MODEL

4.1 Economic Modelling

The use of modelling in medical decision making has been growing over the last ten years. The application of this technique in health care has allowed clinicians to make complex decisions like which antibiotic should be used for a patient with a life threatening infection, or which osteoporosis preventative therapy should be prescribed for this postmenopausal woman. There are four common elements to making a decision, these are: choice, consequences, probabilities, and outcomes.

Decisions involve making a choice between two or more alternatives. The compilation of the possible choices needs to be made carefully narrowing down the number of alternatives to the smallest number, since the larger the number of alternatives along the modelling process the more complex the model. This relates to the fact that the impact of most therapies are not confined to the disease of interest but also carry other risks/benefits and the impact of these must also be included in the decision making. Germaine to this thesis is the fact that HRT use for the prevention of hip fractures also carries with it other benefits, including cardiovascular benefits (ie. reduced coronary heart disease events), potential improvements/maintenance of cognitive function, as well as increased risk of breast cancer and thrombosis. Thus, comparison of the current ‘gold standard’ to the strategy of interest, calcium/vitamin D (CaVD), must include the broader impact of HRT despite the fact that there is currently no evidence that CaVD will impact on these other pathologic states. The third element is the certainty or probability of an event’s occurrence (either a consequence, or the outcome under study). If the administration of CaVD resulted in the prevention of hip fractures in 100% of the
postmenopausal women treated, without any untoward effects, then one would not need to make a decision about its use. Clearly, this is not the case for any current treatment strategy aimed at reducing hip fracture incidence. Consequently, estimates of risk reduction and/or enhancements for all events including the primary outcome (hip fracture) as well as secondary outcomes (e.g., increased breast cancer risk) must be established. Lastly, for all decisions, a final outcome measure is identified and tracked to judge the impact of the intervention on an event (i.e., hip fractures averted) or cost.

4.2 Steps In The Medical Decision Making Process

Application of the decision analysis process was applied to health care by Ledley et al. (1959) in the late fifties, and decision analysis reached the medical literature in the early 1970’s (Lusted, 1971). Generally there are six major steps involved in decision analysis:

i) identify, define, and set the timeframe of the decision

ii) explicitly structure the decision and the consequences of each decision over time

iii) estimate the probabilities of each consequence considered in the decision

iv) determine the value and units of measure of each outcome

v) select the option with the optimal expected outcome

vi) determine the robustness of the decision by conducting sensitivity analysis

These six steps will now be described in more detail.

i) identify, define, and set the timeframe of the decision
The objective of this first step is to set the ground rules for the decision. This includes defining what options will be considered, the perspective, the population considered, the time horizon of the analysis, as well as the outcome of interest and the associated units of measurement.

There are five decision options (choice nodes) that need to be considered in the model in order to address the hypotheses of this thesis, these are: no intervention (NI; do not treat), CaVD initiated at age 50 (CaVD50), and 65 (CaVD65) years respectively, and HRT initiated at age 50 (HRT50), and 65 (HTR65) years respectively.

The conduct of the cost-effectiveness analysis of CaVD and HRT strategies requires the use of a probabilistic model. This thesis used an economic model since the analysis involves the evaluation of these prevention strategies which are run over a 40 year (age 50-90 years) time frame. Obviously long-term clinical data on the strategies is limited, consequently one has to resort to these probabilistic models to estimate the impact of the therapy over the long-term.

The perspective of the analysis taken in this economic evaluation has been coined the “Health System” perspective. In this perspective all costs and consequences relating to the medical events (hip fracture, CHD, and breast cancer) described in section 4.1 above are included. Using this perspective we will also include the costs of drugs not borne by the provincial Ministry of Health in those individuals who are under the age of 65 years, and the cost of calcium and vitamin D which is not currently paid for by any provincial drug plan. In the case of HRT, the acquisition cost and two dispensing fees (one for the estrogen, and one for the progestin component of HRT) will be applied to all postmenopausal women who initiate HRT therapy. The dispensing fee will be $8.70 per
prescription for those women under the age of 65, since this is the most current Canadian average dispensing fee (Welds et al, 1996). In postmenopausal women over the age of 65 the dispensing fee will be $6.11, based on the current fee reimbursed to pharmacists in Ontario for prescriptions dispensed to seniors (age 65 and older). In the case of calcium and vitamin D supplements the cost that will be included in this Health System perspective is the retail price (acquisition cost plus 40% mark-up) for all postmenopausal women. No dispensing fees are required.

The consequences evaluated in this analysis for each intervention will be the incidence of hip fractures, CHD events, and breast cancer and the costs associated with their management. The metric of (incremental) Life Years Gained (LYG) will also be evaluated for the CaVD or HRT strategies versus the no intervention scenario. The LYG metric identifies the average number of additional life years that each subject will gain on a particular intervention, beyond those under the NI strategy.

ii) explicitly structure the decision and the consequences of each decision over time

The decision to use a model is followed by the need to “map out” the management of the clinical problem using decision trees. These trees are useful in focusing the decision maker to identify the relationships that exist between the decision options and the consequences of selecting each of the options. Similarly this tool can be used to think through a decision. It is imperative that both the effectiveness and adverse events be included in the analysis (Barr et al, 1996). The first step in this process involves identification of the “health states” that are important in the disease of interest. The thesis
is focused on the prevention of hip fractures, since these fractures are the most costly from both a patient and health care system perspective. Consequently, all of the potential health states (chance nodes) of the target population (50 year old community-dwelling postmenopausal women) need to be listed. An exhaustive list was compiled on the sequelae following a hip fracture event based on the capture of these events from the literature, presentations at osteoporosis conferences/meetings, and through discussions with clinicians who routinely deal with hip fracture patients. The primary health states were distilled to eight in order to minimize the complexity of the model:

1) **Community**: community dwelling postmenopausal women (PMW) which currently are “healthy” (i.e. they have not had a hip fracture, CHD or breast cancer (BrCA) event during that year). These women may have suffered other events during this year however this model does not consider these events. Intrinsic to this state is the fact that the average age of menopause is 50 years (Carr et al, 1987).

2) **Long Term Care**: PMW residing in long-term care (LTC)

3) **Hip Fracture Com**: community-dwelling PMW who have suffered a hip fracture this year

4) **Hip Fracture LTC**: those PMW who have suffered a hip fracture while residing in LTC facilities

5) **Long Term Care Hip**: PMW that suffered a hip fracture while residing in the community, however as a result of this fracture they now permanently reside in LTC.
In chapter 2 a full discussion was presented on the determinants of optimal bone health as well as the impact of two preventative strategies (CaVD and HRT). Inherent in the clinical profile of HRT however was this strategy’s impact on BrCA and CHD in addition to its impact in preventing hip fractures. The conduct of the evaluation without these two elements (BrCA and CHD), would be met with criticism, since economic evaluations of interventions are to encompass all relevant outcomes associated with each strategy. Emerging evidence is suggesting that HRT use may have other benefits, including decreased risk of cognitive decline (Rozenberg et al, 1998). Unfortunately these data are in their infancy and no estimates for risk reduction are available. Consequently this model is presently confined to health events for which estimates of risk are reasonably well defined.

6) **Dead: BrCA**: This state encompasses both the management of newly diagnosed breast cancer patients as well as those who died as a result of the disease. The approach taken for this estimation is described in detail in chapter 5 of this thesis.

7) **Dead: CHD**: A large number of possible states within CHD are possible (ie. myocardial infarct, angina, silent myocardial infarct, etc), including death from these events. If each of these individual states were included, the resulting decision tree would be very cumbersome to manage over the 40 year time horizon. In order to simplify the process, the CHD states including death from CHD were collapsed into the **Dead: CHD** state. The approach taken for this estimation is described in detail in chapter 5 of this thesis.
8) **Dead:** This state captured all PMW who died during that year from causes other than CHD and BrCA.

The impact of hip fractures, myocardial infarcts and BrCA in Canadian women age ≥ 50 years in fiscal 1993/1994 is presented in Figure 4.1 (Statistics Canada, 1996). The data in this figure demonstrate the impact of these age-related diseases to the health care system.

The hip fracture model developed for this thesis is a Markov model that utilizes the Markov process, and the cohort approach (Beck et al, 1983). Use of the decision tree approach would result in a very "bushy" tree with $10^8$ branches emanating from the eight initial states. Markov models are considered when subjects fluctuate among a finite number of clinical states over time, and when events can recur because patients remain exposed to risk (Barr et al, 1996). In order to simplify the process the Markov modelling approach has been selected due to its simplification on the number of branches. A limitation of the Markov approach is the "lack of memory" associated with each of these states. This means that once one leaves a specific state and enters into the new state that there is no memory of them being in the previous state, and that the probability of going back into the previous state is the same as if they had never been in it. Nonetheless Markov modelling is used extensively in economic evaluation due to its flexibility in dealing with complex iterative processes. The Markov cohort approach was used since this method requires only point estimates of the age-specific probability of an event (Beck et al, 1983). The Monte Carlo type of Markov model on the other hand requires
Figure 4.1 The number of hip fractures, myocardial infarcts and new breast cancer cases in Canadian postmenopausal women in fiscal 1993/1994.
distribution curves surrounding the probability of an event for its operation. Use of the Monte Carlo type of Markov model is limited if this level of data is lacking. Since access to age-specific probability distributions of entering all of the states in the thesis hip fracture model were not available, the Markov cohort approach was used.

The resulting Markov cohort model incorporated the eight health states reflective of the management of PMW using CaVD, HRT or NI strategies, and is presented in Figure 4.2. One thousand women were run through each strategy in the model, and the number of events that resulted from each approach are presented in chapter 8.

iii) estimate the probabilities of each consequence considered in the decision

Once the consequences have been identified at each of the chance nodes, the age-related probability of an event's occurrence is required. The sum of all of the probabilities in each of the chance nodes must sum to 1.0. Ideally probability data obtained from the conduct of large randomized clinical controlled trials will result in both the accurate capture of the appropriate consequences (chance node identification), and probabilities of event occurrence. This level of data for inclusion in a model are rarely found in the literature. Typically these probabilities are obtained from poorly designed studies/surveys, databases, meta-analyses, expert opinion/consensus, and discussions with clinicians. These sources may underestimate frequent occurrences and overestimate rare events (Tversky et al, 1974). The age-dependent probabilities for each of the chance nodes used in the model, their source, and their limitations, are described in detail in chapter 5 of this thesis.
Figure 4.2 Canadian hip intervention model for prevention of fractures (CHIMP)
Figure 4.2 Canadian hip intervention model for prevention of fractures (CHIMP) (cont’d)
Figure 4.2 Canadian hip intervention model for prevention of fractures (CHIMP) (cont’d)
Figure 4.2 Canadian hip intervention model for prevention of fractures (CHIMP)
Figure 4.2 Canadian hip intervention model for prevention of fractures (CHIMP) (cont’d)
iv) determine the value and units of measure of each outcome

The fifth step in developing an economic model is to identify and to quantify the economic costs and other outcomes for each of the treatment options. This process requires the valuation of each of the outcomes and adverse events that are identified in the model. Costing of events can be obtained from a number of sources, and the values obtained can vary based on the perspective taken, the type of institution that provides care for an event (i.e. community versus teaching hospital), geographic location, and others. Chapter 7 of this thesis addresses the approach taken for estimating the costs required in this model.

v) select the option with the optimal expected outcome

Once the model is complete and is “populated” with the probabilities (step iii) and costs associated with each of the events in a chance node (step iv) then the model can be “rolled back” to generate the “expected value” for each treatment option (Sonnenberg et al, 1993). The process of rolling back involves weighing the probability of occurrence of each event in a chance node and assigning an expected value. This expected value is based on probabilistic estimates that events of different valuations will occur. The outcome values at each chance node is then weighted by its probability of occurring for each choice node and is then automatically ranked in comparison to other choice nodes in the model, highlighting the choice node that has the most favourable expected value.

vi) determine the robustness of the decision by conducting sensitivity analysis

The last step in the decision analytic process is the implementation of a sensitivity analysis. Sensitivity analysis challenges the robustness of the conclusions reached by the
model under base case assumptions. This is accomplished by varying the values of the probabilities and outcomes over a likely range of values. Ideally confidence intervals around a variable provide the optimal upper and lower ranges for sensitivity analysis. In running the sensitivity analysis around one variable (one-way sensitivity analysis) the model recalculates the expected value for that option. If that option had the highest expected value in the base case scenario and it continued to have the highest value throughout the sensitivity range tested for that factor, then the decision is said to be robust and is not sensitive to that factor. Sensitivity analyses can also be conducted in which two or three variables are also varied simultaneously; these simulations allow one to see if there is interaction between the factors under evaluation over the range tested.

Changes in the ranking of options can occur during sensitivity analysis, where for example an option that used to have the highest expected cost under base case assumptions, now has the second highest cost when the upper range of its value is used. The value of the factor at which the shift in ranking in expected cost occurs is referred to as the threshold value. The existence of a threshold value during sensitivity analysis indicates that the factor under analysis has an impact on the robustness of the model and may impact results.

4.3 The Canadian Hip Intervention Model for Prevention of Fractures (CHIMP)

The structure of a Markov model requires that the problem be separated into discrete, manageable units, however the integration of these key states must be clinically relevant (Beck et al, 1983). The development of the thesis state-transition model has resulted in eight Markov states for which age-related probabilities have been calculated.
based principally on Canadian-specific event rates and costs. The eight states and their allowed transitions have been represented graphically in Figure 4.2, and are further defined in Table 4.1, Figure 4.3, and section 4.3.1.

4.3.1 The Canadian Model States And Associated Transitions

The model transitions in the thesis model are depicted in Figure 4.3 and are further defined in this section.

A) COMMUNITY BRANCH

A1. COMMUNITY -------> COMMUNITY
In this scenario, the patient continues to reside in the community; no costs are incurred for anything beyond routine MD visits, and the cost of the treatment (ie CaVD or HRT).

A2. COMMUNITY -------> HIP FRACTURE COM
In this situation the patient sustains a hip fracture while residing in the community. It is assumed that the fracture occurs at the end of the period. Therefore, the costs incurred in this state is the cost of routine medical care, and the cost of the treatment (ie CaVD or HRT).

A3. COMMUNITY -------> LONG TERM CARE
In this case it is assumed that at the end of the cycle(year), the patient is admitted into a long-term care institution for reasons other than hip fracture. Therefore the only costs incurred in this state are the costs of routine medical care, and the cost of the treatment (ie CaVD or HRT).
Table 4.1: Transition states in the Canadian osteoporosis model

<table>
<thead>
<tr>
<th>States</th>
<th>Definition of state</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community</td>
<td>Functioning in the community with typical health care support for age.</td>
</tr>
<tr>
<td>Long Term Care (LTC)</td>
<td>Refers to patients who have been placed in this type of institution. Once patients enter this state they stay here for the rest of their lives.</td>
</tr>
<tr>
<td>Hip Fracture Com</td>
<td>Suffered a hip fracture while residing in the community. Costs captured in this state includes acute care hospital stay, and other support for year following fracture event (includes costs associated with rehabilitation stay, and home care).</td>
</tr>
<tr>
<td>Hip Fracture LTC</td>
<td>Suffered a hip fracture while residing in a LTC facility. Costs captured in this state includes acute care hospital stay and incremental LTC support for one year following the fracture event.</td>
</tr>
<tr>
<td>Long Term Care Hip</td>
<td>Suffered a hip fracture while in the community, and has been transferred to LTC. Support includes cost of LTC for this new LTC patient</td>
</tr>
<tr>
<td>Dead: Breast Cancer</td>
<td>Patients entering this state incur cost to the health care system for typical care for breast cancer. *</td>
</tr>
<tr>
<td>Dead: Coronary Heart Disease (CHD)</td>
<td>Patients entering this state incur cost to the health care system for typical care for treating CHD (ICD-9: 410-414), and the typical sequelae associated with these events. *</td>
</tr>
<tr>
<td>Dead</td>
<td>Captured as a death only. No costs are attributed to this event.</td>
</tr>
</tbody>
</table>

* Each woman that enters this absorbing state, invokes a toll (cost) to the analysis, in order to cover those women who have also been diagnosed with breast cancer or CHD but survive; the survivors also incur costs to the health care system for their care.
A4. COMMUNITY -------> DEAD: Breast Cancer
In this circumstance we assume that the patient dies at the end of the year from breast cancer. In addition to the cost of routine medical care, the cost of the treatment (ie CaVD or HRT) and the costs associated with breast cancer treatment were added. For model simplification, the costs of breast cancer treatment for women who survive are also added to the cost of this cycle.

A5. COMMUNITY -------> DEAD: CHD
In this circumstance we assume that the patient dies at the end of the year due to a CHD event. In addition to the cost of routine medical care, the cost of the treatment (ie CaVD or HRT), we also added costs associated with acute care treatment of myocardial infarct (ICD9:410) and other ischemic coronary events(ICD9:411-414). Similar costs for treatment of women who survive CHD have been added to the cost of this cycle.

A6. COMMUNITY -------> DEAD
In this circumstance the patient dies at the end of the cycle (year) due to causes other than BrCA or CHD. Therefore the only costs incurred in this state are the costs of routine medical care, and the cost of the treatment (ie CaVD or HRT).

B) LONG TERM CARE
In this arm in the tree the patient enters the long term care facility and resides there till the end of the year, all of the events that fall out are assumed to occur at the end of the year. The cost of the treatment (ie CaVD or HRT) is included in each of the states listed below (ie B1 to B5).

B1. LONG TERM CARE -------> LONG TERM CARE
In this case it is assumed that following admission the patient continues to habitate in the LTC facility. No additional charges are applied in this state.
Figure 4.3 The associated transitions in the thesis model
B2. LONG TERM CARE -----> HIP FRACTURE LTC
In this case we assume that the patient suffers a hip fracture when in the institution at the end of the cycle, additional costs related to the fracture will be captured at the next cycle.

B3. LONG TERM CARE -----> DEAD: Breast Cancer
In this circumstance we assume that the patient dies at the end of the year with this condition and consequently is charged for the care that they would have received for cancer treatment (includes costs for those diagnosed with breast cancer who survive).

B4. LONG TERM CARE -----> DEAD: CHD
In this circumstance we assume that the patient dies at the end of the year due to CHD and consequently is charged for the care that they would have received for CHD treatment (includes CHD costs for CHD survivors).

B5. LONG TERM CARE -----> DEAD
In this case the resident is dead at the end of the year. No additional costs are attached to this state.

C) HIP FRACTURE COM
In this case the patient enters the acute care hospital and gets charged the cost of surgery, the cost of acute care stay, the cost of regular MD visits (those as a result of the fracture,) while in the acute care, and the cost of the treatment (ie calcium/vitamin D or HRT) is added to each of the transitions below (ie C1 to C5).

C1. HIP FRACTURE COM-------> COMMUNITY
In this case the patient is discharged from the acute care hospital and either enters a rehabilitation facility with the objective of ending up back in the community, or is discharged to the community without support or with home care.

C2. HIP FRACTURE COM --------> LONG TERM CARE
In this case it is assumed that following the index hospitalization for hip fracture that the patient enters the long term care institution and will be charged the cost of that stay.

C3. HIP FRACTURE COM --------> DEAD: Breast Cancer
In this circumstance we assume that the patient dies at the end of the year with this condition and consequently is charged for the care that they would have received for cancer treatment (includes costs for those diagnosed with breast cancer who survive).
It is assumed that women in the HIP FRACTURE COM state have the same probability of developing and dying of BrCA and CHD as in the other states in the model.

C4. HIP FRACTURE COM --------> DEAD: CHD
In this circumstance we assume that the patient dies at the end of the year due to CHD and consequently is charged for the care that they would have received for CHD treatment (includes CHD costs for CHD survivors).
It is assumed that women in the HIP FRACTURE COM state have the same probability of developing and dying of CHD and BrCA as in the other states in the model.

C5. HIP FRACTURE COM --------> DEAD
In this circumstance the patient dies sometime during the acute care setting. In this circumstance no additional costs are added in this state.
D) HIP FRACTURE LTC
In this case the patient enters the acute care hospital and gets charged the cost of surgery, the cost of acute care stay (18 days assumed as base case), and the cost of regular MD visits (those as a result of the fracture,) while in the acute care. The cost of the treatment (ie CaVD or HRT) is included in each of the states listed below (ie D1 to D4).

D1. HIP FRACTURE LTC------> LONG TERM CARE
In this case it is assumed that following the index hospitalization for hip fracture that the patient enters the long term care institution and will not be charged the cost of that stay, however a surcharge is included for a period of one year to cover the additional nursing support as a result of this event.

D2. HIP FRACTURE LTC -------> DEAD: Breast Cancer
In this circumstance we assume that the patient dies at the end of the year with this condition and consequently is charged for the care that they would have received for cancer treatment (includes costs for those diagnosed with breast cancer who survive).

It is assumed that women in the HIP FRACTURE LTC state have the same probability of developing and dying of BrCA and CHD as in the other states in the model.

D3. HIP FRACTURE LTC -------> DEAD: CHD
In this circumstance we assume that the patient dies at the end of the year due to CHD and consequently is charged for the care that they would have received for CHD treatment (includes CHD costs for CHD survivors).

It is assumed that women in the HIP FRACTURE LTC state have the same probability of developing and dying of BrCA and CHD as in the other states in the model.
D4. HIP FRACTURE LTC ---> DEAD
In this circumstance the patient dies sometime during the acute care setting stay. Consequently no charges for LTC stay are incurred for that cycle if they die while in the acute care setting.

E) LONG TERM CARE HIP
In this state the patient is charged the cost of the treatment (ie calcium/vitamin D or HRT) is added to each of the states listed below (ie E1 to E4), and then is shunted to one of four states.

E1. LONG TERM CARE HIP ---> LONG TERM CARE HIP
In this case the patient either has a hip fracture (determined using the rate of hip fracture in LTC residing individuals), or if they do not fracture they are charged the annual charges relating to a LTC stay to the next cycle.

E2. LONG TERM CARE HIP ---> DEAD: Breast Cancer
In this circumstance we assume that the patient dies at the end of the year with this condition and consequently is charged for the care that they would have received for cancer treatment (includes costs for those diagnosed with breast cancer who survive), but not charged LTC costs.

E3. LONG TERM CARE HIP ---> DEAD: CHD
In this circumstance we assume that the patient dies at the end of the year due to CHD and consequently is charged for the care that they would have received for CHD treatment (includes CHD costs for CHD survivors).

E4. LONG TERM CARE HIP ---> DEAD
In this circumstance the patient dies sometime during the LTC stay. No charges for LTC stay are incurred for that cycle.
F) **DEAD: Breast CA** No additional costs incurred here. This is a terminal absorbing state.

G) **DEAD: CHD** No additional costs incurred here. This is a terminal absorbing state.

H) **DEAD** No additional costs incurred here. This is a terminal absorbing state.

The same Markov structure was applied to all five interventions.

### 4.4 Model Data Requirements

Having defined the Markov states in the model, there are two primary data requirements for the model: Canadian-specific transition probabilities (ie probability of moving from one Markov state to another each year and over time); and the health care costs of treating and managing persons in each state for each cycle over time (Sonnenberg et al, 1993). The following three chapters describe the data sources and methodology used for these data.
5. PROBABILITY PARAMETERS

5.1 Probabilities in the Hip Fracture Model

The model as described in the last chapter requires age-specific probabilities for a number of sequelae resulting from the treatment and the events of hip fracture, coronary heart disease and breast cancer. These events are listed in Table 5.1. Table 5.2 lists a number of relationships based on the probabilities derived for the model. Sources for probabilities can be broadly divided into those obtained from existing literature and those specifically derived within the context of this thesis.

5.2 Hip Fracture Analysis In Canada

An analysis of a Canadian hospital discharge database (Canadian Institute for Health Information (CIHI)) for the fiscal year 1993/1994 was conducted with the primary objectives of determining the annual number and fracture rate of proximal femoral fractures (PFFs) by sex and age (Papadimitropoulos et al, 1997a). Other data obtained included the associated length of stay and death rates in the acute care setting for these patients. The current PFF incidence data was then combined with Statistics Canada (1996c) population projections to estimate the number of hip fractures (PFFs) in Canada to the year 2041. The complete study has been peer reviewed, recently published, and is attached as Appendix A. The data from the study were used directly to define a number of the required variables and tables in the model. The following subsections will identify the probabilities used in the model and their limitations.
Table 5.1  Required age-specific probabilities of events for the hip fracture model and the source of these data.

<table>
<thead>
<tr>
<th>Description</th>
<th>Abbreviations</th>
<th>SOURCE</th>
<th>THESIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of Hip Fracture (HF) if in community (no intervention)</td>
<td>pWHFNo[stage]</td>
<td>CIHI dataset (Fiscal 1993/1994)</td>
<td></td>
</tr>
<tr>
<td>Probability of HF if in long term care (no intervention)</td>
<td>pLTCHF[stage]</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Probability of HF if in community (initiation of therapy at 50 years (CaVD50))</td>
<td>pWHFVbase[stage]</td>
<td>CIHI dataset /Cochrane Meta Analysis</td>
<td></td>
</tr>
<tr>
<td>Probability of HF if in long term care (initiation of therapy at 50 years (CaVD50))</td>
<td>pLHFCVr80[stage]</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Probability of HF if in community (initiation of therapy at 65 years (CaVD65))</td>
<td>pWHFV62[stage]</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Probability of HF if in long term care (initiation of therapy at 65 years (CaVD65))</td>
<td>pLHFCV62[stage]</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Probability of HF if in community (initiation of therapy at 50 years (HRT50))</td>
<td>pWHFHRT[stage]</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Probability of HF if in long-term care (initiation of therapy at 50 years (HRT50))</td>
<td>pLHFHRT[stage]</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Probability of HF if in community (initiation of therapy at 65 years (HRT65))</td>
<td>pWHFHRT65[stage]</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Probability of requiring home care following HF</td>
<td>pH[stage]</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Probability of requiring rehabilitation care following HF</td>
<td>pR[stage]</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Probability of permanently entering LTC following HF</td>
<td>pHLTC[stage]</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Probability of dying from Breast Cancer</td>
<td>pWDCA[stage]</td>
<td>Stats Canada</td>
<td></td>
</tr>
<tr>
<td>Probability of dying from Breast Cancer if on HRT from age 50 years</td>
<td>pWDCAHRT[stage]</td>
<td>Literature review/analysis</td>
<td></td>
</tr>
<tr>
<td>Probability of dying from Breast Cancer if on HRT from age 65 years</td>
<td>pWDCAHRT65[stage]</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Adjustment factor for breast cancer by age to account for survivors</td>
<td>ADJBRCA[stage]</td>
<td>Statistics Canada</td>
<td></td>
</tr>
<tr>
<td>Probability of death by myocardial infarct (MI) ICD-9:410</td>
<td>pWDMI[stage]</td>
<td>Statistics Canada</td>
<td></td>
</tr>
<tr>
<td>Probability of death by MI if on HRT from age 50</td>
<td>pWDMIHRT[stage]</td>
<td>Literature review/analysis</td>
<td></td>
</tr>
<tr>
<td>Probability of death by MI if on HRT from age 65</td>
<td>pWDMIHRT65[stage]</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Adjustment factor for MI by age to account for survivors</td>
<td>ADJMI[stage]</td>
<td>Stats Canada</td>
<td></td>
</tr>
<tr>
<td>Probability of death by other coronary heart disease (CHD) event ICD-9:411-414</td>
<td>pWDOTHR[stage]</td>
<td>Statistics Canada</td>
<td></td>
</tr>
<tr>
<td>Probability of death by other CHD event if on HRT from age 50</td>
<td>pWDOTHRT[stage]</td>
<td>Literature review/analysis</td>
<td></td>
</tr>
<tr>
<td>Probability of death by other CHD event if on HRT from age 65</td>
<td>pWDOTHRT65[stage]</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Adjustment factor for other CHD event by age to account for survivors</td>
<td>ADJOTHRT[stage]</td>
<td>Statistics Canada</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
Table 5.1(Cont'd)  
Required age-specific probabilities of events for the hip fracture model and the source of this data (Cont’d).

<table>
<thead>
<tr>
<th>VARIABLES &amp; TABLES</th>
<th>LITERATURE SOURCE</th>
<th>THESIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Symbol</td>
<td></td>
</tr>
<tr>
<td>Probability of death following HF if from community</td>
<td>pHFD[_.stage]</td>
<td></td>
</tr>
<tr>
<td>Probability of death following HF if from long term care</td>
<td>pHFDL[_.stage]</td>
<td></td>
</tr>
<tr>
<td>Probability of well to death</td>
<td>pWDeath[_.stage]</td>
<td>Stats Canada</td>
</tr>
<tr>
<td>Probability of entering LTC from community</td>
<td>pWLTC[_.stage]</td>
<td>Stats Canada</td>
</tr>
<tr>
<td>Number of calcium tablets</td>
<td>nCAL</td>
<td>Literature review/analysis</td>
</tr>
<tr>
<td>Number of vitamin D tablets</td>
<td>nVITD</td>
<td></td>
</tr>
<tr>
<td>Number of estrogen tablets</td>
<td>nESTROGEN</td>
<td></td>
</tr>
<tr>
<td>Number of progestin tablets</td>
<td>nPROGEST</td>
<td></td>
</tr>
<tr>
<td>Number of dispensing fees in one year</td>
<td>nDISPFEE</td>
<td></td>
</tr>
<tr>
<td>Number of MD assessments</td>
<td>nMD</td>
<td>Discussion with family physician</td>
</tr>
<tr>
<td>Number of MD reassessment</td>
<td>nMDRE</td>
<td></td>
</tr>
<tr>
<td>Number of Orthopedic assessments</td>
<td>nMDOP</td>
<td>Discussion with orthopedic surgeon</td>
</tr>
<tr>
<td>Number of Orthopedic reassessments</td>
<td>nMDOPRE</td>
<td></td>
</tr>
<tr>
<td>Number of Geriatric assessments</td>
<td>nMDGER</td>
<td>Discussion with geriatrician</td>
</tr>
<tr>
<td>Number of Geriatric reassessments</td>
<td>nMDGERRE</td>
<td></td>
</tr>
<tr>
<td>Number of extra LOS beyond 17 days</td>
<td>nHOTEL</td>
<td>CIHI dataset</td>
</tr>
</tbody>
</table>
Table 5.2  Functions in the model using variables and tables described in Table 5.1

<table>
<thead>
<tr>
<th>Description</th>
<th>Symbol</th>
<th>Description of equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of going from well to dead removing deaths due to all CHD events and breast cancer</td>
<td>pWD</td>
<td>(((pWDeath[stage]) - (pWDMI[stage] + pWDOTH[stage] + pWDCA[stage]))</td>
</tr>
<tr>
<td>Probability of going from well to dead due to all CHD events (ICD-9: 410-414)</td>
<td>pWDCHD</td>
<td>(pWDMI[stage]+pWDOTH[stage])</td>
</tr>
<tr>
<td>Probability of going from well to dead due to all CHD events (ICD-9: 410-414) if on HRT @ 50 years</td>
<td>pWDCHDHRT</td>
<td>(pWDMIHRT[stage]+pWDOTHRT[stage])</td>
</tr>
<tr>
<td>Probability of going from well to dead due to all CHD events (ICD-9: 410-414) if on HRT @ 65 years</td>
<td>pWDCHDHRT65</td>
<td>(pWDMIHRT65[stage]+pWDOTHRT65[stage])</td>
</tr>
<tr>
<td>Life years lost if 3% discounting</td>
<td>LLDISC3</td>
<td>(((1-(1/(1.03^LYL[stage+1])))/.03)*(1/1.03^death[stage+1]))</td>
</tr>
<tr>
<td>Cost discounting, if no discounting</td>
<td>DISC0</td>
<td>1</td>
</tr>
<tr>
<td>Cost discounting, if 3% discounting</td>
<td>DISC3</td>
<td>1.03^(-death[stage])</td>
</tr>
</tbody>
</table>
5.2.1 Rates of Hip Fracture in Canadian Women

The original published manuscript reports data on all individuals experiencing a proximal femoral fracture (PFF) in Canada during the fiscal year 1993/1994 (Papadimitropoulos et al. 1997a). As the model developed, it became apparent that analysis should be separated by place of residence at the time of fracture. This was necessary to separate the incremental health care cost associated with the transfer of an individual originally in the community to LTC, from the continuing LTC charges associated with those individuals who fractured while in LTC, accumulated acute care costs, and then returned to the LTC facility. The data presented here provides the probabilities used for each group (community versus LTC residents).

Analysis of the discharge data for Canadian women residing in either community or LTC resulted in exponential relationships between hip fracture rate and age (Figure 5.1). This exponential relationship was used to estimate the probability of hip fracture in community-dwelling Canadian postmenopausal women in whom no preventative intervention was used (pWHFNO). The probability for this event was required for the model for Canadian women from the age of 50 to 90 years. The analysis of the CIHI dataset was initiated at 65 years of age, hence the probability for hip fracture in women 65 years and older were generated from this analysis. The probability of hip fracture in women occurring between the age of 50 to 64 years is small with approximately 10% of the annual number of fractures occurring during this age band (Statistics Canada, 1996a). The hip fracture rates for this younger age band of women was obtained from Statistics Canada data (1996a) and used in the model.
Figure 5.1  Rate of Hip Fracture by residence type (LTC versus community) in Canadian postmenopausal women in fiscal 1993/1994.
In our model we assumed that all the hip fractures that occurred in Canada were osteoporosis related. The majority of women (75%) captured in the CIHI data experienced hip fractures when they were 75 years of age or older, hence they potentially would not be on estrogen intervention in their fifties, as this would have required treatment to commence pre-1968. Long-term HRT use for prevention of osteoporosis was initiated on a larger scale in the general postmenopausal population in the 1980s.

The probabilities generated for the incidence of hip fracture by age for community-dwelling women under the no intervention assumption (pWHFNO) were calculated. Similarly the CIHI dataset was used to calculate the rate of hip fracture for those patients who were residing in long term care facilities at the time of fracture (pLTCHF). The probabilities of hip fracture occurrence in LTC facilities are listed in Supplement A, as are all of the probability tables for the model.

5.2.2 Length Of Stay In Acute Care Hospitals Following The Hip Fracture Event

The discharge data for the fiscal year 1993/1994 was also analyzed to determine the mean length of stay (LOS) for female hip fracture patients. It was observed that these patients were in hospital a mean of 21 days in fiscal 1993/1994 (Figure 5.2) (Papadimitropoulos et al, 1997a). Reviews of hospital stays in these patients over the past 15 years have been demonstrating a trend toward a decrease in LOS, resulting in the shunt of these patients to less resource intensive facilities and programs (Jaglal et al, 1996). A review of the costing database for a teaching hospital in Ontario (Sunnybrook Health...
Figure 5.2  Mean length of stay by hip fracture patients in acute care hospitals by five year age groups. Error bars represent standard deviation.
Centre), was used to calculate the cost of a number of interventions in our model, for older female hip fracture patients in the fiscal year 1995/1996, showed a mean LOS of 17 days (ie a reduction of four days). In order to accurately evaluate the model for the fiscal year 1993/1994 hip fracture data, we adjusted the LOS to 21 days by adding 4 days of hotel costs (nHOTEL) to the 1995/1996 Sunnybrook costing data (mean LOS 17 days) in order for the model to be more reflective of the practice pattern in Canada captured from the CIHI dataset. The mean LOS for all women was used in the analysis since the Sunnybrook costing dataset did not have enough female hip fracture patients within each age group for generating mean LOS and cost for the acute care stay in this institution. Consequently we used the mean LOS from the CIHI dataset and the Sunnybrook dataset for all ages. Similarly, because of a small number of women within each age group in the Sunnybrook dataset, separate LOS values for hip fracture patients were not generated based on residence at fracture (i.e. those admitted from the community versus LTC facilities).

5.2.3 Mortality In Acute Care Hospitals Following The Hip Fracture Event

Mortality of hip fracture patients has been calculated from the 1993/1994 fiscal year dataset. It was found that a mean 7% of all hip fracture patients expired in the acute care facility while being treated for their fracture (Papadimitropoulos et al, 1997a). The relationship between death rate, age and residence (community vs LTC facility) at time of fracture is presented in Figure 5.3. The exponential relationship derived from the rates of death in female hip fracture patients has been used to calculate the probability of death
Figure 5.3  Rate of death in the acute care setting for women by residence type on admission (community versus LTC) in Ontario, fiscal 1993/1994.
while in the acute care setting for both those patients who were originally living in the community at the time of the fracture (pHFD), and those who were in a long term care facility prior to the fracture (pHFDL). It is realized that excess mortality beyond the acute care stay (one year post hip fracture) is likely greater than the mean 7% and has been reported (Wiktorowicz et al, 1997), based on a smaller sample size, hence reliable estimates of mortality rate are not available. Therefore for the model a conservative estimate for death rate will be used.

5.2.4 Discharge Destination Following The Acute Care Stay

The destination of hip fracture patients following their discharge from the acute care hospital has an impact on determining the fate of these patients and on health-care resource use. Evaluation of the dataset for the 1993/1994 fiscal year demonstrated that of those patients who were community living at the time of hip fracture, a certain proportion (based on their age) were discharged back to the community without any formal support, some were sent to the community with home care (pHC), others to rehabilitation care (pRC) with the ultimate objective of having them return to the community, and the balance were discharged to long-term care (pHFLTC) (Papadimitropoulos et al, 1997; Wiktorowicz et al, 1997). The destination data from these two studies has been distilled in the form of probability tables identified in this sub-section and the probability data (pHC, pRC, and pHFLTC) are presented in Supplement A. Estimates of the percentage of patients by “discharge destination”, generated from the CIHI discharge dataset for fiscal 1993/1994, have been supported by the data from the Hamilton Hip Fracture...
Study (Papadimitropoulos et al, 1997a). Typically patients who fractured in long-term care, returned to those facilities following their discharge from acute care hospitals.

5.2.5 **Probability Of Entering Long-Term Care From The Community**

Currently limited data are available on the rate of entry of older Canadians into long-term care (LTC) facilities. The probability of entry into these facilities has been estimated using the data provided through Statistics Canada on Residential Care Facilities (1996b) based on the number of women by age in residential care facilities during fiscal year 1993, and using population estimates for that year based on the 1991 Canada Census (Statistics Canada, 1992a). Table 5.3 outlines the number of older Canadian women residing in LTC facilities in fiscal year 1993/1994, and the associated probabilities by age. Residential care data is not routinely collected and suffers from a number of limitations. The number of facilities that currently collect these data is starting to increase with more structured databases being developed to collect resource use details of the patients within a facility as well as key outcomes such as death rate and primary diagnosis for entry. In our estimation of entry to LTC we used all of the data on women who resided in these facilities over the fiscal period covered. An evaluation of the data revealed that it was almost impossible to account for all the women that entered, remained and stayed in the facility at the end of the year. Hence data used for entry are actually based on residence. This limitation may result in overestimating the entry of older women into these facilities, and underestimate the entry of younger women. Consequently, use of the Statistics Canada data for generation of probability tables to
Table 5.3  The number of women in residing in long term care facilities in fiscal year 1993/1994, and the associated probabilities of residence in these facilities by age.

<table>
<thead>
<tr>
<th>Age</th>
<th>Number residing in LTC</th>
<th>Probability of residing in LTC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(fiscal year 1993/1994)</td>
<td></td>
</tr>
<tr>
<td>50-64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-69</td>
<td>4045</td>
<td>0.0068</td>
</tr>
<tr>
<td>70-74</td>
<td>8095</td>
<td>0.0157</td>
</tr>
<tr>
<td>75-79</td>
<td>15868</td>
<td>0.0419</td>
</tr>
<tr>
<td>80-84</td>
<td>28093</td>
<td>0.1071</td>
</tr>
<tr>
<td>85+</td>
<td>66292</td>
<td>0.2993</td>
</tr>
</tbody>
</table>
describe the entry of community residing women into LTC facilities was overestimated since it was not possible to separate those women who entered LTC due to hip fracture.

5.3 **Probability of Death - All Causes**

Statistics Canada publishes life-tables periodically for Canadian men and women. The probability of death from all causes for Canadians is available in tabular format (Statistics Canada, 1995). The data presented by age includes the probability of death, the number of life years lost if one dies at a particular age. These parameters were used directly to define two tables in the model, namely the probability of death by age (pWDeath), and the number of life years lost (pLYL) by age. These probability tables (pWDeath and pLYL) were prepared and used to populate the Markov model.

5.3.1 **Incidence and Death Rates Due to Breast Cancer in Canadian Women**

It is estimated that thirty percent of new cancer cases in women identified annually in Canada will be breast cancer; the second leading cause of death by cancer (National Cancer Institute of Canada, 1997). The etiology of breast cancer is of major concern, since the incidence of breast cancer in Canada has been rising over the last twenty years. The lifetime probability of breast cancer is 10.17% at birth and peaks at 10.34% at the age of twenty-five (National Cancer Institute of Canada, 1997). The probability of developing breast cancer increases steadily from the age of thirty (Bryant et al, 1994). Using the most recent publication on cancer incidence produced by Statistics Canada (1997), the incidence of breast cancer by age, as well as the incidence of deaths from breast cancer (pWDCA) was calculated. Since the ratio of cancer incidence to
deaths varies by age (ie the ratio is greater in the younger ages, and drops to just over one by age 80), this ratio was calculated for all age groups > 50 years (ADJBRCA). The ADJBRCA ratio was used in the model to account for the cases of cancer by age which occurred, but did not lead to death so that the costs associated with the management of the survivors, as well as the total number of breast cancer patients could be captured.

5.3.2 Assumptions for the Hip Fracture Prevention Model

The review of the published literature to date (provided in chapter 2 of this thesis) support the potential for increased breast cancer risk after 10 years of HRT intervention. The assumption in the osteoporosis model is that women will continue to take the interventions for a period of time that will exceed twenty years unless they are removed from the model (via death). It has been assumed that the risk of breast cancer after ten years of HRT intervention will increase by 50% independent of the age at which HRT use commenced. The rates of breast cancer death were then calculated based on whether a woman initiated HRT at age 50 (pWDCAHRT), or at 65 years (pWDCAHRT65).

5.4 Probability of Coronary Heart Disease

Coronary heart disease (CHD), is the major cause of death in postmenopausal women (Statistics Canada, 1997). CHD is characterized by a number of well defined events leading to death and disability. In this thesis the CHD category has been divided into two by use of ICD-9 codes 410 (myocardial infarcts - MIs) and 411-414 (other CHD events). Interest in capturing CHD events in the model is a result of the documented beneficial effects of HRT on this disease in postmenopausal women.
5.4.1 **Myocardial Infarcts**

Myocardial infarcts (MIs) are the most debilitating and costly CHD events to manage. Using Statistics Canada morbidity data for the fiscal year 1993/1994 (Statistics Canada, 1996a), the incidence of MIs in women by age was calculated. Similarly using Death by Cause tables (Statistics Canada, 1995) publication the death rates of this group of women by MIs was calculated (pWDMI). In an effort to simplify the model, yet capture the number of survivors and their associated management costs at the acute care level, a ratio of MIs reported over deaths due to MI for fiscal 1993/1994 was calculated (ADJMI). The benefits of HRT intervention on reducing the risk of CHD events has been estimated in a number of publications as occurring immediately upon HRT initiation, and being in the order of a 50% reduction in risk (Col et al, 1997). Using these published assumptions we modified the risk of death by MI to HRT users who initiated therapy at 50 years (pWDMIHRT) and 65 years (pWDMIHRT65), once again assuming that the risk reduction is independent of age at which HRT use is commenced.

5.4.2 **Other CHD events**

CHD events other than MIs are more difficult to define, and are characterized as less threatening events. Nonetheless the implications to the patient and the financial management of these events are costly. Statistics Canada morbidity data on the incidence of these other CHDs in women by age were provided (1996). Similarly using the Death by Cause tables (Statistics Canada, 1995) publication, the death rates of this group of women were calculated (pWDOTHR). In an effort to simplify the model, yet
capture the number of survivors and their associated management costs at the acute care level, a ratio of other CHDs reported over deaths due to CHD for fiscal year 1993/1994 was calculated (ADJOTHR). The benefits of HRT intervention on reducing the risk of these CHD events has been estimated in a number of publications as occurring immediately upon HRT initiation, and being on the order of a 40% reduction in risk (Col et al, 1997). The study by Col et al (1997) calculated these risk reductions using results from the Framingham study, Nurses study, reviews of HRT efficacy, and a Markov state transition model. Their results confirm previous estimates of risk reduction of hip, CHD and breast cancer incidence (Grady et al, 1992). Using these published assumptions we modified the risk of death by other CHD for HRT users who initiated therapy at 50 years (pWDMIOTHRT) and 65 years (pWDOTHRT65).

5.5 Interventions Used In The Model

There are three intervention arms in this model. The no intervention arm assumes the “do-nothing” approach where events relating to hip fractures, breast cancer and coronary heart disease will continue as are reported in the general population.

In the calcium/vitamin D intervention two treatment approaches are implemented; in the first scenario the subjects take the intervention from age 50 onwards, and in the second case they are in the do-nothing phase till they reach age 65 at which time they initiate active therapy. In the HRT arm the same choices are provided as in the calcium/vitamin D arm, where subjects can initiate lifetime therapy at either 50 years of age or 65 years of age.
An important assumption is that the subjects are compliant, and take therapy as directed daily (ie >95% compliance). If this is the case then patients will consume daily one each of calcium carbonate (one 500mg and one 250mg elemental calcium) (nCAL), and vitamin D (400 IU) (nVITD) tablets. In the HRT arms the subjects will take daily one estrogen tablet (0.625mg conjugated estrogen) (nESTROGEN), and one progesterone tablet (medroxyprogesterone 2.5mg) (nPROGEST). This HRT combined regimen is used frequently in postmenopausal women for the benefits associated with this treatment.

5.5.1 Dispensing Fees

Pharmacist dispensing fees are typically applied to prescription products, hence these apply to the HRT intervention only. HRT is considered a maintenance medication, hence typically a three month supply will be dispensed at one time. A number of provincial plans will not reimburse more than a three month supply, hence in the base case analysis four dispensing fees (nDISPFEE) for the estrogen, and four dispensing fees for the progestin were used to cover one year’s supply of medication.

5.6 Physician Services

Physician services surrounding a hip fracture event are accentuated during the year that the fracture occurred. In order to ensure that these additional fees were captured conservatively in the model, a geriatrician (nMDGER, nMDGERRE) and an orthopedic surgeon (nMDOP, nMDOPRE) were consulted for typical fees requested from the Ontario Hospital Insurance Plan (Ministry of Health, 1992), for the additional care resulting from the fracture event. In the case of a hip fracture patient who returned to the
community a number of family physician visits were assumed (nMD, nMDRE) over and above maintenance visits and would continue till the patient’s death. In the case of a newly-admitted hip fracture patient to LTC (who was formerly community-dwelling), or a LTC dwelling resident who fractured a hip, a geriatrician was approached (Dr. Alexandra Papaioannou) for her opinion on the number and type of additional physician visits that these patients require. The geriatrician suggested that one general assessment and two reassessments would cover the additional fees submitted for a hip fracture patient who returned to/entered a long-term care facility. Discussions with the orthopedic surgeon (Dr. Robert Luba, Centennary Hospital) suggested that besides the routine follow-up in the acute care setting, that the orthopedic surgeon would perform one general assessment with the patient, and two reassessments over the course of the patient’s hospital stay.
6. EFFICACY OF CALCIUM AND VITAMIN D IN OSTEOPOROSIS PREVENTION

6.1 Efficacy Of Treatment Regimens In Preventing Hip Fractures

The impact of interventions on the prevention of postmenopausal bone loss and ultimately the prevention of hip fractures has been studied more effectively over the last fifteen years, due to the introduction of a number of evaluative bone mass techniques. Nonetheless, long-term studies are lacking in which the clinically relevant outcome (fracture prevention) have been studied, especially with the intervention of calcium and vitamin D. Generally, the primary outcome of these studies is a change in BMD or other markers of bone turnover over a short period of time (1-2 years). In order to estimate the impact of an intervention on fracture prevention, when faced with a limited number of randomized controlled trials (RCTs) of short duration, one must conduct a meta-analysis of the existing studies. The meta-analysis is conducted to establish an argument on the impact that these changes in surrogate markers (bone mineral density, urinary markers of resorption, etc), will have on fracture prevention at the site of interest. In order to establish the impact of calcium and vitamin D on fracture risk at the hip (femoral neck), a meta-analysis was conducted to determine if a significant change in BMD existed at this site. Significant changes in BMD due to an intervention have recently been used to estimate, based on the magnitude of this change, the reduction of risk of fracture at the hip (Marshall et al, 1996; deLaet et al, 1997).
6.2 Meta-Analysis Of The Effect Of Calcium With Vitamin D Supplementation On Bone Loss In Postmenopausal Women.

6.2.1 Introduction

Consensus conferences have been held in a number of countries to establish practice guidelines for the management of osteoporosis. Examples being those established by the American Association of Clinical Endocrinologists (AACE, 1996), by the European Foundation for Osteoporosis (Kanis et al., 1997), and by the Scientific Advisory Board of the Osteoporosis Society of Canada (OSC, 1996). Generally, the clinical guidelines for a woman at risk suggest a step-wise approach of diet, exercise, calcium/vitamin D supplementation, and HRT.

Despite these guidelines, the effectiveness of these recommendations, particularly those relating to calcium and/or vitamin D supplementation, have not been well addressed and their overall efficacy not well documented. Most importantly, only limited data are available from RCTs, which evaluate the impact of calcium alone, or calcium/vitamin D (CaVD) versus placebo on hip fracture risk reduction per se. Rather most published studies evaluate changes in BMD (not fracture risk reduction) and are of variable clinical research design quality. Furthermore, attempts to collectively evaluate the outcomes of these trials, using meta-analysis, to address efficacy have not been conducted. The focus of our study was to determine the effectiveness of CaVD, using a meta-analysis, to evaluate the impact of CaVD on BMD loss. These data were then used to estimate the potential fracture reduction at the hip.

A meta-analysis to address the efficacy of calcium versus placebo in preventing postmenopausal bone loss at the hip (femoral neck) (Shea et al., 1998) was already in progress at the Musculoskeletal subgroup of the Cochrane Collaborative in Ottawa when the meta-analysis on CaVD was being planned for the thesis. Their calcium analysis was well on its way and the summary data were to be shared imminently. The interest for the
thesis was to extend the original analysis by the Ottawa group on calcium by looking at the combined effects of calcium plus vitamin D. Thus, the intention was to establish the effectiveness of the combined treatment, CaVD, as well as to determine the incremental benefit of supplementing with vitamin D along with calcium. Working in collaboration with the Cochrane Collaborative Musculoskeletal group, a meta-analysis was conducted (Chalmers et al, 1995) to address the efficacy of CaVD versus calcium in preventing postmenopausal bone loss at the hip. The analysis was conducted versus calcium for two reasons: to identify the incremental effect of vitamin D on calcium supplementation, and to increase the number of RCTs evaluating CaVD which fit the Cochrane criteria since these CaVD studies were predominantly versus calcium.

Conduct of the CaVD versus calcium meta-analysis was critical since it would address the fundamental issue of the need to add vitamin D to calcium supplementation in guidelines being developed globally by a number of national osteoporosis societies. These societies have been adding vitamin D to their recommendations over the last two years (OSC, 1996) despite the lack of clear documentation of the benefits of the combined approach. Nevertheless, the addition of vitamin D to their guidelines has been supported by the growing evidence that if vitamin D levels are insufficient then calcium absorption by the gut is suboptimal resulting in a smaller impact on increasing BMD.

A preliminary MEDLINE search of the more recent clinical trials (last ten years) in which CaVD interventions were evaluated for their efficacy in bone loss prevention revealed that the control arm in these trials was usually calcium (not placebo). These trials typically were of one to three years in duration, and since growing evidence supports a positive impact of calcium on bone health, researchers consider a long-term osteoporosis trial in which the control group is on placebo unethical. Consequently, the meta-analysis on the efficacy of calcium and vitamin D in preventing postmenopausal bone loss was compared to calcium alone.
6.2.2 Objectives

The objective for the meta-analysis was to obtain a pooled estimate of the benefits of calcium and vitamin D versus calcium (control) on femoral neck (FN) BMD from published RCTs. Once this analysis was completed, the second objective was to estimate the impact of calcium and vitamin D versus no intervention (placebo) on bone loss using the recently published Cochrane meta-analysis on calcium versus placebo (Shea et al. 1998), and to then estimate the impact in risk reduction of hip fracture based on these BMD changes.

6.2.3 Methods

In order to address the first objective, a meta-analysis was conducted. A meta analysis is defined as a systematic review of the literature, in order to reduce random errors, and to yield a summary statistic (Der Simonian and Laird, 1986). These analyses used the Cochrane Collaborative process for systematic review as recently described by Chalmers et al (1995). For the conduct of a Cochrane Collaborative review there are five elements that need to be defined in this process. These are:

a) definition of eligibility criteria for the studies used in the analysis

For the analysis RCTs were sought, in which changes in BMD were reported for postmenopausal women. The intervention evaluated was calcium and vitamin D versus calcium, with a duration of treatment of one or more years.

b) identification of the outcome measures

The primary outcome evaluated was the % BMD change from baseline, at the FN, at one year of treatment. Studies in which any calcium salt and level of supplementation were used to evaluate the primary outcome, since there were only a limited number of published trials upon which to base the analysis. Similarly, for the same reason, all of the metabolites and analogues of cholecalciferol were pooled.
c) development of the literature search strategy
The search strategy was prepared using the structured Cochrane Collaborative approach for identifying RCTs as described by Dickersin et al (1994) and modified for the Cochrane Musculoskeletal Group (CMSG). Osteoporosis, calcium, vitamin D, bone mineral density, postmenopausal, fractures, were used as text words. There were no limits on language in the search strategy. The search strategy was applied to the MEDLINE database covering citations from 1 January, 1966, to 28 February, 1997. In some cases the principal authors were contacted for clarification, or additional information.

d) performance of a quality assessment
A quality assessment, as defined by Jadad et al (1994), was also performed on the eligible studies, with the following questions being asked:

1. Was the randomization blinded?
2. Was placebo treatment assigned as part of the randomization?
3. What was the comparability of the two groups pre-treatment?
4. Were the assessors of the outcome blinded?
5. Was there an intention-to-treat-analysis conducted and reported in the paper?

e) the use of appropriate statistical methods
The Cochrane Collaborative process uses the weighted mean difference (WMD), as the approach in studies having outcomes with continuous variables, to evaluate differences between the treated group versus the control group across a number of RCTs (Deeks J, 1995). Tests for significance are also employed by calculation of 95% confidence intervals about the WMD. Lastly a test for heterogeneity between trials is also conducted using either a fixed-effects or random-effects model. Both of these models were tested in this meta-analysis. These statistical tests are described in more detail in the section which follows.
6.2.3.1 **Mean Difference Observed In An RCT**

In the analysis of an RCT with an outcome variable that is continuous, the effect of treatment versus control is calculated as the mean difference (MD). For each trial the mean difference is calculated as:

\[
\text{MD} = \bar{x}_t - \bar{x}_0
\]

SEMD = standard error of \(\bar{x}_t - \bar{x}_0\) using the formula:

\[
\sqrt{\frac{SD_t^2}{n_t} + \frac{SD_0^2}{n_0}}
\]

where

- \(n_t\) = the number of patients treated
- \(\bar{x}_t\) = mean value of outcome measure in active group (in thesis: BMD change from baseline)
- \(SD_t\) = standard deviation of \(\bar{x}_t\)
- \(n_0\) = the number of patients in control group
- \(\bar{x}_0\) = mean value of outcome measure in control group (in this thesis, BMD change from baseline)
- \(SD_0\) = standard deviation of \(\bar{x}_0\)

6.2.3.2 **The 95% Confidence Interval Of MD**

The 95% confidence interval of MD:

\[
= \text{MD} \pm 1.96 \text{SE}_{\text{MD}}
\]

These confidence intervals indicate that in 95 out of 100 replications of the trial it would be expected that the mean difference would fall within this interval. If the 95% confidence interval values do not cross zero, then the treatment effect is significant at the 0.05 level. Alternatively, if the confidence interval includes zero, then the mean difference does not meet the nominal p-value of 0.05.
6.2.3.3 The Weighted Mean Difference

The weighted mean difference (WMD) is a measure of how well the treatment prevented the loss of bone in comparison to the control or placebo group in a number of trials. The WMD is calculated by evaluating the MDs of a number of RCTs and is defined as:

\[ WMD = \frac{\sum_{i=1}^{n} w_i (MD)}{\sum_{i=1}^{n} w_i} \]  

(4)

where for each trial:

\[ w_i = \frac{1}{SE_{MD}^2} \]  

(5)

6.2.3.4 The 95% Confidence Interval About A WMD

The standard error about the WMD is defined as:

\[ SE_{wMD} = \frac{1}{\sum_{i=1}^{n} w_i} \]  

(6)

hence the 95% confidence interval about the WMD is:

\[ WMD \pm 1.96 SE_{wMD} \]  

(7)

In the calcium/vitamin D meta-analysis the WMD was calculated to evaluate the mean difference of BMD, as a percent change from baseline, for calcium + vitamin D vs calcium.

6.2.3.5 Tests For Heterogeneity

Tests of heterogeneity were also conducted since the RCTs used in the meta-analyses can have small sample size, may come from different populations (ie early postmenopausal, or elderly in nursing homes), use different treatment protocols (different
analogues of vitamin D), or length of study period. In order to estimate the heterogeneity of trials included in the meta-analysis, tests were conducted to evaluate the degree of heterogeneity between studies. Even when such tests are conducted they do not provide high reassurance that heterogeneity is not present, even when a hypothesis for heterogeneity is rejected (Greenland, 1987).

The statistical analysis was performed using the MetaView software developed by the Cochrane collaboration (Cochrane Collaboration 1996, version 3.0). This software tests for heterogeneity by using random-effects and fixed-effects models.

Having defined the 5 elements of the meta-analysis (described in section 6.2.3), and developing the meta-analysis protocol, the analysis was conducted.

### 6.2.4 Results Of Meta-Analysis

There were 6 studies that met the selection criteria in the calcium+vitamin D analysis (Table 6.1), of which 2 studies focused on the FN (Papadimitropoulos et al, 1997b). The other four studies met the criteria for inclusion in the evaluation of calcium/vitamin D however they evaluated the impact on BMD changes at the spine and forearm. The overall WMD on the FN was calculated as 1.41, with 95% confidence intervals of 0.32, and 2.51 (Table 6.2). These data suggested that calcium/vitamin D had a significant impact on BMD.

### 6.2.5 Discussion On Meta-Analysis Results

The overall WMD for calcium/vitamin D of 1.41, with confidence intervals of 0.32, and 2.51 demonstrated the significant impact of this management strategy in modifying BMD at the femoral neck. This statistically significant impact on BMD change at the femoral neck however needs to be put into the perspective of the CaVD
Table 6.1: Two eligible studies for the calcium/vitamin D meta-analysis evaluating differences in BMD at the femoral neck

<table>
<thead>
<tr>
<th>Study</th>
<th>Calcium intake</th>
<th>Vitamin D Intake</th>
<th># of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ooms et al (1995)</td>
<td>800-1000mg via diet</td>
<td>400IU Vitamin 25D₃</td>
<td>177 treatment/171 control</td>
</tr>
<tr>
<td>Orimo et al (1994)</td>
<td>300mg via supplement</td>
<td>1mcg 1α(OH)D₃</td>
<td>34 treatment/40 control</td>
</tr>
</tbody>
</table>
Table 6.2: Weighted mean difference (WMD) at the femoral neck for calcium + vitamin D versus calcium intervention indicating an overall statistically significant impact at this site when the data from the two studies were pooled.

<table>
<thead>
<tr>
<th>Study</th>
<th>WMD</th>
<th>CI(95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ooms (1995)</td>
<td>1.40</td>
<td>[0.30, 2.50]</td>
</tr>
<tr>
<td>Orimo (1994)</td>
<td>2.46</td>
<td>[-7.62, 12.54]</td>
</tr>
<tr>
<td>Overall</td>
<td>1.41</td>
<td>[0.32, 2.51]</td>
</tr>
</tbody>
</table>
meta-analysis which evaluated the incremental impact of vitamin D over calcium supplementation. The full benefit of this treatment strategy versus placebo can only be ascertained by taking into consideration the results of the meta-analysis of calcium versus placebo conducted by Shea et al (1998).

In Figure 6.1, the overall WMDs at the FN for interventions of calcium vs placebo, and CaVD vs calcium, are represented graphically. The WMD is plotted on the x axis, where a positive WMD favours the active treatment. The WMD estimated via the CaVD meta-analysis is the incremental benefit associated with the addition of vitamin D to the calcium alone intervention. The non-significant results of the calcium alone meta-analysis suggest that this regimen is not effective at increasing BMD at the hip. Consequently the observed WMD from the CaVD versus calcium meta-analysis can be used directly to estimate the impact of CaVD on fracture risk, without requiring the addition of the calcium benefits to this combined intervention.

At the last annual Cochrane Colloquium conference (1997), the results of another meta analysis using the Cochrane Collaborative approach, conducted by the Cochrane Musculoskeletal Group in Ottawa, was presented (Tugwell et al, 1997). The statistically significant overall WMD for HRT versus placebo at one year was presented as 2.86, with a CI of 1.91, and 3.81. This analysis indicates that combination therapy of calcium+vitamin D vs calcium has about half the impact on BMD at the femoral neck as does combination estrogen/progestin therapy at one year.

The overall WMD at the spine and forearm for the calcium and CaVD interventions was also evaluated, and the data are summarized in Table 6.3. The analyses indicate that a small statistically significant impact of calcium and vitamin D vs calcium, on BMD was observed also at the spine.
Figure 6.1 The comparative weighted mean difference (WMD) and 95% confidence intervals at the femoral neck of three Cochrane Collaborative meta-analyses conducted on three interventions: calcium versus placebo, calcium and vitamin (CaVD) versus calcium, and hormone replacement therapy (HRT) versus placebo. The analyses indicate a significant WMD after one year of primary preventative therapy in the CaVD versus calcium and HRT versus placebo analyses.
Table 6.3: The weighted mean difference (WMD) at three skeletal sites based on two interventions: calcium (Ca) versus placebo and calcium/vitaminD (CaVD) versus Ca. The meta-analyses indicate that a statistically significant benefit is observed in the CaVD versus Ca intervention at the hip and spine.

<table>
<thead>
<tr>
<th>Site</th>
<th>Calcium vs Placebo</th>
<th>Calcium + Vitamin D vs Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of studies</td>
<td>Overall WMD (95%CI)</td>
</tr>
<tr>
<td>Femoral Neck</td>
<td>5</td>
<td>1.22 (-0.16, 2.61)</td>
</tr>
<tr>
<td>Spine</td>
<td>7</td>
<td>0.22 (-0.65, 1.10)</td>
</tr>
<tr>
<td>Forearm</td>
<td>3</td>
<td>0.42 (-0.80, 1.64)</td>
</tr>
</tbody>
</table>
6.2.6 Impact Of BMD On Fracture Risk Reduction At The Hip

The data from this meta-analysis (WMD 1.41 CI: 0.32, 2.51) were used to estimate the reduction in hip fracture risk using the approach described by Black in the Office of Technology Assessment's (OTA's) HRT cost-effectiveness analysis (OTA, 1995b). In their analysis, the data from the Study of Osteoporotic Fractures (SOF) was used to establish a relative risk of hip fracture per standard deviation below the peak adult mean BMD in women (Black, 1992). Their analysis found a relative risk of 1.65 per SD below the mean BMD in women. Analysis of the SOF dataset suggest that the relationship of bone mass to hip fracture risk follows a linear pattern, since a statistical test for the goodness of fit of the data to a logistic model did not reject the null hypothesis (that the relationship is logistic) (Cummings et al, 1990a). The logistic relationship between BMD and hip fracture risk used by Black (1992) is given as:

\[
P = \frac{1}{1 + e^{(\alpha + \beta x)}}
\]  

(8)

where:  
\(P\) = probability of hip fracture at a given age  
\(\alpha\) = is a constant term that varies with age  
\(\beta\) = is a term that varies with BMD, but not with age  
\(x\) = is the individual’s BMD at the age in question

Calculation of the standardized relative risk (RR) of fracture based on bone mass (BM) is defined as the ratio of:  
\[
\frac{\text{person whose BM is at 1 SD below mean}}{\text{person whose BM is at the mean}}
\]  

(9)

The prediction model makes a critical assumption which has been used in virtually all published models: that the relative risk of fracture is constant across all age groups (i.e. if the RR of fracture of a 75 year-old woman whose BMD is 1 SD below the mean BMD of a 70 year-old woman is 3.0, then the RR of a 50 year-old woman with a
BMD of 1 SD below mean BMD of a 50 year-old woman is also 3.0.) This assumption implies that there is no interaction between bone mass and age in predicting hip fractures (Black et al, 1992; Gardsell et al, 1989).

The logistic regression (equation 8) has been modified to incorporate the WMD data of the meta-analysis by the Cochrane Musculoskeletal Group in Ottawa as:

$$% \text{RiskReduction} = \frac{\ln A \times \% \text{WMD} \times \overline{BMD}}{SD}$$ (10)

where:

- $A$ = relative risk per SD below the mean BMD
- $\% \text{WMD}$ = the % weighted mean difference observed
- $\overline{BMD}$ = age-specific average BMD for women
- $SD$ = age-specific standard deviation of bone mass

The results of the meta-analysis that was conducted on calcium/vitamin $D$ using the Cochrane approach indicates that supplementation with calcium/vitamin $D$ resulted in a WMD of 1.41 (0.319, 2.51). The data from the meta-analysis along with the age-specific data from the OTA report (1995b) were inserted in the equation 10, assuming that therapy would be initiated at age 50 or 65 in postmenopausal women ($A=1.65$, $\overline{BMD}=0.650$, and $SD=0.102$). The hip fracture risk reduction calculated corresponding to the WMD data from the meta-analysis of CaVD intervention was 4.5% after one year of treatment (1.0% RR, 7.7% RR; lower and upper 95% confidence intervals). The WMD data on the femoral neck at one year was 2.86 (1.91, 3.81) (Figure 6.1, Wells et al, 1997). These data were used in equation 10 and the % RR based on one year treatment data was calculated as 9.1% (6.1%, 12.1).

Long-term studies (5 years or more) evaluating changes in BMD of CaVD intervention meeting the Cochrane Collaboration requirements were lacking.
Consequently the impact of long-term CaVD supplementation on hip fracture risk had to be estimated using the one year data from the Cochrane HRT meta-analysis, the associated fracture risk reduction at one year using equation 10, and hip fracture reductions observed from the Weiss et al (1980) study in long-term HRT users (50% (31%, 70%): section 2.7.3.1.1). The ratio of the base case estimated risk reduction of long-term HRT use from the Weiss study (50%) to the Cochrane one year HRT base case analysis (9.1%), was calculated as 5.5. Using this adjustment factor on the results of the Cochrane meta analysis one year of HRT treatment then a base case reduction of 50% is calculated with the lower and upper risk reductions of hip fracture of 33% and 67% (based on the confidence intervals of the analysis). These confidence interval-associated risk reductions correspond closely with the lower and upper ranges of the Weiss et al (1980) study of 31% and 70% respectively.

The projected impact of long-term CaVD supplementation was estimated using the factor described above (5.5), to calculate base case, pessimistic and optimistic risk reductions for CaVD based on the one-year data from our meta-analysis. The base case RR of hip fracture for CaVD supplementation based on this approach was estimated as 24.7%, with the lower and upper confidence intervals corresponding to 6% and 42% risk reductions respectively. Conservative estimates in reduction of hip fracture with long-term CaVD therapy were set to: 5%, 20%, and 35% reduction of hip fracture for the pessimistic, base case, and optimistic scenarios, and were used in the model.

The literature was reviewed that dealt with fractures in individuals on CaVD, to assess whether the calculated 20% reduction in hip fracture risk with CaVD was a likely estimate. A number of studies evaluated fracture reduction, however these were not used in the CaVD meta-analysis since they did not include measures of BMD, or if included were only conducted on a small sub-set of individuals. A large study reported by Chapuy et al (1992), in which over 3,200 women were randomized to supplementation with 1,200 mg calcium and 800 IU of vitamin D or a double placebo, demonstrated a 43% reduction
in hip fractures over an 18 month period. A 29\% risk reduction was observed in this cohort after three years of therapy (Chapuy et al, 1994). The study by Chapuy et al was in institutionalized women with a mean age of 84 years. It was anticipated that the Chapuy study would show greater benefits since their population was nursing home residents. Intuitively, it is speculated that this population would be more frail than the general population, at greater risk for fracture and more likely to benefit from intervention. Indeed, analysis of the hip fracture incidence data in Canadian women by age and residence type upon admission to the acute care setting, demonstrated a statistically significant and higher hip fracture rate in women who were residing in a long-term care institution than those who were community-dwelling (Figure 5.1). The higher rate of fracture in older long-term care residing women would suggest that studies in this group may demonstrate a greater hip fracture preventative effect than in a younger community-dwelling population. Hence a form of selection bias, while intentional, was present in the Chapuy study (1992) and these results would likely overestimate the anticipated benefits to the general population.

Recently, Dawson-Hughes et al (1997), found that three year supplementation with calcium 500mg and vitamin D 700IU resulted in a 60\% reduction in non-vertebral fractures. The study by Dawson-Hughes et al was in 176 men and 213 women over the age of 65 years who were community-dwelling. If these data are correct, then they suggest that CaVD would compare favourably with HRT, and indeed may be more effective. This goes against the prevailing dogma in the field since these women were only using CaVD for the prevention of osteoporotic fractures in this study.

On the surface, the Dawson-Hughes (1997) data suggest that the CaVD analysis may have underestimated the fracture risk reduction, however upon closer evaluation the majority of the non-vertebral fractures were in a number of sites in the arm, and ankle or foot. Only one fracture was observed in the hip and this was in the placebo group. Thus
there were insufficient fractures occurring at the hip in order to specifically determine risk reduction at this site.

The data from this meta analysis will be used in the economic model, and the statistically significant changes in BMD at the femoral neck during use of calcium and vitamin D, at one year of treatment, will be used as the basis to support a base case reduction risk of hip fracture by 20%. This is a conservative, yet defensible reduction in hip fracture risk. Nevertheless, it is clear from the previous discussion that the estimated risk reduction of hip fractures with CaVD intervention based on the meta-analysis may either underestimate or overestimate this event. Consequently, for the economic evaluation, both a pessimistic (5%) and an optimistic (35%) risk reduction was selected by the author based on reviews of the literature, estimated using the approach described above, and impressions (although not a rigorous approach) on what constitutes anticipated extremes of effectiveness of these interventions as seen in the literature. This approach deviates from that used for other estimates of sensitivity in the conduct of the economic evaluation. That is, upper and lower confidence limits were used when sufficient data were available to provide reasonable estimates of these ranges. If this approach were taken in the case of CaVD, then the upper and lower confidence intervals (6%, 42%) based on an extremely limited number of studies, may not truly represent the range encompassing likely risk reductions.

The other important assumption in determining risk reduction for the combined therapy was that calcium supplementation alone has no effect. As stated, this assumption was based on the outcome of the Cochrane Musculoskeletal Group’s meta-analysis. Nevertheless, Cumming and Nevitt (1997), conducted a meta-analysis of calcium using studies of various study designs (randomized and non-randomized). They concluded that supplementation with 1,000mg of calcium daily for a period of 10 years had a 22% reduction in fracture risk at the femur. Once again, these data could indicate that the approach taken in this thesis underestimates the efficacy of the combined treatment.
6.2.7 **Conclusions**

The meta analysis of RCTs have demonstrated an incremental benefit of CaVD strategy in the order of a potential 20% reduction in hip fracture risk under base case assumptions. Since the meta-analysis on calcium alone versus placebo (Shea et al, 1998) failed to observe a statistically significant benefit of calcium alone, these data strongly support the recommendations by a number of osteoporosis societies for a combined CaVD supplementation regimen.
7. COSTING

7.1 Costing and the Hip Fracture Model

Costing methodology for events in health care has been evolving over the last two decades. The allocation of costs and the biases that can influence costing have recently been addressed by Jacobs et al (1996). The perspective of the analysis has an obvious impact on the approach used in the collection of costs. In our model we evaluated costs from the Health System perspective, hence costs arising from the use of publicly funded programs, and out of pocket costs relating to acquisition of the intervention therapies (pharmacist dispensing fees for women aged <65 years, and the cost of calcium/vitamin D) were considered (defined in section 4.1.1 of this thesis). All costs entered into the economic model are in 1996 Canadian dollars.

It is acknowledged that costs for each of these resources and support services vary across Canada and by type of institution (teaching versus non-teaching, and urban versus rural). In order to confirm the generalizability of the results, extensive sensitivity analyses (in chapter 8 of the thesis) were conducted on all cost variables.

The cost variables associated with each of the events in the hip fracture model are listed in Table 7.1, with a brief description on the source of these data. In the model discounting was also used, with a base case rate of 3%. 
<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>Symbol</th>
<th>SOURCE OF DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost of home care</td>
<td>cHC</td>
<td>ICES review</td>
</tr>
<tr>
<td>Cost of Hospital Stay based on 17 day LOS for hip fracture</td>
<td>cHF</td>
<td>Acute care hospital costing database</td>
</tr>
<tr>
<td>Cost of per diem hotel costs</td>
<td>cHOTEL</td>
<td>&quot;</td>
</tr>
<tr>
<td>Cost of treating an MI (ICD-9: 410)</td>
<td>cMI</td>
<td>&quot;</td>
</tr>
<tr>
<td>Cost of treating other ischemic heart disease events (ICD-9:411-414)</td>
<td>cOTHG</td>
<td>&quot;</td>
</tr>
<tr>
<td>Cost of treating Breast cancer</td>
<td>cBRCA</td>
<td>Analysis conducted based on multiple databases</td>
</tr>
<tr>
<td>Cost of MD visit assessment</td>
<td>cMD</td>
<td>Ministry of Health (Ontario) Fee Schedule</td>
</tr>
<tr>
<td>Cost of MD reassessment</td>
<td>cMDRE</td>
<td>&quot;</td>
</tr>
<tr>
<td>Cost of Orthopedic assessment</td>
<td>cMDOP</td>
<td>&quot;</td>
</tr>
<tr>
<td>Cost of Orthopedic reassessment</td>
<td>cMDOPRE</td>
<td>&quot;</td>
</tr>
<tr>
<td>Cost of Geriatric assessment</td>
<td>cMDGER</td>
<td>&quot;</td>
</tr>
<tr>
<td>Cost of Geriatric reassessment</td>
<td>cMDGERRE</td>
<td>&quot;</td>
</tr>
<tr>
<td>Cost of surgery of hip fracture</td>
<td>cSURGER</td>
<td>&quot;</td>
</tr>
<tr>
<td>Daily cost of acute care</td>
<td>cHOTEL</td>
<td>OCCP teaching hospital</td>
</tr>
<tr>
<td>Daily cost of LTC</td>
<td>cLTC</td>
<td>Ministry of Health (Ontario) - LTC division</td>
</tr>
<tr>
<td>Daily cost of rehab care</td>
<td>cRC</td>
<td>Riverdale Hospital</td>
</tr>
<tr>
<td>Cost of daily calcium</td>
<td>cCAL</td>
<td>Pharmacy Wholesaler/Retail</td>
</tr>
<tr>
<td>Cost of estrogen tablet</td>
<td>cESTROGEN</td>
<td>Pharmacy Wholesaler/Retail</td>
</tr>
<tr>
<td>Cost of progestin tablet</td>
<td>cPROGEST</td>
<td>Pharmacy Wholesaler/Retail</td>
</tr>
<tr>
<td>Cost of vitamin D tablet</td>
<td>cVITD</td>
<td>Pharmacy Wholesaler/Retail</td>
</tr>
<tr>
<td>Cost of dispensing fees</td>
<td>cDISPFEE</td>
<td>Community pharmacy publication</td>
</tr>
</tbody>
</table>
7.2 Acute Care Facility Costs

Costs for procedures conducted in an acute care facility were obtained from an Ontario teaching hospital’s costing database (Sunnybrook Health Science Centre, Toronto, Ontario). This teaching hospital is a participant in the Ontario Case Costing Project (OCCP) and therefore uses the fully-allocated costing methodology where costs from overhead and support departments are allocated to patient service and care areas. This approach is used in estimating the total cost for each service hospital stay (encounter). Each encounter is linked to a primary diagnosis and the components of that stay are clearly identified at the level of unit costs and quantities of resource use.

Event cost data related to an acute care stay were collected from the hospital database using the Most Responsible Diagnosis (MRD) code (same as the ICD-9 code). Summary costs were made available in a disaggregated fashion for the fiscal year 1995/1996. Each of the events costed were also assigned a Case Mix Group (CMG) designation. CMGs are used to categorize hospital patients into groups (Pink and Bolley, 1994). All hospital patients in Canada are assigned an ICD-9 or ICD-9-CM code after discharge. The use of this coding however is awkward to use in costing a hospital stay due to the large number (there are more than 10,000) of these codes. CMGs were employed to summarize hospitalizations using a more reasonable number of patient groups that could be used for managerial purposes, although they would not be as clinically accurate. The development of CMGs by the Health Medical Research Institute (HMRI; now the Canadian Institute for Health Information (CIHI)), is analogous to DRGs used in the United States called the diagnosis-related groups (DRGs). There were four criteria that were used to categorize patients into CMGs, these were: the patient groups
had to make good clinical sense; they had to be based on routinely collected data; there had to be a manageable number of groups; and they had to be statistically homogeneous with respect to length of stay in hospital (Pink et al., 1994a). Currently there are more than 567 CMGs in 25 major clinical categories in use. The other ratio used in evaluation of hospital efficiency is the Resource Intensity Weights (RIWs). RIWs show the relative use of hospital resources for a typical case (successful course of treatment in an acute care hospital and discharge when the patient no longer requires the hospital's services) and atypical cases (death, transfer, sign-out and substantially longer than average stay) in each CMG. Consequently CMGs and RIWs (if they are Canadian and are not borrowed from U.S. studies) are valuable in defining the relation between the medical and financial dimensions of hospital cases, and are used in the planning, management, and financing decisions by hospital boards and government funding agencies (Pink et al., 1994b).

In 1992 the Ontario Case Cost Project (OCCP) was launched with the objective of developing: 1) a more Canadian specific case weight system than the New York system (that was currently in use), 2) more valid standards for comparisons across hospitals and 3) better information to manage hospitals (Ontario Case Cost Project, 1993). The project initially had thirteen participating hospitals, however the number of participating hospitals has grown since that time.

The costs required for the model were obtained as described above and the methodology employed to obtain these costs as well as their value are listed in the sections which follow.
7.2.1 Cost of Hip Fracture (cHF) Repair and Per Diem Hotel Costs (cHOTEL) at an Acute Care Hospital

The data collected from the Sunnybrook costing database for all hip fracture patients (MRD 820.0 to 820.9) admitted in fiscal year 1995/1996 to the hospital were obtained. There were 151 women, age ≥50 years of age, that were treated during this time period, with a mean length of stay of 16.69 days, (SD 12.05). The mean cost for all women ≥ 50 years of age was $10,745 (Table 7.2) for the mean stay of almost 17 days. Estimates of hip fracture repair costs have been reported in the literature for Canadian patients at $10,000 (Goeree et al, 1996) and are in reasonable agreement with the values obtained from the OCCP data. In the analysis of the CIHI database (in the previous chapter), we found that in fiscal 1993/1994 the mean length of stay in acute care hospitals was 21 days. It was decided to assume, for the base case analysis, that the LOS in an acute care facility would be 21 days for Canadian hip fracture patients. The LOS at Sunnybrook Health Science Centre was almost 17 days hence in order to compensate for this difference an additional four days of the per diem cost in the same acute care facility was included. The daily hotel cost was calculated by the decision support analyst of the acute care facility (Tom Marincic) based on nursing and nutritional support assuming that no additional testing was performed. The total per diem cost was calculated as $423.29 ($241.63 direct costs, $181.66 indirect costs). Thus the total costs for the acute care stay used in our analysis was $12,438.
Table 7.2  Acute care hospital costs (Sunnybrook Health Science Centre - Toronto) of all hip fracture repair in women ≥ 50 years of age admitted during fiscal 1995/1996.

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of women</th>
<th>Mean cost ($, 1995)</th>
<th>Total cost ($, 1996)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>2</td>
<td>5,676.23</td>
<td>11,352.46</td>
</tr>
<tr>
<td>60-64</td>
<td>2</td>
<td>5,450.99</td>
<td>10,901.98</td>
</tr>
<tr>
<td>65-69</td>
<td>10</td>
<td>8,751.64</td>
<td>87,516.40</td>
</tr>
<tr>
<td>70-74</td>
<td>15</td>
<td>8,779.10</td>
<td>131,686.50</td>
</tr>
<tr>
<td>75-79</td>
<td>23</td>
<td>12,588.01</td>
<td>289,524.20</td>
</tr>
<tr>
<td>80-84</td>
<td>44</td>
<td>10,223.21</td>
<td>449,821.20</td>
</tr>
<tr>
<td>85-89</td>
<td>29</td>
<td>12,078.79</td>
<td>350,284.90</td>
</tr>
<tr>
<td>≥90</td>
<td>26</td>
<td>11,207.94</td>
<td>291,406.44</td>
</tr>
<tr>
<td>Totals</td>
<td>151</td>
<td></td>
<td>1,622,494.00</td>
</tr>
</tbody>
</table>

Mean cost/case  10,745
7.2.2 Cost of Home Care (cHC)

Upon discharge from an acute care facility, following the repair for the hip fracture, the destination of the patient can be variable. Ultimately the patient’s discharge back to the community at a level of functioning which does not require any support from the health care system is the preferred scenario. Typically, a proportion of the community residing patients prior to the fracture event will be discharged back to the community with home care support. The home care function provides a number of services including physiotherapy, nursing, homemaking, meals on wheels and other associated supports. Recently a review of patients discharged from musculoskeletal type of surgical interventions in selected parts of the province of Ontario found that the average total cost per patient for this service was $941.00 (Coyte et al, 1997). The average length of providing these services was 42 days (Coyte et al, 1997).

Using the average cost of home care has its limitations. The summary data provided to the author did not identify and disaggregate the unit costs and quantity of services provided to these patients. The cost of $941.00 used in our economic model for home care (cHC) is based on a mean of unweighted resource use in a variety of Ontario communities. The level of auxiliary support in these communities may vary greatly which may skew the mean cost of home care. Similarly, the home care concept is not universally available in Canada with the provinces of Ontario and Nova Scotia currently being the only two that are using this support system. The other provinces care for patients who would qualify to go back to the community, by placing them in rehabilitation/long term care facilities until they are ready to be introduced back to the community with minimal support systems. The evaluation of the management
approaches (home care versus rehabilitation/nursing homes) for those patients who are
good candidates for returning to the community continues.

7.2.3 Cost Of Treating Myocardial Infarcts (cMI) In Women ≥50 Years Of Age

Myocardial infarcts are serious medical events impacting on the mortality of patients. The management of this event in the acute care setting was evaluated using the
costing database (MRD 410), for 83 women (≥50 years of age) who were treated in the
fiscal year 1995/1996 at Sunnybrook. It was found that patients were in the hospital for a
mean length of stay of 8.89 days (SD 8.24). Resource use during this stay, especially in
the first four days, was intense. The mean cost for this event was $7,290.93 (Table 7.3).
Treatment of myocardial infarcts (MI) in Canada have been estimated in a number of
et al (1997) estimated the cost of MI at the acute care level in Canada in 1995 dollars at
$7,505. A base case cost of $7,300 for the treatment of MIs was used in the model.

7.2.4 Cost Of Treating Other Ischemic Heart Disease Events (cOTHR) In Women
≥50 Years Of Age

Costing of other ischemic heart disease events beyond MIs (ICD-9 411-414
events), were difficult to obtain from the hospital dataset, consequently the cost for
treating these events was estimated. The estimate was based on the reported average
Table 7.3. Acute care hospital costs (Sunnybrook Health Science Centre) for the management of myocardial infarcts (MIs) in women ≥ 50 years of age during fiscal 1995/1996, and estimated cost of treating non-MIs at the same institution.

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of women</th>
<th>Mean MI cost with MIs ($, 1996)</th>
<th>Total MI cost ($, 1996)</th>
<th>Age</th>
<th>Other CHD</th>
<th>Mean cost/day ($) (1996)</th>
<th>Total cost/episode ($) (1996)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-54</td>
<td>1</td>
<td>3,840.73</td>
<td>3,840.73</td>
<td>50-64</td>
<td>6.5</td>
<td>423.29</td>
<td>2,751.39</td>
</tr>
<tr>
<td>55-59</td>
<td>4</td>
<td>9,244.81</td>
<td>36,979.24</td>
<td>65-74</td>
<td>8.1</td>
<td>423.29</td>
<td>3,428.65</td>
</tr>
<tr>
<td>60-64</td>
<td>4</td>
<td>20,324.14</td>
<td>81,296.56</td>
<td>≥ 75</td>
<td>15.8</td>
<td>423.29</td>
<td>6,687.98</td>
</tr>
<tr>
<td>65-69</td>
<td>5</td>
<td>11,808.51</td>
<td>59,042.55</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-74</td>
<td>12</td>
<td>4,685.77</td>
<td>56,229.24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75-79</td>
<td>18</td>
<td>6,647.71</td>
<td>119,658.80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80-84</td>
<td>17</td>
<td>6,793.68</td>
<td>115,492.60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>85-89</td>
<td>13</td>
<td>6,212.78</td>
<td>80,766.14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥90</td>
<td>9</td>
<td>5,760.14</td>
<td>51,841.26</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>83</td>
<td></td>
<td>605,147.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean cost/case 7,290.93
LOS data for these events was then used to calculate the cost of the hospital stay for women by multiplying the per diem hospital cost for the institution by the length of stay of different age groups since the average LOS varies significantly with age (Table 7.3). The costs that have been calculated are underestimates since the cost of medications, medical procedures and tests have not been included. We will evaluate the impact of our assumed cost for the treatment of these events via sensitivity analysis in the economic model. Coyle (1997) has estimated the mean cost for the treatment of these types of coronary events to be $4,087 for women \( \geq 50 \) years of age, which lies between our estimate for women \(< 74\) years and \(>75\) years of age.

### 7.2.5 Cost of Treating Breast Cancer (cBREAST) in Women \(>50\) Years of Age

An in-depth cost of illness study on breast cancer was conducted in Ottawa by Earle et al (1997), in which the author of this thesis was a co-author. The data pertaining to women greater than 50 years of age by stage of breast cancer diagnosis was conducted. A summary of the first year costs for treating Canadian women using breast cancer staging is presented in Table 7.4. Across all stages, initial first-year mean treatment costs were estimated at $9,560. The comprehensive cost of illness report is referenced (Earle et al, 1997).

### 7.3 Cost of Physician Services

Reimbursement for physician services is a provincial responsibility. In the model a number of assumptions were made regarding the role of physicians in the management of the Canadian postmenopausal woman. The assumptions on the frequency and nature
Table 7.4  Estimated first year treatment costs for breast cancer events in women ≥ 50 years of age based on Statistics Canada data, and the SEER (Surveillance, Epidemiology, and End Result) database of the United States (Earle et al, 1997).

<table>
<thead>
<tr>
<th>Stage of breast cancer</th>
<th>Initial treatment ($, 1996)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>9,419</td>
</tr>
<tr>
<td>II</td>
<td>10,072</td>
</tr>
<tr>
<td>III</td>
<td>10,044</td>
</tr>
<tr>
<td>IV</td>
<td>8,707</td>
</tr>
<tr>
<td>Mean treatment cost</td>
<td>9,560</td>
</tr>
</tbody>
</table>
of the visits of "typical" postmenopausal women were derived based on discussions with a geriatrician, an orthopedic surgeon and a family physician. Costs (base case) applied to the model for these visits was obtained from the Schedule of Benefits produced by the Ministry of Health - Ontario (1992), and are presented in Table 7.5. Although the fee schedule and all the associated physician and facility costs are from Ontario, it has been assumed that these rates will not vary between the provinces. The Canadian Medical Association currently does not have a standard fee schedule for Canada. We will test via sensitivity analysis the impact of varying these fees on the model outcome of costs for the interventions in chapter 8 of the thesis.

7.3.1 Costs Of Surgeon And Anesthetist (cSurgery) Related To Hip Fracture Repair

Surgery costs (cSURGERY) were estimated based on the cost of hip fracture repair by the orthopedic surgeon and the anesthetist. Typically orthopedic surgeons have two billing codes for the repair of a hip based on the type of fracture. For the analysis it was assumed that an average between the two rates be used and that a standard anesthetist’s fee be applied to the total of the cSURGERY variable. The result is listed in Table 7.5

7.3.2 Costs Of Long-Term Care Stay (cLTC)

The Long-Term Care division of the Ministry of Health (Ontario) has responsibility for administering and reporting the costs associated with the operation of
Table 7.5 The physician variables used in the osteoporosis model and the fees reimbursed by the Ministry of Health in Ontario

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>LITERATURE SOURCE</th>
<th>THESIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description and fee code</strong></td>
<td><strong>Symbol</strong></td>
<td><strong>Source</strong></td>
</tr>
<tr>
<td>Cost of MD assessment</td>
<td>cMD</td>
<td>Ministry of Health (Ontario 1992) Fee Schedule</td>
</tr>
<tr>
<td>Cost of MD reassessment</td>
<td>cMDRE</td>
<td>&quot;</td>
</tr>
<tr>
<td>Cost of orthopedic assessment</td>
<td>cMDOP</td>
<td>&quot;</td>
</tr>
<tr>
<td>Cost of orthopedic reassessment</td>
<td>cMDOPRE</td>
<td>&quot;</td>
</tr>
<tr>
<td>Cost of geriatric assessment</td>
<td>cMDGER</td>
<td>&quot;</td>
</tr>
<tr>
<td>Cost of geriatric reassessment</td>
<td>cMDGERRE</td>
<td>&quot;</td>
</tr>
<tr>
<td>Cost of surgery of hip fracture; surgeon and anesthetist fees</td>
<td>cSURGERY</td>
<td>&quot;</td>
</tr>
</tbody>
</table>
these facilities in Ontario. The costs for providing this care range from $59.11 to $128.23 per day, based on the level of care provided (Levels A to G). The average provincial per diem cost for care is $77.00 (Thiele, 1996). This value has been used as the long-term care cost in our model since a typical hip fracture patient entering these facility will not require the maximal level of care.

7.3.3 Costs Of Rehabilitation Care (cRC)

Rehabilitation care can be provided either through a stand-alone rehabilitation facility, or via a specialized unit within an acute care hospital. The per diem costs of operating these facilities is variable, however in general a lower level of care is required in comparison to acute care facilities. Papadimitropoulos et al (1997b) estimated the per diem cost for this type of care at $275 (cRC). Recently a survey was conducted in a rehabilitation facility in Hamilton-Wentworth area, in which an average per diem cost was calculated for hip fracture patients entering rehabilitation to be $268.00 (Wiktorowicz et al, 1998). The per diem estimate for rehabilitation care of $275 will be used in the evaluation since this value is a reasonable approximation of the data generated by Wiktorowicz et al (1998).

7.4 Costs Of Treatment

The administration of a daily intervention to postmenopausal women who are at risk of osteoporosis has been limited to the treatment options of: calcium 750 mg/ vitamin D 400 IU daily, or HRT (conjugated estrogen 0.625 mg/medroxyprogesterone 2.5 mg daily) for this evaluation. The calcium/vitamin D intervention does not require a
physician’s prescription, and consequently is not covered by most provincial and private drug plans. HRT on the other hand is covered by almost all Canadian drug plans for women over the age of 65 years, and requires the prescription of a physician. In the model it was assumed that the cost of all interventions would be included in the analysis. The costs associated with treatment are listed in Table 7.6.

7.4.1 Cost of Calcium/Vitamin D

Supplementation of postmenopausal women with combination calcium-vitamin D therapy, is accessible without a prescription. In our model we assumed that 750 mg of calcium via supplements would be an appropriate intervention to ensure that Canadian postmenopausal women have a minimal intake of 1,200 mg daily. Similarly supplementation with 400 IU of vitamin D was assumed in the model.

Calcium via the calcium carbonate salt (Novopharm) are generically available at a retail cost of $3.60 for 100 tablets, containing 250mg calcium per tablet. The 500mg calcium tablets (Novo) retail for $5.06/100 tablets. These costs were obtained from a retail pharmacy in Ontario based on a 40% mark-up on the cost from the wholesaler. The daily cost of one 250mg and one 500mg calcium tablet (cCALCIUM) were estimated to be $0.0866.

Vitamin D₃ (cholecalciferol) 400IU (Swiss) is available at a retail cost of $2.70/90 tablets based on a 40% mark-up from the wholesaler. The daily cost of vitamin D used in the model (cVITD) was $0.03.
Table 7.6  Costs associated with providing the evaluated interventions to Canadian postmenopausal women

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>SYMBOL</th>
<th>SOURCE</th>
<th>THESIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Symbol</td>
<td>Description of approach</td>
<td>Cost ($, 1996)</td>
</tr>
<tr>
<td>Cost of daily calcium</td>
<td>cCAL</td>
<td>Pharmacy Wholesaler/Retail</td>
<td>0.0866</td>
</tr>
<tr>
<td>Cost of daily vitamin D</td>
<td>cVITD</td>
<td>Pharmacy Wholesaler/Retail</td>
<td>0.03</td>
</tr>
<tr>
<td>Cost of estrogen tablet</td>
<td>cESTROGEN</td>
<td>Pharmacy Wholesaler/Retail</td>
<td>0.0927</td>
</tr>
<tr>
<td>Cost of progestin tablet</td>
<td>cPROGEST</td>
<td>Pharmacy Wholesaler/Retail</td>
<td>0.09009</td>
</tr>
<tr>
<td>Cost of dispensing fees</td>
<td>cDISPFEE50</td>
<td>Community pharmacy publication</td>
<td>$8.70 &lt; 65 years</td>
</tr>
<tr>
<td></td>
<td>cDISPFEE65</td>
<td>Ontario Ministry of Health</td>
<td>$6.11 ≥ 65 years</td>
</tr>
</tbody>
</table>
7.4.2 Cost of Estrogen (cESTROGEN) and Progestin (cPROGEST) Therapy

HRT is available by prescription of a physician. Currently a number of oral HRT regimens are used. In the model the continuous combined administration of conjugated estrogen 0.625 mg and medroxyprogesterone 2.5 mg have been used. The cost of administering these two drugs is based on the Ontario Drug Benefit (ODB) Formulary schedule which allows a mark-up of 10% above the best available price (BAP) of an allowed prescription product. This mark up excludes appropriate dispensing fees.

The acquisition cost plus the 10% mark-up of generically available 0.625 mg conjugated estrogen tablets (CES - Pharmascience) is $9.27/100 tablets. In the model the daily cost of estrogen (cESTROGEN) of $0.0927 is used. Medroxyprogesterone 2.5 mg (Kenral) is also generically available at $9.09/100 tablets. The daily cost of progestin in the model (cPROGEST) is set at $0.09009.

7.5 Cost of Dispensing Fees (cDISPFEE50 and cDISPFEE65)

Prescription dispensing fees (pharmacis fees) vary across Canada. A recent cross-Canada survey was conducted with average provincial dispensing fees ranging from $6.70 to $9.80 (Welds et al, 1996). These average dispensing fees however are a composite of the fees paid by cash, third party and government coverages. In the model we have used the maximal Ontario Drug Benefit Program (OBD) fee that pharmacies are reimbursed for the indigent and majority of seniors (≥ 65 years of age) of $6.11. The dispensing fee used in this evaluation for women <65 years of age is $9.80. This fee is based on the average fee that pharmacists are reimbursed for prescriptions filled in the province of Ontario. Typically for maintenance medications a three month quantity is
dispensed, consequently the two drugs (estrogen and progestin) will be dispensed four times in one year. A dispensing fee will apply to each of the two components of HRT (conjugated estrogen and medroxyprogesterone) every three months.

7.6 Discounting

Considerable support for the application of discounting to costs and benefits in an economic evaluation exists (Drummond et al, 1987). The objective of discounting is to bring all of the costs and consequences of an evaluation to their present value. Discounting is used because individuals exhibit a positive rate of time preference; that is their preference is to receive benefits early and to incur the costs later.

The discounting process of future costs to present values is calculated by use of the following formula:

\[ P = \sum_{n=1}^{t} F_n (1+R)^n \]

where \( P \) = present value; \( F_n \) = future cost at year \( n \); \( R \) = annual discount rate (e.g. 0.03 indicates 3%); and \( t \) = number of years of the intervention. This formula was used to discount all costs.

Discounting of effects is also necessary. The principal effectiveness outcome in the osteoporosis model is the number of Life Years Lost (LYL) due to premature death as a result of hip fractures, coronary heart disease, and breast cancer. The present value of life years lost at the premature death was calculated also using this approach.
7.7 Base Case Assumptions for Economic Model

Table 7.7 lists the base case assumptions for the hip fracture model. The base case assumptions used in the model are supported by current literature and were discussed in chapter 2, and supported by the contents of chapters 5,6 and 7.
Table 7.7. Base case assumptions used in the hip fracture model

**a) General**

<table>
<thead>
<tr>
<th></th>
<th>Discount rates costs</th>
<th>Discount rates benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Compliance rates costs</td>
<td>Cost attributed to those patients obtaining prescribed product, assumed compliance in base case were similar to clinical trials.</td>
<td></td>
</tr>
<tr>
<td>Compliance rates benefits</td>
<td>Compliance rate benefits also assumed to be 100% of literature values in base case assumption.</td>
<td></td>
</tr>
<tr>
<td>Long term care costs</td>
<td>Based on a per diem rate of $77.</td>
<td></td>
</tr>
<tr>
<td>Duration of therapy</td>
<td>40 years for women beginning therapy at age 50, and 25 years for those women who initiate therapy at age 65.</td>
<td></td>
</tr>
<tr>
<td>Skeletal status of population</td>
<td>Assumption that we are dealing with preventative treatment in normal and osteopenic women with BMDs of &lt; 1 SD from the mean (for women).</td>
<td></td>
</tr>
<tr>
<td>Age at intervention</td>
<td>50 years of age for immediate therapy, and 65 years of age for delayed therapy.</td>
<td></td>
</tr>
</tbody>
</table>

**b) Bone**

<table>
<thead>
<tr>
<th>Skeletal effect (hip)</th>
<th>Calcium/Vitamin D</th>
<th>20% reduction based on thesis (Cochrane meta-analysis - Chapter 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HRT</td>
<td>50% reduction (Weiss et al, 1980)</td>
</tr>
<tr>
<td></td>
<td>No Intervention</td>
<td>Assume rates of fracture are as those reported in the CMAJ paper (Papadimitropoulos et al, 1997)</td>
</tr>
<tr>
<td>Skeletal onset</td>
<td>Calcium/Vitamin D</td>
<td>5 years based on literature</td>
</tr>
<tr>
<td></td>
<td>HRT</td>
<td>5 years based on literature (Weiss et al, 1980)</td>
</tr>
<tr>
<td></td>
<td>No Intervention</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**c) CHD**

<table>
<thead>
<tr>
<th>CHD effect</th>
<th>Calcium/Vitamin D</th>
<th>No reduction in effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRT</td>
<td>40% reduction (Grodstein et al, 1996)</td>
<td></td>
</tr>
<tr>
<td>No Intervention</td>
<td>No effect</td>
<td></td>
</tr>
<tr>
<td>CHD onset</td>
<td>Calcium/Vitamin D</td>
<td>N/A</td>
</tr>
<tr>
<td>HRT</td>
<td>Immediate (Col et al, 1997)</td>
<td></td>
</tr>
<tr>
<td>No Intervention</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

**d) Breast cancer**

<table>
<thead>
<tr>
<th>Breast Cancer</th>
<th>Calcium/Vitamin D</th>
<th>No effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRT</td>
<td>46% increase after 10yrs therapy (Colditz et al, 1995)</td>
<td></td>
</tr>
<tr>
<td>No Intervention</td>
<td>No effect</td>
<td></td>
</tr>
<tr>
<td>Onset Breast Cancer effects</td>
<td>Calcium/Vitamin D</td>
<td>No effect</td>
</tr>
<tr>
<td>HRT</td>
<td>10yrs</td>
<td></td>
</tr>
<tr>
<td>No Intervention</td>
<td>No effect</td>
<td></td>
</tr>
</tbody>
</table>
8. RESULTS

8.1 OVERVIEW

Once the costs and probabilities of events relating to hip fracture prevention strategies were collected, and the Markov model was validated, the analysis comparing the expected cost and outcome of each strategy was conducted. The model was loaded with all of the data collected and described in chapters 2, 5, 6 and 7, and set to the base case assumptions (Table 7.7).

8.2 EXPECTED COSTS FOR EACH MANAGEMENT STRATEGY

The expected cost and the outcome of life years lost (LYL) for each strategy was calculated for a forty year period and the results are summarized in Table 8.1 under base case assumptions, and two additional discounting scenarios (5%, and 0% respectively). The analysis showed that calcium/vitamin D therapy initiated at age 65 (CaVD65), and the no intervention arm were the second and third lowest expected cost strategies ($5,937.57 and $5,942.50 respectively). Calcium/vitamin D therapy initiated at age 50 (CaVD50) was the second highest in cost, and the HRT arm initiated at 50 years (HRT50) in general had the highest expected cost. Expected costs were the lowest at all discount rates for the HRT strategy initiated at age 65 (HRT65), with values of $5,763.59, $4,087.77 and $10,577.87 using 3%, 5% and 0% discounting rates respectively. Expected cost data for each management strategy presented in Table 8.1, demonstrate that the model is sensitive to the discounting rate, that is the no intervention scenario was lower than the CaVD65 scenario at 5% discounting rate. The CaVD65 and no
Table 8.1 Expected costs under base case assumptions for each management strategy under 3%, 5% and 0% discounting rates per woman followed over a forty year period (age 50-90 years).

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Base-case ($, 3% discount rate)</th>
<th>5% discounting ($)</th>
<th>No discounting ($)</th>
<th>Life Years Lost (3% discounting)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. No intervention</td>
<td>5,942.50</td>
<td>4,130.85</td>
<td>11,333.21</td>
<td>3.7799</td>
</tr>
<tr>
<td>B. Calcium/Vitamin D initiated at age 50 years (CaVD50)</td>
<td>6,359.81</td>
<td>4,546.75</td>
<td>11,631.03</td>
<td>3.7755</td>
</tr>
<tr>
<td>C. Calcium/Vitamin D initiated at 65 years (CaVD65)</td>
<td>5,937.57</td>
<td>4,157.98</td>
<td>11,156.40</td>
<td>3.7763</td>
</tr>
<tr>
<td>D. HRT initiated at age 50 years (HRT50)</td>
<td>7,330.14</td>
<td>5,493.95</td>
<td>12,434.46</td>
<td>3.6534</td>
</tr>
<tr>
<td>E. HRT initiated at age 65 years (HRT65)</td>
<td>5,763.59</td>
<td>4,087.77</td>
<td>10,577.87</td>
<td>3.6501</td>
</tr>
</tbody>
</table>
intervention scenarios have a very close expected cost in the base case, however the relative rankings of these two scenarios are sensitive to discounting rates above 3%. The relative ranking of CaVD50 and HRT50 alternatives did not change across discount rates.

The model was also run to evaluate the impact on expected costs when the clinical efficacy parameters were varied under two additional scenarios: the optimistic scenario, and the pessimistic scenario for each treatment strategy described in detail in Table 2.6. The optimistic scenario assumes more clinical benefit for calcium and vitamin D and HRT and therefore minimizes the expected LYL for these strategies. The pessimistic scenario assumes less clinical benefit, therefore the expected LYL are maximized.

The rank order of expected costs did not change when the optimistic assumptions were applied to the model (Table 8.2), with the CaVD65 strategy having the second lowest expected cost ($5,684.15), and the HRT65 strategy being the lowest once again ($5,241.84). When the model was run under the pessimistic scenario however, the no intervention strategy had the lowest expected cost ($5,942.50) followed by CaVD65, HRT65, CaVD50, and HRT50 strategies, with expected costs of $6,184.53, $6,283.72, $6,676.78, and $8,039.55 respectively.

8.3 DISTRIBUTION OF EXPECTED COSTS BY MAJOR COMPONENTS

The expected cost data (under a 3% discount rate, base case assumptions) were disaggregated into their individual components, and are presented in Figure 8.1, and Table 8.3. The resource components captured in the model are the costs of: physician fees (surgeon and anesthetist fees excluded), long term care, hip fractures, breast cancer, coronary heart disease, HRT, and calcium/vitamin D supplements.
Table 8.2 Expected costs under base case, optimistic, and pessimistic assumptions for each management strategy per woman followed over a forty year period.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Expected cost by intervention and assumption scenario, per woman followed over a forty-year period under a 3% discount rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base-case scenario ($$)</td>
</tr>
<tr>
<td>A. No intervention</td>
<td>5,942.50</td>
</tr>
<tr>
<td>B. CaVD50</td>
<td>6,359.81</td>
</tr>
<tr>
<td>C. CaVD65</td>
<td>5,937.57</td>
</tr>
<tr>
<td>C. HRT50</td>
<td>7,330.14</td>
</tr>
<tr>
<td>E. HRT65</td>
<td>5,763.59</td>
</tr>
</tbody>
</table>
Costs associated with routine monitoring over a calendar year in all postmenopausal women, was the largest cost component in the CaVD, no intervention and HRT65 management strategies. In the HRT50 arm, the cost of HRT was the largest component. In the non-HRT strategies, the cost of CHD was the next largest following physician costs. Physician costs were approximately the same in all management strategies since these costs reflect routine care.

Long term care costs were ascribed to all hip fracture patients who were community-residing at the time of the fracture event and who were subsequently admitted permanently to a LTC facility. Incremental costs associated with a temporary heavier level of care for the previously LTC-residing women, as well as the LTC costs for previously community-living women, were captured in the overall LTC cost presented in Table 8.3, and Figure 8.1. LTC costs associated with active preventative strategies were the highest for CaVD65 ($821.64) and CaVD50 ($781.75) followed by HRT65 ($617.73); the HRT50 management strategy was the lowest at $514.13. The costliest management approach from a LTC perspective was the no intervention strategy with an expected cost of $971.00. LTC costs vary by treatment strategies since it is those strategies which result in more hip fractures that have higher expected costs associated with this resource.

Hip fracture costs for the repair of the hip in an acute care hospital, follow-up rehabilitation, and support system care were captured for all patients who fractured. The cost of hip fractures followed the same ranking pattern as LTC costs for the same reasons. The CaVD65 management strategy had the highest hip fracture cost of all active intervention followed by CaVd50, HRT65, and HRT50 strategies. The no intervention
Figure 8.1 Expected cost by cost component and management strategy. The 4 management strategies include calcium and vitamin D initiated at 50 (CaVD50), or 65 (CaVD65) years of age, or HRT initiated at 50 (HRT50) or 65 (HRT65) years of age versus no intervention (No Interv). Costing is presented separately for treatment costs (CaVD or HRT), treatment of CHD (CHD), breast cancer (BrCA) or hip fracture (hip #), and long-term care (LTC) costs for individuals entering long-term care, and routine physician visit costs (MD).
Table 8.3 Distribution of expected costs by cost component (under a 3% discount rate) per woman followed over a forty-year period under a number of management strategies.

<table>
<thead>
<tr>
<th>Cost Element</th>
<th>No Intervention</th>
<th>CaVD50</th>
<th>CaVD65</th>
<th>HRT50</th>
<th>HRT65</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Calcium/Vitamin D</td>
<td>$0.00</td>
<td>$840.67</td>
<td>$331.54</td>
<td>$0.00</td>
<td>$0.00</td>
</tr>
<tr>
<td>B. HRT</td>
<td>$0.00</td>
<td>$0.00</td>
<td>$0.00</td>
<td>$2,654.88</td>
<td>$919.49</td>
</tr>
<tr>
<td>C. Hip Fractures</td>
<td>$1,243.02</td>
<td>$1,008.63</td>
<td>$1,055.73</td>
<td>$673.19</td>
<td>$793.28</td>
</tr>
<tr>
<td>D. Long-term care</td>
<td>$971.00</td>
<td>$781.75</td>
<td>$821.64</td>
<td>$514.43</td>
<td>$617.73</td>
</tr>
<tr>
<td>E. Breast cancer</td>
<td>$591.87</td>
<td>$592.05</td>
<td>$592.01</td>
<td>$815.60</td>
<td>$655.09</td>
</tr>
<tr>
<td>F. CHD</td>
<td>$1,219.83</td>
<td>$1,220.61</td>
<td>$1,220.49</td>
<td>$746.36</td>
<td>$851.58</td>
</tr>
<tr>
<td>G. Physician Fees</td>
<td>$1,916.76</td>
<td>$1,916.08</td>
<td>$1,916.15</td>
<td>$1,925.68</td>
<td>$1,926.40</td>
</tr>
<tr>
<td>Total</td>
<td>$5,942.48</td>
<td>$6,359.79</td>
<td>$5,937.56</td>
<td>$7,330.14</td>
<td>$5,763.59</td>
</tr>
</tbody>
</table>
arm was the most costly in terms of hip fracture related costs.

Costs related to breast cancer treatment or death from breast cancer were also captured in the analysis. The no intervention, CaVD50, and CaVD65 interventions had almost identical breast cancer costs ($591.87, $592.05, and $592.01 respectively) since the model assumed that CaVD did not impact on breast cancer. The slight differences observed would be secondary to different overall mortality rates in these three groups. HRT65 management strategy had the next highest cost associated with breast cancer ($655.09), and the HRT50 strategy had the highest cost of all interventions ($815.60). These higher expected costs were linked to the increased risk of developing breast cancer in those women who were HRT users.

Coronary Heart Disease (CHD) costs were also captured in the model. The three strategies of no intervention, CaVD50 and CaVD65, had higher but similar costs associated with CHD ($1,219.83, $1,220.61, and $1,220.49 respectively) than HRT strategies due to the same assumptions as with breast cancer (ie. these interventions were assumed not to impact CHD). HRT50 strategy had the lowest CHD cost ($746.36), followed by the HRT65 arm at $851.58. These lower costs were a result of HRTs protective effects from CHD.

Costs associated with the acquisition of calcium/vitamin D, and HRT were the last two cost components captured. The cost of CaVD for the CaVD50 and CaVD65 strategies was lower than that for the HRT interventions. HRT costs, composed of the cost of the estrogen, progestogen, and the associated pharmacy mark-up and dispensing fees was high ($2,654.88, and $919.49 for the HRT50, and HRT65 management
strategies respectively). Obviously these costs were applied to the appropriate management strategy, with costs varying based on the duration of active treatment.

8.4 EXPECTED OUTCOMES BY MANAGEMENT STRATEGY

The primary outcome in this evaluation is the number of life years lost (LYL) in each of the treatment strategies. Table 8.1 lists the LYL value for each strategy under base case assumptions. The no intervention strategy has the largest LYL of 3.7799 years, followed by the CaVD65, CaVD50, and HRT50 strategies, while the HRT65 strategy has the lowest LYL of 3.6501. In other words, someone treated with HRT at age 65 would be expected to live 0.1298 years longer than someone not treated. The HRT50 strategy on the other hand has a higher LYL than the HRT65 strategy, suggesting that the HRT50 strategy is not as effective in preventing overall death as the HRT65 therapy.

Summary data on hip fractures, deaths, and permanent admission to LTC per 1000 Canadian postmenopausal women under base case, optimistic and pessimistic scenarios are presented in Table 8.4. These findings indicate that under base case assumptions the smallest number of hip fractures from both community and LTC dwelling women using the CaVD strategy were those that initiated preventative therapy at 50 years of age. The CaVD50 intervention had 165 hip fractures, while the CaVD65 group had 171. The lowest number of hip fractures were observed with HRT50 strategy, with a total of 111, followed by 124 fractures in the HRT65 group. The no intervention arm had the largest number of hip fractures (205 fractures). The rank ordering for number of hip
Table 8.4  Expected outcomes and events per 1000 postmenopausal women, by management strategy (under 3% discount rate), followed for over a forty-year period.

<table>
<thead>
<tr>
<th>Outcome/Event</th>
<th>No Intervention</th>
<th>CaVD50</th>
<th>CaVD65</th>
<th>HRT50</th>
<th>HRT65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip fractures in community-dwelling women</td>
<td>102</td>
<td>82 (68.97)</td>
<td>86 (75, 98)</td>
<td>55 (35.72)</td>
<td>65 (49.78)</td>
</tr>
<tr>
<td>Hip fractures in LTC-residing women</td>
<td>103</td>
<td>83 (68.98)</td>
<td>85 (71.98)</td>
<td>56 (35.73)</td>
<td>59 (40.75)</td>
</tr>
<tr>
<td>Total number of hip fractures</td>
<td>205</td>
<td>165 (136, 195)</td>
<td>171 (146, 196)</td>
<td>111 (70, 145)</td>
<td>124 (89, 153)</td>
</tr>
<tr>
<td>Breast cancer deaths</td>
<td>31</td>
<td>31 (31,31)</td>
<td>31 (31,31)</td>
<td>45 (38.51)</td>
<td>38 (35, 41)</td>
</tr>
<tr>
<td>Coronary heart disease deaths</td>
<td>152</td>
<td>152 (152,152)</td>
<td>152 (152,152)</td>
<td>94 (69,127)</td>
<td>98 (74, 129)</td>
</tr>
</tbody>
</table>

Expected number of events by intervention over a 40-year follow-up per 1000 Canadian postmenopausal women base case (optimistic, pessimistic)
fractures remained the same under the optimistic and pessimistic scenarios, with the HRT50 strategy continuing to have the lowest and the no intervention strategy having the highest.

Deaths resulting from breast cancer are also presented in Table 8.4. The no intervention, CaVD50, and CaVD65 strategies each had 31 deaths under base case, pessimistic and optimistic scenarios (since breast cancer (BrCA) did not vary under these scenarios). In contrast, the HRT50 and HRT65 interventions had higher deaths due to BrCA of 45 and 38 respectively. There were 7 more deaths due to BrCA in the HRT50 than the HRT65 scenario. The ranking in breast cancer deaths were the same with the optimistic and pessimistic scenarios with HRT50 and HRT65 having the highest number of these events (38 and 35 respectively under the optimistic scenario; 51 and 41 respectively in the pessimistic scenario).

Coronary heart disease (CHD) deaths over the forty-year period were the greatest in the no intervention, CaVD50, and CaVD65 management strategies (152 deaths/1000 women) since it was assumed that CaVD had no effect on CHD, whereas the HRT50 and HRT65 approaches had only 94 and 98 deaths from CHD respectively under base case assumptions (Table 8.4). Under base case assumptions in the HRT interventions there were a similar number of deaths due to CHD (94 and 98) for HRT50 and HRT65 respectively. This number should be contrasted with the no intervention scenario in which there were 152 CHD deaths. The number of deaths due to CHD continued to be low under both the optimistic (69 and 74), and pessimistic scenarios (127 and 129) for HRT50 and HRT65 interventions respectively. Therefore an internal trade-off exists between deaths, fractures and cost.
8.5 INCREMENTAL COSTS, EFFECTS, AND COST-EFFECTIVENESS

Table 8.5 summarizes the expected costs of the five management strategies using the base case assumptions defined in Table 7.7, under a 3% discounting rate. CaVD65 had the lowest cost ($5,937.57), of the CaVD strategies however a small LYG value (0.0036) resulted from this intervention. The CaVD65 strategy was considered to have weak dominance since it had the smallest incremental LYG and about the same expected cost, as the no intervention (NI) arm. The CaVD50 intervention had a higher incremental LYG than CaVD65 (0.0044 years), however at higher expected cost ($6,359.81). A trade-off also exists for the CaVD50 strategy between increased cost and a small increase in LYG ($94,843/LYG). HRT therapy initiated at age 65 (HRT65) was dominant over all strategies, having the lowest total cost ($5,763.59; $178.91 lower than the no intervention strategy), and the largest LYG over all strategies (0.1298 years over no intervention). HRT initiated at 50 years (HRT50) had the highest expected cost ($7,330.14), however 0.1265 years of life were gained over no intervention. Consequently, a trade-off exists with this management strategy, in which it costs more than NI, however it is also more effective ($10,969/LYG).

The data in Table 8.5 is presented graphically in Figure 8.2. In this type of plot, the x co-ordinate captures the efficacy of the intervention in incremental units of life-years gained (LYG) compared to no intervention; the y co-ordinate captures the incremental cost of the intervention compared to the no intervention scenario. Each of the four quadrants of this figure graphically describes the costs and consequences of each strategy in comparison to the no intervention scenario. Since each intervention is
Table 8.5 Incremental costs and Life Years Gained of each strategy relative to no intervention under base case assumptions.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Base-case (3% discount rate)</th>
<th>Incremental costs (versus no intervention)</th>
<th>Life Years Lost (3% discounting)</th>
<th>Incremental LYG</th>
<th>Incremental cost-effectiveness ratio to NI ($/LYG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. No intervention (NI)</td>
<td>5,942.50</td>
<td>-</td>
<td>3.7799</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>B. CaVD50</td>
<td>6,359.81</td>
<td>417.31</td>
<td>3.7755</td>
<td>0.0044</td>
<td>94,843</td>
</tr>
<tr>
<td>C. CaVD65</td>
<td>5,937.57</td>
<td>(4.93)</td>
<td>3.7763</td>
<td>0.0036</td>
<td>WEAK DOMINANCE</td>
</tr>
<tr>
<td>D. HRT50</td>
<td>7,330.14</td>
<td>1387.64</td>
<td>3.6534</td>
<td>0.1265</td>
<td>10,969</td>
</tr>
<tr>
<td>E. HRT65</td>
<td>5,763.59</td>
<td>(178.91)</td>
<td>3.6501</td>
<td>0.1298</td>
<td>DOMINANT</td>
</tr>
</tbody>
</table>
Figure 8.2 Cost versus efficacy plot under base case assumptions for four treatment scenarios versus the no intervention approach. The 4 management strategies include calcium and vitamin D initiated at 50 (CaVD50), or 65 (CaVD65) years of age, or HRT initiated at 50 (HRT50) or 65 (HRT65) years of age versus no intervention.
compared to the no intervention scenario, the no intervention scenario has the co-ordinates of (0,0). Scenarios whose co-ordinates lie in the north-east quadrant of Figure 8.2 (or upper right quadrant), are interventions that are more costly (increased $), but more effective (increased LYG) than the NI scenario. Those interventions which have data lying in the south-east quadrant (bottom right), indicate that they are less costly and more effective than the NI scenario. Typically these interventions provide a compelling economic argument for adoption compared to the origin. Alternatively, data found in the north-west (upper left) quadrant describe interventions that are more costly and less effective than the no intervention scenario. Clearly interventions lying in the north-west quadrant are inefficient and should not be considered for support in health care. Lastly, interventions whose data lie in the south-west corner (bottom left) are less costly, but are also less effective than the NI scenario.

The data from the four interventions all lie in the north-east and south-east quadrant of the graph, indicating that all of the interventions under the base case assumptions are at least as efficacious as the NI scenario.

In the north-east quadrant the CaVD50 scenario and the HRT50 scenario are presented, indicating that both of these strategies cost more than NI, however they are also more effective. In the case of the CaVD50 scenario there is a relatively large incremental cost ($417.31) associated with a very small increment in LYG (0.0044 years) in comparison to the NI approach. On the other hand the HRT50 intervention provides a more favourable incremental efficacy (0.1265 LYG) in comparison to NI, however at an incremental cost of $1,387.64 per patient treated over the forty years that the model runs.
effectiveness of the strategies (Figure 8.2). The lower the slope, the less the intervention costs per unit of effect (LYG in this case).

Data presented in the south-east quadrant are more favourable (from a cost perspective) than any scenarios in the north-east quadrants. Under base case assumptions the CaVD65 intervention was only slightly less costly per patient treated ($4.93) than the NI approach, however it was moderately effective in incremental LYG (0.0036) years. Clearly the HRT65 strategy dominates all interventions evaluated in the model (i.e. lowest expected cost and highest expected LYG). The HRT65 scenario was less costly ($178.91) and considerably more effective (0.1298) than the CaVD65 intervention when compared incrementally to the NI approach. This finding clearly supports that the HRT65 strategy is "dominant" since it is not only least costly (cost-saving), but it provides the greatest efficacy (incremental LYGs) than all the other interventions, including the do-nothing approach (NI scenario). It should be noted that the CaVD65 intervention is also less costly and more effective than the NI approach, however both the incremental savings and incremental efficacy are small in comparison to the HRT65 strategy, consequently the CaVD65 strategy is considered as "dominated" by the HRT65 scenario.

The HRT65 strategy is dominant because all other interventions lie to the northwest of it (that is, they cost more and are less effective). HRT65 and the CaVD65 strategies are considered to be dominant and weakly dominant respectively, due to the lower cost of these management strategies as well as the incremental LYG in comparison to the NI arm.
The incremental cost and primary outcome of LYG were then used to calculate cost-effectiveness ratios. Using no intervention as a reference, cost-effectiveness ratios were calculated for the strategies in the north-east quadrant (HRT50 and CaVD50) (Table 8.5). This ratio shows the additional cost required to gain one year of life. The cost-effectiveness ratio for HRT50 is $10,969/LYG and the ratio for CaVD50 is $94,843/LYG.

8.6 SENSITIVITY ANALYSIS OF COSTS USED IN THE MODEL

A number of key model cost and probability of occurrence variables were evaluated for their impact on the expected cost of each intervention, since there are a number of assumptions and parameters about which there is some uncertainty. The uncertainty in these cost parameters were evaluated using sensitivity analyses. In sensitivity analysis a range of values for each variable is established, and then the model is re-evaluated to assess the impact of this range on expected costs or outcomes. The source of the base case values for each parameter and the justification for these values has been documented in chapters 5 and 7. The lower and upper ranges for each parameter were either based on cost/probability values available in the literature, or a range was estimated based on plausible and defensible ranges. The following cost parameters were evaluated:

8.6.1 Cost of Hip Fracture Repair

Based on the average cost to treat all hip fractures from the Sunnybrook costing data base a cost of $10,745 was set as the base case for treating a hip fracture at the acute care
hospital setting (Table 7.2). This base case was varied -48% to 50% ($5,182 to $16,100) to reflect potential differences in costs and practice patterns for treating a hip fracture patient in a teaching versus non-teaching acute care hospital, or in facilities that typically may discharge patients more quickly. The lower range ($5,182) was selected based on reported cost for treating a hip fracture in the Alberta standard cost list (Jacobs et al, 1998). The upper range is 50% higher than the cost of treating a hip fracture at Sunnybrook Hospital. The results of the sensitivity analysis are presented in Figure 8.3. This figure shows that the ranking of expected costs across strategies is sensitive to the cost of hip fracture at the acute care hospital. The expected cost of each strategy increased with higher cost estimates for hip fracture treatment in all arms, however a cross-over occurred at the lower end of the range at a cost of hip fracture repair of $5,331.80 and an expected value of $5,449.76 between the no intervention and HRT65 strategy. The no intervention arm has a lower expected cost than HRT65 strategy, below this threshold, and a higher expected value above the threshold. Similarly a crossover occurred between no intervention and CaVD65 at an expected cost of $5,920 and a cost of hip fracture below $10,600.

The difference in expected costs between the no intervention and the HRT65 strategy is small. The expected cost of the other two strategies increased across the sensitivity range (without crossing) with the CaVD50 being the lowest of the two, followed by the HRT50 strategy.
Figure 8.3 The 4 management strategies include calcium and vitamin D initiated at 50 (CaVD50), or 65 (CaVD65) years of age, or HRT initiated at 50 (HRT50) or 65 (HRT65) years of age versus no intervention. The expected cost for the 4 treatments examined was tested, varying the cost of hip fracture repair (base case cost of $10,745) from -48% to +50%. A threshold for the HRT65 and the no intervention strategy occurs at an Expected Value (EV) of $5,449.76 and a cost of hip fracture repair of $5,331.80, similarly a cross-over occurs between no intervention and CaVD65 strategy at an expected value of $5,920 and a cost of hip fracture of $10,600.
8.6.2 Hotel Costs at Acute Care Hospitals

The base case acute care hospital hotel cost was set to $400 per diem. This hotel cost was incremental to the cost of hip fracture repair to compensate for the additional four days needed to capture the total costs of a 21 day length of stay (LOS) (since the Sunnybrook cost data captured an average 17 day LOS). This cost was varied between $200 and $600 to reflect the potential differences between teaching and non-teaching institutions, practice pattern variation as well as resource intensity in different wards within a hospital. The results of this sensitivity analysis are presented in Figure 8.4. The expected cost increased slightly over all interventions (Figure 8.4). The HRT65 had the lowest expected cost followed by the CaVD65, no intervention, CaVD50 and HRT50 strategies throughout the per diem range tested. The changes in expected costs for each strategy remained very small throughout the range of hotel costs tested in the sensitivity analysis.

8.6.3 Cost of Home Care

The cost of home care for the base case was set to $941 per community residing hip fracture patient (ICES, 1998). This cost was varied between $500 and $2,000 to capture potential differences in the cost for provision of this care across the country, and the results are presented in Figure 8.5. Small increases in expected cost were observed for all the intervention arms, however the rank ordering in cost across all strategies was not affected by the cost of home care. The HRT65 had the lowest expected cost followed by the CaVD65, no intervention, CaVD50 and HRT50 strategies. The changes in expected
Figure 8.4 The 4 management strategies include calcium and vitamin D initiated at 50 (CaVD50), or 65 (CaVD65) years of age, or HRT initiated at 50 (HRT50) or 65 (HRT65) years of age versus no intervention. The expected cost for the 4 treatments examined was tested, varying the cost of daily hotel costs (base case cost of $400) from -50% to +50%.
Figure 8.5 The 4 management strategies include calcium and vitamin D initiated at 50 (CaVD50), or 65 (CaVD65) years of age, or HRT initiated at 50 (HRT50) or 65 (HRT65) years of age versus no intervention. The expected cost for the 4 treatments examined was tested, varying the cost of home care (base case cost of $941) from -53% to +213%.
costs for each strategy remained very small throughout the range of home care costs tested.

8.6.4 Cost of Acute Care Treatment of Myocardial Infarct

Varying the cost of the acute myocardial infarct (AMI) event from its base case cost of $7300 by a range of -30% and +50% ($5,218 to $10,950) resulted in almost parallel changes in expected cost of all management strategies (Figure 8.6). The lower range value ($5,218) was set based on the cost for the management of an AMI with no cardiovascular complications, from the Alberta costing list published by Jacobs et al (1997). The upper range was set to +50% over base case to capture the eventuality of a complicated AMI. The HRT65 had the lowest expected cost followed by the CaVD65, no intervention, CaVD50 and HRT50 strategies generally throughout the AMI cost range tested. The changes in expected costs for each strategy remained very small throughout the range of myocardial infarct costs at the acute care setting.

8.6.5 Cost of Breast Cancer Treatment

The cost of breast cancer treatment used in the base case analysis was $9,560. This cost was varied -46% to +50% from the base case value ($4,144 to $14,340) (Figure 8.7). The lower cost value in the range was obtained from the Alberta Case costing initiative (Jacobs et al, 1997). This lower cost value ($4,144) may be an under-estimate since the publication by Jacobs et al (1997) did not provide the elements used to arrive at the total cost for breast cancer treatment in a disaggregated manner. The upper range was set to 50% higher ($14,340) than the base case cost since it was anticipated to
Figure 8.6 The 4 management strategies include calcium and vitamin D initiated at 50 (CaVD50), or 65 (CaVD65) years of age, or HRT initiated at 50 (HRT50) or 65 (HRT65) years of age versus no intervention. The expected cost for the 4 treatments examined was tested, varying the cost of managing a myocardial infarct (base case cost of $7,300) from -30% to +50%.
Figure 8.7 The 4 management strategies include calcium and vitamin D initiated at 50 (CaVD50), or 65 (CaVD65) years of age, or HRT initiated at 50 (HRT50) or 65 (HRT65) years of age versus no intervention. The expected cost for the 4 treatments examined was tested, varying the cost of breast cancer treatment from the base case cost of $9,560 from -46% to 50%.
represent a generous over-estimate of actual costs. Varying the cost through this range had an impact on the expected cost of each intervention, however the rank ordering of the interventions did not change through the range. Throughout, the range of values for breast cancer costs did not have a large impact on the expected costs of the no intervention, CaVD50, and CaVD65 strategies.

8.6.6 Surgery Fees for Hip Fracture Repair

Surgery fees related to hip fracture repair were set to $554.15 for the base case analysis with a range of +/- 50% ($277 to $831) to account for variability in surgeon/anesthetist’s time to complete the surgery and to account for premiums in the fees as a result of performing surgery at “off-hours”. The results of the sensitivity analysis are presented in Figure 8.8. Varying the surgery fees over this range resulted in slight and almost parallel expected cost changes for all treatment arms (Figure 8.8).

8.6.7 Daily Rate of LTC Stay

The base case per diem rate for LTC care was $77. This rate was varied over the range of $59.11 (-23%) to $128.23 (+66%) reflecting the range in per diem rates using the LTC facilities classification (i.e. levels A-G) (Ontario Ministry of Health, 1998). Almost parallel changes in expected costs were seen with all interventions, with a divergence seen in costs for the no intervention and calcium/vitamin D initiated at 65 years arms (Figure 8.9). Once again, the HRT65 had the lowest expected cost followed by the CaVD65, no intervention, CaVD50 and HRT50 strategies throughout the LTC per
Figure 8.8 The 4 management strategies include calcium and vitamin D initiated at 50 (CaVD50), or 65 (CaVD65) years of age, or HRT initiated at 50 (HRT50) or 65 (HRT65) years of age versus no intervention. The expected cost for the 4 treatments examined was tested, varying the cost of surgeon and anesthetist fees (base case cost of $554) from -50% to +50%.
Figure 8.9 The 4 management strategies include calcium and vitamin D initiated at 50 (CaVD50), or 65 (CaVD65) years of age, or HRT initiated at 50 (HRT50) or 65 (HRT65) years of age versus no intervention. The expected cost for the 4 treatments examined was tested, varying the cost of daily stay in a long-term care (LTC) facility (base case cost of $77) from -23% to +66%. A cross-over was observed at a daily cost of $71 per diem or lower resulted in the no intervention strategy expected cost becoming lower than the CaVD65 strategy.
diem range tested, with the exception of a cross-over which occurred at a LTC cost of $71. At an expected cost of $71 or lower, the no intervention strategy had the second lowest expected cost next to the HRT65 strategy. CaVD65 was no longer dominant over NI at LTC per diem costs of < $71. The changes in expected costs for each strategy remained very small throughout the range of daily cost of LTC tested in the sensitivity analysis.

8.6.8 **The Extra Cost for Care of Hip Fracture Patients Who Were Residing in LTC**

Additional costs for taking care of hip fracture patients (who returned to LTC) for the first year following their hip fracture was set to an incremental $23 a day for the base case analysis. The addition of $23 per day was assigned temporarily to LTC costs, since it was assumed that once a resident returned to this facility following the hip fracture event they would need additional support until they adapted to the new functional level. The base case cost was varied with a range of $10 (-57%) to $50 (+215%), to test the impact that this range would have on expected cost. This variability resulted in parallel changes in all arms (Figure 8.10). It was observed once again that throughout this range the expected costs increased with extra LTC service costs, however the rank ordering of the interventions remained the same generally with a cross-over occurring at an LTC extra cost of $20 or less, where the no intervention strategy had a modestly lower expected cost than CaVD65 strategy. At this cost the CaVD65 strategy lost its dominance over the NI strategy. The HRT65 had the lowest expected cost over the whole range of the sensitivity analysis.
8.6.9 Rehabilitation Care Costs

Daily rehabilitation care costs were varied by +/- 50% ($137.50 to $412.50) from the base case cost of $275 (Figure 8.11). The lower and upper cost range were estimated based on discussions with administrative staff at Riverdale hospital; a rehabilitation hospital in Toronto. Although the average daily rate is $275, the daily rate may vary based on the level of nursing care, the facilities required, equipment use and input from other health care providers during the rehabilitation stay. The resultant changes in expected cost were almost flat in all arms with no cross-over being observed. The ordering of the four strategies and the no intervention arm were unchanged.

8.6.10 Cost of Calcium/Vitamin D Intervention

A base case cost of $0.1166 was used to account for the retail cost of one day's therapy of 750mg calcium and 400IU of vitamin D. This cost was varied in the sensitivity analysis by +/-50% ($0.0583 to $0.1749), and the results are presented in Figure 8.12. These upper and lower ranges were assigned in this sensitivity analysis assuming that a +/- 50% range was appropriate for a product that would be retailed in a pharmacy. Figure 8.12 shows that the ranking of expected costs across strategies is sensitive to the cost of calcium/vitamin D. Initiating calcium/vitamin D at 65 years of age (CaVD65) resulted in a slightly lower expected cost as no intervention at the base case cost of $0.1166, and a higher expected cost than no intervention above a cost of $0.1183. The ranking of expected cost for the CaVD50 strategy is also sensitive to the cost of calcium/vitamin D, however a threshold occurs at the lower limit of the sensitivity analysis ($0.0584). The CaVD50 strategy has a higher expected value than CaVD65 throughout the range of calcium/vitamin D tested.
Figure 8.10 The 4 management strategies include calcium and vitamin D initiated at 50 (CaVD50), or 65 (CaVD65) years of age, or HRT initiated at 50 (HRT50) or 65 (HRT65) years of age versus no intervention. The expected cost for the 4 treatments examined was tested, varying the cost of extra LTC cost (base case cost of $23) from -57% to +215%.

A threshold exists for the CaVD65 strategy at an extra LTC cost of less than $20 per day.
Figure 8.11 The 4 management strategies include calcium and vitamin D initiated at 50 (CaVD50), or 65 (CaVD65) years of age, or HRT initiated at 50 (HRT50) or 65 (HRT65) years of age versus no intervention. The expected cost for the 4 treatments examined was tested, varying the cost of rehabilitation stay (base case cost of $275) from -50% to +50%.
Figure 8.12 The 4 management strategies include calcium and vitamin D initiated at 50 (CaVD50), or 65 (CaVD65) years of age, or HRT initiated at 50 (HRT50) or 65 (HRT65) years of age versus no intervention. The expected cost for the 4 treatments examined was tested, varying the cost of calcium/vitamin D supplements from the base case cost of $0.1166 from -50% to 50%.
in this sensitivity analysis. The HRT50 strategy had the highest expected value throughout the range tested.

8.6.11 Cost of HRT

The base case cost of HRT was set to $0.1828 to reflect the acquisition cost and mark-up by the pharmacist. HRT therapy is composed of generically available conjugated estrogen 0.625mg/medroxyprogesterone 5mg daily. This cost was varied in the sensitivity analysis by -10% to +50% ($0.1645 to $0.2742). A 10% reduction in the base case cost was used as the lower range in the sensitivity analysis, since costs of generic HRT is unlikely to be much lower than costs used in the base case. The upper range value was set to 50% above the base case cost to reflect an overly generous rise in market price, and the results are shown in Figure 8.13. This figure shows that the ranking of expected costs across strategies is sensitive to the cost of HRT. HRT50 strategy had the highest expected cost of all strategies throughout the range tested for sensitivity and a increase in expected cost from $7,200 to $8,100 was observed through the range tested. HRT65 strategy on the other hand had the lowest expected cost of all strategies until it reached a threshold HRT cost of $0.2427. Above this threshold cost the CaVD65 followed by the no intervention strategy have the lowest expected cost (value). The CaVD50 strategy obviously did not vary and had the fourth highest expected cost throughout the range of HRT cost tested.
Figure 8.13 The 4 management strategies include calcium and vitamin D initiated at 50 (CaVD50), or 65 (CaVD65) years of age, or HRT initiated at 50 (HRT50) or 65 (HRT65) years of age versus no intervention. The expected cost for the 4 treatments examined was tested, varying the cost of HRT treatment from the base case cost of $0.1828 from -10% to 50%. A threshold for the HRT65 and the no intervention strategy occurs at an Expected Value (EV) of $5,937.57 and a cost of HRT of $0.2427.
8.6.12 Cost of Pharmacist's Dispensing Fee

In this model the dispensing fee used in the base case analysis was $9.80 for those prescriptions filled to women under the age of 65, and $6.11 to women aged 65 and over (Welds et al., 1997). These fees apply to each component of HRT (estrogen and progestogen).

The base case dispensing fee for women under the age of 65 (cDISPFEE50) was varied from $6.70 (the lowest average provincial prescription rate - Saskatchewan) to $12.00 (25% higher than the base case fee). Figure 8.14 demonstrates that the ranking of expected costs across strategies is sensitive to the cost of the pharmacist’s dispensing fee for the HRT50 strategy since the dispensing fee for the women in the HRT65 strategy was held constant at $6.11. Clearly the HRT50 strategy continues to have the highest expected value of all the interventions studied throughout the dispensing fee range tested. The dispensing fee applied to women over the age of 65 years (cDISPFEE65) is based on the maximal fee ($6.11) that is currently reimbursed by the Ontario Drug Benefit (ODB) program for prescription products provided to recipients of their plan (Figure 8.15). The ODB program reimburses a maximum of $4.11 and the patient may pay up to a $2.00 co-pay. These dispensing costs were varied in the sensitivity analysis from $2.00 to $8.00 reflecting the typical pharmacy dispensing fee range across Canada, and the age of the postmenopausal woman to whom the medication was prescribed (Welds et al., 1996). The expected cost for the HRT65 strategy is also sensitive to the dispensing fee (Figure 8.15). At a dispensing fee below $8.00, HRT65 has lower expected cost than all other strategies. HRT65 is the dominant strategy below a dispensing fee of $8.00, above the range tested it appears that HRT65 may reach a threshold and have a higher expected cost.
Figure 8.14 The 4 management strategies include calcium and vitamin D initiated at 50 (CaVD50), or 65 (CaVD65) years of age, or HRT initiated at 50 (HRT50) or 65 (HRT65) years of age versus no intervention. The expected cost for the 4 treatments examined was tested, varying the dispensing fee in women under age 65 (the base case fee of $9.80) from $6.70 to $12.00.
Figure 8.15 The 4 management strategies include calcium and vitamin D initiated at 50 (CaVD50), or 65 (CaVD65) years of age, or HRT initiated at 50 (HRT50) or 65 (HRT65) years of age versus no intervention. The expected cost for the 4 treatments examined was tested, varying the dispensing fee in women aged 65 and over from the base case fee of $6.11 from $2.00 to $8.00.
than the no intervention strategy. An analysis was run to determine the value of the dispensing fee threshold ($8.92), however this threshold was not presented in Figure 8.14. HRT50 strategy is also sensitive to the dispensing fee for women aged of 65 or over since the women in this strategy have the new (lower) fee assigned to them when they reach 65 years of age. The HRT50 strategy expectedly has the highest expected cost of all strategies. The ranking in expected cost for the three strategies between the lowest (HRT65) and the highest expected cost (HRT50) strategies, are the CaVD65, no intervention, and CaVD50 interventions respectively (the expected cost of these strategies do not change with dispensing fees).

Table 8.6 summarizes the impact of varying the cost data for all of the model elements tested.

8.7 SENSITIVITY ANALYSIS ON RESOURCE UTILIZATION ASSUMPTIONS USED IN THE MODEL

A number of probabilities relating to resource use in the model were varied in sensitivity analyses to determine the impact they would have on the results. The range that was ascribed to each of these probabilities in the sensitivity analysis were generally reflective of the level of confidence for the value of the resource. The probabilities varied in this analysis were: the probability of entering a nursing home from the community, the probability of receiving home care post discharge from the acute care hospital and the probability of rehabilitation care post discharge from the acute care hospital.
Table 8.6 One-way sensitivity analysis of costs to evaluate changes in the ranking of strategies from the base case state of: (HRT65, CaVD65, NI, HRT50, CaVD50).

<table>
<thead>
<tr>
<th>Variable Evaluated</th>
<th>Cost range with unaltered strategy ranking ($, 1996)</th>
<th>Costs under which strategy ranking is altered from base case state ($, lowest to highest expected cost strategy ranking)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip fracture cost</td>
<td>10,600 - 16,100</td>
<td>5,182 - 10,599 (HRT65, NI, CaVD65, HRT50, CaVD50)</td>
</tr>
<tr>
<td>Daily acute care hotel cost</td>
<td>200 - 400</td>
<td></td>
</tr>
<tr>
<td>Home care</td>
<td>500 - 2,000</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarct treatment</td>
<td>5,218 - 10,950</td>
<td></td>
</tr>
<tr>
<td>Breast cancer treatment</td>
<td>4,144 - 14,340</td>
<td></td>
</tr>
<tr>
<td>Surgery fees for hip fracture</td>
<td>277 - 831</td>
<td></td>
</tr>
<tr>
<td>Daily long term care (LTC) costs</td>
<td>71 - 128</td>
<td>59 - 70 (HRT65, NI, CaVD65, HRT50, CaVD50)</td>
</tr>
<tr>
<td>Extra LTC costs</td>
<td>20 - 50</td>
<td></td>
</tr>
<tr>
<td>Rehabilitation care</td>
<td>137.50 - 412.50</td>
<td></td>
</tr>
<tr>
<td>Calcium/vitamin D cost</td>
<td>0.0583 - 0.1183</td>
<td>0.1183 - 0.1749 (HRT65, NI, CaVD65, HRT50, CaVD50)</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>0.1645 - 0.2427</td>
<td>0.2427 - 0.2742 (HRT65, NI, CaVD65, HRT50, CaVD50)</td>
</tr>
<tr>
<td>Dispensing fee for &lt;65 year-olds</td>
<td>6.70 - 12.00</td>
<td></td>
</tr>
<tr>
<td>Dispensing fee for ≥65 year-olds</td>
<td>2.00 - 8.00</td>
<td></td>
</tr>
</tbody>
</table>
8.7.1 **Probability of Entering Long Term Care from the Community**

The probability of entering LTC from the community (from the well state) was derived from data available through Statistics Canada for these facilities (described in section 5.2.5). The data available from this publication made it difficult to define precise rates of new entries into LTC from the community since that data was not residential and not entry. In order to evaluate the impact on the uncertainty of entry into LTC, the probability was varied from 50% and 75% to 125% of the base case probability for entry from the community to a LTC facility, due to the limited detail in the data on admission to, and discharges from, LTC. The reason for using the 50% lower bound is that the probabilities used in our base case may have overestimated the rate of entry of women in the well state into LTC. The results of this sensitivity analysis is presented in Table 8.7. Varying the probability of entry into LTC from the well state had a slight impact on expected costs but did not alter the rank ordering of results.

8.7.2 **Probability of Receiving Home Care Post Discharge from the Acute Care Hospital**

The probability of being discharged from an acute care facility back to the community with home care or to rehabilitation care was obtained from the CIHI database (section 5.2.4). The reliability of data on the probability of receiving home care or rehabilitation from the CIHI database post discharge may be limited, due to the structured approach in which discharge data is collected. In order to account for this uncertainty, the probability of receiving home care was varied by -50% to +25% from the base case probability (Table 8.7). The rank order of the expected cost was not altered with these
Table 8.7 Expected costs under varying resource use probabilities, by management strategy (under 3% discount rate) per postmenopausal woman followed over a forty-year period.

*Expected cost by intervention over a 40-year period ($, 1996)*

<table>
<thead>
<tr>
<th>Outcome/Event</th>
<th>No Intervention</th>
<th>CaVD50</th>
<th>CaVD65</th>
<th>HRT 50</th>
<th>HRT 65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>5,942.50</td>
<td>6,359.81</td>
<td>5,937.54</td>
<td>7,330.14</td>
<td>5,763.59</td>
</tr>
<tr>
<td>Entry to LTC from the community state:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% of base case</td>
<td>6,025.62</td>
<td>6,462.63</td>
<td>6,023.09</td>
<td>7,462.47</td>
<td>5,746.28</td>
</tr>
<tr>
<td>75% of base case</td>
<td>5,979.77</td>
<td>6,406.66</td>
<td>5,970.77</td>
<td>7,390.34</td>
<td>5,746.28</td>
</tr>
<tr>
<td>125% of base case</td>
<td>5,912.14</td>
<td>6,320.31</td>
<td>5,901.60</td>
<td>7,277.27</td>
<td>5,686.39</td>
</tr>
<tr>
<td>Probability of receiving home care:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% of base case</td>
<td>5,939.92</td>
<td>6,357.69</td>
<td>5,935.23</td>
<td>7,328.69</td>
<td>5,634.41</td>
</tr>
<tr>
<td>125% of base case</td>
<td>5,943.80</td>
<td>6,360.88</td>
<td>5,938.69</td>
<td>7,330.87</td>
<td>5,637.28</td>
</tr>
<tr>
<td>Probability of receiving rehabilitation care:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% of base case</td>
<td>5,914.71</td>
<td>6,337.22</td>
<td>5,913.72</td>
<td>7,315.04</td>
<td>5,618.09</td>
</tr>
<tr>
<td>125% of base case</td>
<td>5,956.40</td>
<td>6,371.11</td>
<td>5,949.44</td>
<td>7,337.71</td>
<td>5,645.44</td>
</tr>
</tbody>
</table>

Strategies include calcium and vitamin D initiated at 50 (CaVD50), or 65 (CaVD65) years of age, or HRT initiated at 50 (HRT50) or 65 (HRT65) years of age.
alternate probabilities with only small changes in the absolute results. Varying this probability does not have a significant impact on the model results.

8.7.3 Probability Of Rehabilitation Care Post Discharge From The Acute Care Hospital

The probability of being discharged from an acute care facility back to the community with rehabilitation care was varied to evaluate its impact on the expected cost of each intervention. In order to test the sensitivity of this assumption the probability of receiving rehabilitation care was varied by -50% to +25% from the base case probability (Table 8.7). The lower probability range was set to 50% below the base case probability to test the impact that this would have on expected cost if rehabilitation was offered to half of the current hip fracture patients. The focus on streamlining resource use within the health care system has resulted in a more careful allocation of resources. The objective of this increased pressure on resource has resulted in fewer cases being allocated to more labour intense programs (i.e. rehabilitation care) if the medical staff feels that an individual will not benefit from the intervention. Consequently a conservative increase of 25% above the base case was estimated as the upper range for sensitivity testing. The rank order of the expected cost was not altered even though the range of probabilities was varied substantially. Similarly, the relative magnitude of change in the expected cost was minor over the probability range tested. This analysis demonstrated that varying the probability of the rehabilitation resource use did not have a significant impact on the model results.
8.8 SENSITIVITY ANALYSIS ON INTERVENTION EFFECTIVENESS

The efficacy of HRT strategies in preventing hip fractures as well as their associated impact on breast cancer and CHD sequelae for the base case have been summarized in Table 2.6. Uncertainty exists surrounding the efficacy of each strategy on outcomes and sequelae. Consequently, sensitivity analyses were conducted on the efficacy of CaVD intervention on preventing hip fractures, and the associated impact of HRT intervention on preventing hip fractures and CHD events, while increasing the risk of breast cancer development and death.

8.8.1 Impact of Varying the Efficacy of Calcium/Vitamin D and HRT Strategies on Cost and Outcomes Under the Pessimistic Scenario

Calcium/vitamin D (CaVD) therapy in the base case analysis was assigned a 20% risk reduction (RR) on hip fractures versus the rate in the no intervention arm. The efficacy of CaVD in preventing hip fractures under pessimistic conditions was set to 5% RR reduction (Section 6.2.6). Since CaVD was assumed not to have an impact on CHD and BrCA, the risks of these events remained the same as in the base case scenario. In the pessimistic scenario HRT was assumed to have a RR reduction of 31% on hip fractures as supported by the literature. HRT's impact on CHD risk reduction in the pessimistic scenario was set to 17% (base case 40% reduction in risk). The risk of breast cancer was also increased to 76% (base case 46%). The results of the pessimistic scenario for both the CaVD and HRT interventions are summarized in Table 8.8. The data from the pessimistic scenario are also presented via the quadrant diagram (introduced in section 8.5) in Figure 8.16.
Table 8.8 Incremental costs and life years gained of each strategy relative to no intervention under pessimistic assumptions.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Pessimistic (3% discount rate) ($)</th>
<th>Incremental costs (versus no intervention) ($)</th>
<th>Life Years Last (3% discounting)</th>
<th>Incremental LYG</th>
<th>Incremental cost-effectiveness ratio to NI ($/LYG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. No intervention (NI)</td>
<td>5,942.50</td>
<td>-</td>
<td>3.7799</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>B. CaVD50</td>
<td>6,676.78</td>
<td>734.28</td>
<td>3.7788</td>
<td>0.0011</td>
<td>667,527*</td>
</tr>
<tr>
<td>C. CaVD65</td>
<td>6,184.53</td>
<td>242.03</td>
<td>3.7790</td>
<td>0.0009</td>
<td>268,922*</td>
</tr>
<tr>
<td>D. HRT50</td>
<td>8,039.55</td>
<td>2097.05</td>
<td>3.7756</td>
<td>0.0043</td>
<td>487,686*</td>
</tr>
<tr>
<td>E. HRT65</td>
<td>6,283.72</td>
<td>341.22</td>
<td>3.7357</td>
<td>0.0442</td>
<td>7,720</td>
</tr>
</tbody>
</table>

* It should be noted that a small efficacy produces large cost-effectiveness (CE) ratios. The calculation of CE ratios when incremental cost or effectiveness values are very small, should be interpreted with caution. Strategies include calcium and vitamin D initiated at 50 (CaVD50), or 65 (CaVD65) years of age, or HRT initiated at 50 (HRT50) or 65 (HRT65) years of age.
Figure 8.16 Cost versus efficacy plot under pessimistic assumptions for four treatment scenarios versus the no intervention strategy.

(Strategies include calcium and vitamin D initiated at 50 (CaVD50), or 65 (CaVD65) years of age, or HRT initiated at 50 (HRT50) or 65 (HRT65) years of age.)
In the pessimistic scenario all four interventions were in the north-east quadrant. The CaVD50, CaVD65, HRT50, and HRT65 intervention were more costly and more effective than the no intervention (NI) strategy. As discussed in section 8.5, interventions that lie in the north-east quadrant provide more effective treatment at higher cost compared to NI. The CaVD50 intervention provides a marginally more effective (0.0011 LYG) strategy at higher cost ($734.28). Similarly, the HRT50 strategy and CaVD65 strategies provide marginally better efficacy (0.0043 and 0.0009 LYG respectively), at increased cost ($2,097.05 and $242.03 respectively) compared to the NI strategy. The HRT65 intervention on the other hand is more effective (0.0442 LYG) and costs more ($341.22) than NI, but has a favourable incremental cost-effectiveness ratio of $7,720/LYG.

8.8.2 Impact of Varying the Efficacy of Calcium/Vitamin D and HRT Strategies on Cost and Outcomes Under the Optimistic Scenario

The optimistic impact of CaVD on hip fracture prevention have been set to 35% (section 6.2.6). The impact of CaVD on CHD and BrCA was assumed not to change from the base case for CaVD due to the lack of evidence to support CaVDS role in modifying the risk of these events. HRT’s optimistic impact on hip fracture risk reduction was assumed to be 70% based on the literature review. HRT’s impact on CHD risk reduction in the optimistic scenario was set to 57% (base case 40% reduction in risk). The risk of breast cancer was also set to 20% (base case 46% increase in risk). The results of the optimistic scenario for both the CaVD and HRT interventions are summarized in Table 8.9. The data from the optimistic scenario are also presented via the quadrant diagram (introduced in section 8.5) in Figure 8.17.
Table 8.9 Incremental costs and life years gained (LYG) of each strategy relative to no intervention for a postmenopausal woman followed over forty years under optimistic assumptions.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Optimistic Costs ($, 3% discount rate)</th>
<th>Incremental costs (versus no intervention)</th>
<th>Life Years Lost (3% discounting)</th>
<th>Incremental LYG</th>
<th>Incremental cost-effectiveness ratio to NI ($/LYG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. No intervention (NI)</td>
<td>5,942.50</td>
<td>-</td>
<td>3.7799</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>B. CaVD50</td>
<td>6,041.53</td>
<td>99.03</td>
<td>3.7722</td>
<td>0.0077</td>
<td>12,861</td>
</tr>
<tr>
<td>C. CaVD65</td>
<td>5,684.15</td>
<td>(258.35)</td>
<td>3.7736</td>
<td>0.0063</td>
<td>DOMINANT</td>
</tr>
<tr>
<td>D. HRT50</td>
<td>6,597.81</td>
<td>655.31</td>
<td>3.5467</td>
<td>0.2332</td>
<td>2,810</td>
</tr>
<tr>
<td>E. HRT65</td>
<td>5,241.84</td>
<td>(700.66)</td>
<td>3.5827</td>
<td>0.1972</td>
<td>DOMINANT</td>
</tr>
</tbody>
</table>

Strategies include calcium and vitamin D initiated at 50 (CaVD50), or 65 (CaVD65) years of age, or HRT initiated at 50 (HRT50) or 65 (HRT65) years of age.
Figure 8.17 Cost versus efficacy plot under optimistic assumptions for four treatment scenarios versus the no intervention strategy.

(Strategies include calcium and vitamin D initiated at 50 (CaVD50), or 65 (CaVD65) years of age, or HRT initiated at 50 (HRT50) or 65 (HRT65) years of age.)
In the optimistic scenario two interventions were in the north-east quadrant and two were in the south-east quadrant. The CaVD50 intervention was more costly and more effective than the no intervention (NI) strategy. The HRT50 strategy was the most effective of all four strategies, however it was also the costliest. As discussed in section 8.5, interventions that lie in the north-east quadrant generally provide more effective treatment however a trade-off exists with higher cost. The CaVD50 intervention provides a marginally more effective (0.0077 LYG) strategy at higher cost ($99.03). On the other hand the HRT50 strategy provides superior efficacy (0.2332 LYG), at increased cost ($655.31). Calculation of incremental cost-effectiveness ratios for these two interventions, (compared to the NI strategy) in the north-east quadrant, are $12,861/LYG and $2,810/LYG for the CaVD50 and HRT50 interventions respectively. These low cost-effectiveness ratios are considered as compelling evidence for adoption.

Evaluation of the two intervention in the south-east quadrant indicate that both the CaVD65 and HRT65 are dominant over NI since they are both less costly and more effective than the NI strategy. The CaVD65 intervention is cost saving ($258.35 less than the NI strategy) and marginally more effective (.0063LYG). On the other hand the HRT65 intervention is the most cost-saving of all interventions ($700.66) and more effective (0.1972 LYG). The HRT65 strategy dominates the CaVD65 intervention.
9. DISCUSSION

9.1 Overview

A forty year Markov model was developed to evaluate the cost effectiveness of supplementation with calcium/vitamin D or HRT in Canadian postmenopausal women. The economic value of five potential interventions for the prevention of osteoporotic hip fracture in Canadian postmenopausal women were estimated in this analysis. All interventions were continued until death or until these women were 90 years of age, and assumed 100% compliance to the assigned regimen. The events monitored were hip fracture, breast cancer, and CHD. The model assumes that all hip fracture events are osteoporosis-related and hence sensitive to the treatment strategies.

The primary hypothesis of this thesis is that supplementation with calcium and vitamin D or treatment with hormone replacement therapy in Canadian postmenopausal women will result in fewer medical events and lower overall healthcare cost than no intervention if therapy is initiated shortly after menopause. The results of the economic evaluation of calcium and vitamin D intervention initiated at menopause (CaVD50) did result in fewer medical events (hip fractures), however at higher health care costs than no intervention with a prohibitive cost-effectiveness ratio of $94,843/LYG. Initiation of hormone replacement therapy at the menopause (HRT50) also resulted in fewer hip fractures and deaths due to coronary heart disease (CHD) than no intervention, however this intervention resulted in more breast cancer deaths, and cost more than the no intervention strategy. The cost-effectiveness ratio of the HRT50 strategy was calculated as $10,969/LYG, and is considered favourable for adoption by health care systems (Laupacis et al, 1992). Thus particularly for CaVD, the data did not support the primary
hypothesis since the high costs for this intervention could not offset the small benefits in hip fracture prevention from a purely economic viewpoint. Weaker support of the hypothesis is provided for the HRT50 strategy in that it costs more than the NI approach, but the cost-effectiveness ratio would be considered favourable.

The secondary hypothesis is that delay of supplementation (by 15 years) beyond the initiation of the menopause will result in more medical events and additional costs than supplementation initiated shortly after menopause. Initiation of calcium and vitamin D at age 65 years (CaVD65) did result in six more hip fractures per 1000 postmenopausal women than therapy initiated at age 50 years (CaVD50) (Table 8.4). However the CaVD65 strategy cost less ($5,937.56) per postmenopausal woman than both the CaVD50 strategy ($6,359.79) and no intervention ($5,942.50) approaches (Table 8.3). The HRT65 strategy resulted in more hip fractures and deaths due to CHD than the HRT50 strategy, however this intervention resulted in fewer breast cancer deaths and cost less than both the HRT50 and the NI approaches (Table 8.3 and Table 8.4). Thus once again the hypothesis was not supported in this evaluation. Clearly the annual cost savings for both CaVD65 and HRT65 strategies outweighed the cost of the treatment for the additional medical events captured. Hence the analyses presented strongly support the delay of initiation of therapy to age 65, from a purely economic viewpoint.

The economic analysis found that weak dominance was observed with the calcium/vitamin D strategy initiated at age 65 (CaVD65), over the no intervention (NI) approach, since CaVD65 had about the same cost but slightly lower mortality (lower number of life years lost (LYL)) than NI. HRT initiated at age 65 (HRT65) was dominant over the other management strategies under the base case assumptions. Trade-offs
existed when considering initiation of therapy at age 50 (CaVD initiated at 50 years (CaVD50), and HRT initiated at age 50 (HRT50) over the NI arm, since both of these strategies cost more, however they resulted in fewer LYLs. The incremental cost-effectiveness of the two management strategies initiated at age 50 over the NI arm were calculated. The cost-effectiveness ratios were $94,843/LYG and $10,969/LYG for the CaVD50 and HRT50 strategies relative to NI respectively.

9.2 Expected Event Occurrence

Hip fracture occurrence, as well as deaths due to breast cancer and CHD were quantified using the osteoporosis model under base case assumptions (Table 7.7), and presented in Table 8.4. Review of the distinct profile of events for each treatment strategy demonstrates the trade-offs between these intervention arms. The CaVD strategy has a modest effect in preventing hip fractures and was assumed to not impact on either CHD or breast cancer events. HRT has a favourable hip fracture and CHD prevention profile, while its potential for increased incidence of breast cancer means that women will have to trade off these events when deciding which treatment alternative is best for them. The base case assumptions as well as those used for the pessimistic and optimistic scenarios are summarized in Table 9.1. The event data generated by the model will be discussed in detail in the sections that follow.
Table 9.1 The impact of CaVD supplementation and hormone replacement therapy on hip fractures, coronary heart disease and breast cancer in Canadian postmenopausal women under base case, optimistic and pessimistic scenarios.

<table>
<thead>
<tr>
<th></th>
<th>Base case scenario</th>
<th>Optimistic scenario</th>
<th>Pessimistic scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hip fracture</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CaVD</td>
<td>-20%</td>
<td>-35%</td>
<td>-5%</td>
</tr>
<tr>
<td>• HRT</td>
<td>-50%</td>
<td>-70%</td>
<td>-31%</td>
</tr>
<tr>
<td><strong>CHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CaVD</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>• HRT</td>
<td>-40%</td>
<td>-57%</td>
<td>-17%</td>
</tr>
<tr>
<td><strong>Breast</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CaVD</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>• HRT</td>
<td>+46%</td>
<td>+20%</td>
<td>+76%</td>
</tr>
</tbody>
</table>

- : indicates a reduction in relative risk  + : indicates an increase in relative risk
9.2.1 **Hip Fracture Events**

Each of the management strategies had a lower incidence of hip fracture events than the no intervention arm (Table 8.4). Of the four active treatment strategies examined, CaVD65 provided the least protection in terms of hip fracture events. Initiation at age 50 years decreased the number of hip fractures, but CaVD was never as efficacious as HRT no matter the age of initiation of therapy. The CaVD management strategy had the third lowest number of hip fractures (165) per 1000 women who initiated therapy at age 50. The CaVD65 management strategy had the highest number of hip fractures of the four active treatment arms (171 fractures), but still resulted in fewer fractures that were observed in the NI arm (205 hip fractures). Clearly the HRT management strategy initiated at 50 years under the base case assumptions had the smallest number of hip fractures in both community and LTC residing women, in which a rate of 111 fractures per 1000 women was observed when treatment was initiated at age 50. The base case assumption was that the HRT treatment arm would offer a 50% reduction in hip fracture initiating after 5 years of treatment (a five year onset of effect) (Table 7.7). Commencing HRT at age 65 had a smaller impact on hip fracture prevention, however this strategy had the next lowest number of hip fractures (i.e. 124). In comparison, there were 205 hip fractures from both community and LTC residing women who did not take any form of preventative therapy (the NI arm).

Initiation of therapy earlier (i.e. at age 50 years) in both the CaVD and HRT strategies resulted in fewer fractures. Evaluating the prevention of hip fractures in isolation (without the consideration of cost or other events relating to the therapy) would result in a compelling argument for initiation of preventative strategies at 50 years.
9.2.2 **Breast Cancer Events**

The model evaluated the impact of therapy on the development and death due to breast cancer. CaVD management strategies were assumed not to have an impact, however HRT use has been associated with an increased risk of breast cancer incidence (Colditz et al, 1995; Zhang et al, 1997). The impact of the HRT management strategy is influenced by the duration of treatment. In the thesis model, a 46% increase in breast cancer risk was assumed following ten years of HRT therapy (Col et al, 1997). The breast cancer deaths captured under the base case analysis in the thesis model are presented in Table 8.4, with an incremental 14 deaths, and 7 deaths (versus the NI strategy) per 1000 postmenopausal women treated in the HRT50 and HRT65 management strategies respectively.

The analysis recognized that not all women who develop breast cancer die. Indeed, the costing approach used exacted a “toll” (cost) for each BrCA death which reflected the cost of treating those women who develop BrCA but survive. This approach was utilized to confine the number of states in the model. Hence values for total number of women developing BrCA cannot be derived from the model, but clearly exceed those associated with death.

9.2.3 **Coronary Heart Disease Events**

The impact of the interventions on CHD deaths was also captured in the model. The NI, CaVD50 and CaVD65 strategies were considered not to have an impact on CHD consequently only the HRT strategies were affected by efficacy assumptions. Under the base case assumptions the HRT strategies were the most effective in preventing deaths.
with 58 and 54 fewer CHD deaths under the HRT50 and HRT65 management strategies respectively compared to NI. CHD is a costlier and more frequent event in Canada from both a resource use and mortality impact than osteoporosis or breast cancer (Zowall et al, 1992; Statistics Canada 1992). Indeed when the model was run eliminating CHD and BrCA events, HRT was no longer a dominant strategy (data not shown) demonstrating that the benefits of HRT use lie more in the CHD rather than the osteoporosis domain.

9.3 Sensitivity Analysis

Extensive sensitivity analysis on costs, event occurrence, and efficacy of therapy resulted in switches from strategy dominance to trade-offs between higher cost and better outcomes. Sensitivity analyses were conducted on the base case assumptions in the model to evaluate the potential impact on the results of uncertainty surrounding the costs and probabilities used in the model. The results of the sensitivity analyses surrounding the costs in the model demonstrated that the results were sensitive to the cost of the CaVD supplement, HRT, long-term care, and hip fracture repair. Extensive sensitivity testing over reasonable ranges on the costs of physician visits, pharmacist’s fee, orthopedic surgery on the hip, home care, rehabilitative care, breast cancer treatment, and CHD treatment had minor impact on the absolute cost results but did not alter the relative ranking of costs across management strategies. In the base case analysis, the CaVD65 strategy exhibited weak dominance, and the HRT65 strategy was dominant with a lower cost and greater efficacy than the no intervention arm (Table 8.5).

The probability of event occurrence was also evaluated via sensitivity analyses. Events tested included probability of entering long term care facilities from the
community (independent of having a hip fracture), receiving home care following a fracture, and receiving rehabilitation care (Table 8.7). The results from these analyses indicate that the uncertainty surrounding these events did not have an impact on the original rank-ordering of the five strategy arms evaluated.

Lastly, sensitivity analyses on the effectiveness of the strategies and their impact on hip fracture prevention, and deaths resulting from breast cancer and CHD were conducted. These sensitivity analyses resulted in shifts of rank order from the base case analyses. In general, lowering the effectiveness of CaVD management strategies (pessimistic assumptions) resulted in less compelling economic arguments for implementation of the CaVD interventions at both 50 and 65 years of age (Table 8.8). Increasing the effectiveness of CaVD in preventing hip fractures (optimistic assumptions), from the base case value, resulted in a more compelling justification for implementation of these management strategies (Table 8.9). Minimizing the CHD and hip fracture benefits from the HRT interventions and increasing the breast cancer risk (pessimistic assumptions), resulted in the loss of dominance of the HRT65 strategy, and made the HRT50 dominated by NI (Table 8.8). Lowering the probability of hip fracture, CHD and breast cancer in the HRT strategies (optimistic assumptions) provided more favourable arguments for the use of HRT at both ages (Table 8.9). The discussion will focus on each of these results in the subsequent sections.

9.3.1 Calcium/vitamin D Cost

Varying the range of costs in the model demonstrated that the model results were sensitive to CaVD acquisition cost (Figure 8.4) with cross-over occurring at $0.054 and
$0.1183. Daily cost of CaVD below $0.054 per day, will result in lower expected cost of the CaVD65 strategy than the no intervention and HRT65 strategies. At the lower range of the CaVD sensitivity analysis ($0.0583/day) the CaVD50 strategy has the same expected cost as the no intervention strategy. In order for the current costs of calcium and vitamin D to drop below the lower threshold value ($0.054) from the current cost of $0.1166, manufacturers will need to reduce the cost by 50% below current values. This is an unlikely event since these products have been generically available for a number of years, and their unit cost is low (on the order of 3-5 cents a tablet). Daily cost of CaVD above $0.1183 per day, will result in a higher expected cost of the CaVD65 strategy than no intervention strategy. Currently calcium and vitamin D are readily available at a cost of $0.1166/day. In the current environment increases in costs on these types of products have been on the order of 3% per annum (Drug Trading, 1997). If CaVD acquisition cost increases at this rate it is highly likely that this threshold will be reached and that the CaVD65 strategy will have a higher expected cost than the NI arm (Figure 8.4), resulting in the strategy switching in position from weak dominance to a trade-off over NI; that is that the CaVD65 strategy will have a higher expected cost than NI, however it will result in fewer hip fractures and LYG versus the NI strategy. It should be noted that the difference between the CaVD65 and NI expected cost at the upper range of the sensitivity analysis ($0.1749) is very small $160.05. If the cost of CaVD was set to $0.1458 (25% above the current base case value) then the incremental cost-effectiveness ratio of the CaVD65 strategy will be $21,655/LYG (a cost-effectiveness ratio that is considered to be favourable). The ranking of the CaVD50 strategy does not change over the sensitivity range tested.
9.3.2 HRT Cost

HRT acquisition cost has also been identified as being a sensitive variable in the model (Figure 8.5). Increasing HRT cost resulted in increased expected costs for both the HRT50 and HRT65 strategies. Currently the daily base case cost of generically-available HRT is $0.1828. The sensitivity analysis demonstrated that when the daily cost of HRT was increased above $0.2427, that the HRT65 strategy had a higher expected cost than the no intervention and CaVD65 arms, resulting in a loss in the dominance of the HRT65 strategy. The increase in HRT cost from the base case to $0.2427 would represent a 33% increase in cost. This increase is unlikely to occur in the current environment of drug price regulation in Canada, however the results of this sensitivity analysis has implications for other ovarian hormonal therapy available in Canada. A number of OHT products are currently available in Canada, however their acquisition costs range from that quoted as the base case of the thesis analysis to those exceeding the threshold value ($0.2444) of the sensitivity analysis. Clearly improved health benefits relative to HRT would have to be demonstrated in these more costly preparations in order to justify their use.

9.3.3 Pharmacist Dispensing Fees

Pharmacist dispensing costs also demonstrated an impact on the expected cost of the HRT strategies. The base case dispensing fees used in the analysis was $9.80 for women under the age of 65 years based on the average dispensing fee charged to cash-paying customers (Weids et al, 1997), and $6.11 based on the amount reimbursed to pharmacists in Ontario by the Ontario Drug Benefits plan, for each prescription filled by
women aged 65 years and over. Varying the dispensing fee from $6.70 to $12.00 in women under 65 years of age did not have an impact on altering the order ranking of the strategies (Figure 8.6). In those women 65 years of age and over, when the dispensing fee ranged from $2.00 to $8.00, no thresholds were reached (Figure 8.7). A threshold in the dispensing cost appeared to be imminent between the HRT65, CaVD65 and No Intervention strategies above $8.00, however it is not typical for women in this age category to pay more than an $8.00 dispensing fee. Above this threshold the expected value of HRT65 would not be the lowest, but would become higher than that of the NI and CaVD65 management strategies. If the dispensing fee was at $12.00, then the HRT65 strategy would cost more than NI, however it would have a lower LYL than the NI and CaVD65 intervention, and a cost-effectiveness ratio of approximately $2,400/LYG. Dispensing fees in community practice have in recent years been either stable or increasing only modestly. The provincial drug plans over the last three years have either maintained their dispensing fee level, or have effectively reduced it by introducing patient co-pays. Third-party payer insurance plans have also limited their ceiling on dispensing fees, however these are typically higher than the fees reimbursed by provincial plans. Although dispensing fees may generally rise in the future, it is anticipated that these increases will be modest.

9.3.4 Cost of Hip Fracture Repair

The base case cost of hip fracture repair was set at $10,745. This cost was varied in the sensitivity analysis from $5,182 to $16,100. This analysis demonstrated that as the cost of hip fracture repair increased from the lowest range that the expected costs of all
strategies increased with a cross-over occurring at $5,450 (50% below the base case cost). At a cost for hip fracture repair below this threshold the no intervention strategy was the lowest followed by the HRT65, CaVD65, CaVD50 and HRT50 strategies. At a cost above the threshold value the HRT65 strategy had the lowest expected cost followed by the no intervention, CaVD65, CaVD50, HRT50. Similarly a crossover occurred between no intervention and CaVD65 at an expected cost of $5,920 and a cost of hip fracture below $10,600. It is anticipated that the cost of repairing a hip at the acute care setting will decrease in future years from its current level since the length of stay (LOS) in these institutions has been decreasing steadily over the last fifteen years (Jaglal et al, 1996). It is however difficult to estimate what the mean cost will be for hip fracture patients based on costs at the acute care setting, since reduced LOSs may result in higher expenditure at the other levels of care beyond the acute event. Consequently, it is anticipated that this level of care will be higher than the lower threshold cost of $5,450, and possibly over the second threshold of $10,600, if one considers the other services that a hip fracture patient uses beyond the acute care stay. In conclusion it is cautioned that sensitivity analysis of isolated events in the management of a hip fracture patient may result in erroneous conclusions concerning the cost-effectiveness of an intervention.

9.3.5 Entry into LTC facilities from the community

Additional sensitivity testing on events including varying the admission rates to LTC facilities from community dwelling post menopausal women did not have an impact on the rank order of the strategies under base case assumptions (Table 8.7). This variable had a greater level of uncertainty surrounding its collection since information on LTC and
residential care facilities in Canada is currently poor. It is anticipated that more precise data will be available over the next five years, since these facilities are now mandated to initiate collection of more detailed statistics, other than sex and age on its residents.

The model was also run in a separate analysis to evaluate the impact of LTC costs if all admissions to LTC (those who entered these facilities from the community who did not fracture their hip) were included. The expected values in the model jumped from $6,000 to approximately $40,000 for the forty year model highlighting the burden of this resource to the social services/health-care system budget. Indeed, the costs of LTC to the general population were of such a large magnitude that they masked any potential benefit of any of the treatment strategies evaluated. Consequently in the version of the model used in the thesis only LTC admissions as a result of the fracture event were costed and included in the analysis.

9.4 Comparison With Other Cost-Effectiveness Studies

The cost-effectiveness of osteoporosis therapies have been conducted under a number of clinical scenarios and perspectives. The following section highlights some of the key analyses in this field, in order to place the thesis analysis into perspective.

9.4.1 Cost-effectiveness of HRT Management Strategies

Published cost-effectiveness studies have different assumptions about the benefits, and risks of therapy than the thesis model, since the costs and probabilities are generally reflective of practice patterns of the United States. Similarly some of these studies used
bone mineral density (BMD) screening prior to therapy assignment. Hence comparison of the thesis results to published studies are generally not directly comparable.

Total costs for the management of these diseases using the osteoporosis model over a forty year period ranged from $5,763.59 to $7,330.14, per 1,000 postmenopausal women, depending on the intervention (Table 8.1). HRT initiated at 65 years was the intervention option (under base-case assumptions) that was the least costly from the health care system perspective at $5,763.59 using a 3% discount rate. Since the NI approach was evaluated at $5,942.50, HRT therapy initiated at age 65 is cost-saving. In contrast, initiating HRT at 50 years of age was more costly ($7,330.14); nevertheless it resulted in a decreased level of LYL and would be considered cost-effective with a ratio of $10,969/LYG. These findings are supported by a number of other published studies.

Tosteson and Weinstein (1990), concluded that screening women by use of BMD testing to establish their risk for osteoporosis followed by treatment with HRT was a cost-effective intervention, if therapy was initiated at age 50, in a higher risk population. In their analysis however they did not include the CHD benefits associated with HRT, nor the associated potential risk of breast cancer with this therapy. Under their base assumptions, they calculated ratios of $11,700/LYG and $22,100/LYG (1987 $US) in higher risk patients if therapy was initiated at age 50, for a duration of 15 years. Universal treatment of women at age 50 for 15 years resulted in a cost-effectiveness ratio of $68,900/LYG (1987 $US). Thus, the overall conclusions from their study would indicate that initiating HRT therapy at age 50 would only be cost effective when combined with screening. Indeed, as discussed later, when the CHD benefits of HRT was removed from the thesis model, a poor cost-effectiveness ratio was also observed.
Cheung and Wren (1992) evaluated the cost-effectiveness of treating 50 year-old women using a cost-effectiveness economic model. In their model the impact of HRT on CHD was included, under a variety of treatment conditions. Their analysis supported use of HRT if treatment was initiated at age 50 for their lifetime, with cost-effectiveness in the range of $10,000/LYG.

The Office of Technology Assessment (1995) in the United States recently completed a cost-effectiveness analysis on HRT. They concluded that without screening women at the menopause and placing them on long-term therapy resulted an incremental cost-effectiveness of $23,000/LYG ($US, 1993). This cost-effectiveness ratio is higher than the value calculated by the thesis model since a number of base case assumptions differed and unit costs were greater (a combination of factors reflective of the differences in the healthcare systems between the two countries).

Recently, a review of 21 published economic evaluations of treatments for the prevention of osteoporosis was conducted (Torgerson and Reid, 1997). The general finding was that treatment initiated at age 50 was cost-effective, however the authors conclude that interventions started closer to the fracture event will be the most cost-effective. They concluded that initiation of therapy in women at age 65 under a number of treatment conditions is likely to be a cost-saving alternative.

A number of other studies came to similar conclusions when HRT was initiated at age 65 and treatment duration was of 10 years or longer. Daly et al (1992), concluded that long-term prophylactic treatment of women is a cost-effective treatment strategy. They found that the majority of the benefit to a favourable cost-effectiveness ratio they found was due to HRT's impact on reducing CHD events. Their conclusions were
reflective of the findings presented in this thesis through the sensitivity analysis of the model, in which the cost-effectiveness of HRT under both HRT50 and HRT65 strategies became unfavourable when its cardioprotective effects were removed (Table 8.11).

In summary, the data from the thesis model are consistent with the health economic data in the literature. The initiation of the strategies at age 50 are more costly, but they resulted in decreased LYL. A delay in initiation of the intervention becomes a more cost-effective therapy option and may also result in the intervention being cost-saving. Comparison of the results from this Canadian model with models evaluating the impact of these interventions in other industrialized countries have shown that we have generated similar results. These favourable comparisons have been used to validate our model as an acceptable method by which other therapeutic interventions for osteoporosis can be examined.

9.4.2 Cost-effectiveness of Calcium/Vitamin D Management Strategies

In general the application of economic evaluations to assess the effectiveness of nutritional interventions is lacking. This thesis is unique in that a nutritional approach for the prevention of osteoporosis has been evaluated using health economics principles. Clinical trials in which calcium and vitamin D intervention have been studied in the prevention of osteoporosis are limited in number in comparison to those using HRT (Torgerson et al, 1997); evaluation of this intervention using health economics principles are even fewer. Torgerson and Kanis (1995), using the hip fracture outcome data from two calcium and vitamin D trials (Chapuy et al, 1992; Heikinhimo et al, 1992 - discussed in section 2.7.2.2), and the epidemiological survey from the Trent region of England,
evaluated the cost-effectiveness of calcium/vitamin D intervention. The targets for the intervention were women residing in nursing homes or those with a body mass index (BMI) < 20 kg/m² in whom a risk of hip fracture was 1.77 times that of the general population was assumed. In their analysis they evaluated the cost per hip fracture avoided, and did not evaluate a cost per life year saved. The ratio of cost per hip fracture avoided ranged from ≤17,349 in the general population to cost-saving in those women who were institutionalized and had a low BMI. That is, on the surface, their data would be more supportive of screening and implementation of treatment in high risk individuals rather than supplementation of all post menopausal women.

It is important to place the outcome of this analysis into the context of the results obtained here. That is, the thesis model supports population supplementation of all women at age 65, but not at age 50. The better performance of CaVD interventions in the thesis model are most probably reflective of the costing procedures used. That is, Torgerson and Kanis (1995) limited their evaluation to those costs associated with the acute care setting while our model includes more extended costs associated with fracture including home care, rehabilitation care and entry into LTC. Not surprisingly, the broader the costing analyses (which is more reflective of the true burden of cost), the better the cost-effectiveness ratio of the intervention. Torgerson and Kanis limited their scope to a cost per fracture avoided, and did not calculate the more comprehensive cost-effectiveness ratio of cost per life-year gained.

The thesis model is the first attempt that we are aware of that has evaluated the value of calcium/vitamin D intervention in postmenopausal women to the Health System.
The uniqueness of this approach is attributed to five original research elements which have been applied to a nutritional intervention for the first time. The five elements are:

i) the estimation of the incidence of hip fractures by age and sex in Canadians (Papadimitropoulos et al, 1997),

ii) the costing of hip fracture, myocardial infarcts, and other ischemic events at the acute care setting,

iii) involvement in a burden of illness study in breast cancer (Earle et al, 1997),

iv) the conduct of a meta-analysis on calcium and vitamin D intervention using the Cochrane Collaborative process (Papadimitropoulos et al, 1997b), and

v) the establishment of a Markov decision model which is reflective of the impact of osteoporosis preventative interventions on Canadian women (Papadimitropoulos et al, 1998).

The results from the thesis model for HRT interventions are consistent with published osteoporosis models conducted in both the United States and Europe. This finding supports the validity of our model for the HRT intervention, and it is highly likely that the CaVD intervention evaluations are equally plausible. The results of our CaVD interventions are also likely to cross international boundaries (external validity), since the model’s HRT strategy evaluations were producing comparable cost-effectiveness ratios to those found in United States and Europe.
9.5 Cost-Effectiveness Of Strategies Evaluated In The Model

The cost-effectiveness of the five strategies under the base case assumptions were summarized in Table 8.5, with the CaVD65 exhibiting weak dominance while the HRT65 strategy being dominant. The CaVD50 ($94,843/LYG), and the HRT50 ($10,969/LYG) strategies had trade-offs. Varying the base case assumptions on the efficacy of these strategies on the prevention of hip fractures altered the ranking of the strategies (Tables 8.5, 8.7, and 8.8).

Table 9.2 provides a bottom-line summary of the analyses at the cost-effectiveness/dominance level under variable effectiveness assumptions. As discussed previously the CaVD65 management strategy is considered to have weak dominance under the base case assumptions, and dominance under the optimistic scenario. Under the pessimistic scenario the cost-effectiveness ratio is considered to be too high ($268,922/LYG) to support adoption. The CaVD50 strategy under base case assumptions is not considered a cost-effective alternative ($94,843/LYG) for the prevention of hip fractures in postmenopausal women.

The HRT65 strategy is dominant under the base case assumptions. Similarly this strategy remains dominant when the efficacy parameters are set to their optimistic assumptions. The HRT65 strategy is not considered a cost-saving strategy if the efficacy parameters are set to their pessimistic assumptions, however the incremental cost-effectiveness ratio is small ($7,720/LYG) and provides compelling argument for adoption (Laupacis et al, 1992). That is, it has been argued that cost-effectiveness ratios below $20,000/LYG should be considered for adoption.
Table 9.2  Cost-effectiveness of the four active management strategies versus no intervention using variable efficacy assumptions, for the prevention of hip fractures in Canadian postmenopausal women.

<table>
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<th>Outcome/Event</th>
<th>No Intervention</th>
<th>CaVD50</th>
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<th>HRT65</th>
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<tr>
<td>Base Case</td>
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<td>$12,861/LYG</td>
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*It should be noted that a small efficacy impact divides these incremental cost values, consequently the confidence around the cost-effectiveness ratios is weak.
The HRT50 prevention strategy was considered to be a strategy that typically cost more than the NI arm, however the HRT50 outcome provided additional benefits over the HRT65 strategy by avoiding an additional 13 hip fractures and 4 deaths due to CHD. It should be noted that this number does not include the survivors of these events, however the costs associated with the occurrence of these events in those who survive are captured and incorporated into the model results. The only draw back with the HRT50 therapy over the HRT65 therapy is that it resulted in an additional 7 breast cancer deaths. Under the base case and optimistic scenarios the cost-effectiveness ratios of the HRT50 strategy were $10,969/LYG and $2,810/LYG respectively. The magnitude of these incremental cost-effectiveness ratios support adoption.

9.6 Caveats of Model Results

The economic model used in this thesis was based on a number of base case assumptions. A number of these assumptions were based on data that have been studied and well documented, while others were based on a limited number of studies or from databases that were under development. Sensitivity analyses were used to evaluate the impact that these uncertainties had on the bottom line results, and the implications for error were discussed.

The model assumed that mass implementation of these strategies were adopted. This scenario is artificial since a number of factors influence adoption of a strategy by a population. Educational background, biases for therapies available, affordability of the intervention (coverage on the drug plan), physician training/influence, and a myriad of other factors may limit adoption.
The efficacy of HRT in the prevention of osteoporosis has been studied under case control, cohort and the randomized clinical control settings. These studies have demonstrated the ability of HRT to maintain bone mass in postmenopausal women and prevent fractures at the hip and non-hip sites. Consequently, the assumptions used in the osteoporosis model on the efficacy of HRT on osteoporosis are well supported by numerous clinical publications, which have been reviewed using a structured process (Cochrane Collaboration). Other outcomes evaluated through these HRT trials and longitudinal cohort studies is its CHD protective effects, and the associated breast cancer risks.

Calcium/vitamin D efficacy data in osteoporosis prevention are limited. The data on these nutrients under clinical trial settings have been conducted principally in older and typically institutionalized postmenopausal women. The calcium/vitamin D meta-analysis was conducted for the thesis to evaluate the impact on bone mineral density changes in these women under clinical trial conditions. The probabilities for hip fracture prevention were derived from this analysis are from a few well conducted clinical trials. A renewed interest in calcium and vitamin D use in osteoporosis currently exists. More current trials are providing evidence for greater effectiveness of CaVD in preventing fractures than we have estimated in the meta-analysis, however their studies tend to be focused on the nursing home population in which a more frail population resides. These study conditions are likely to produce selection bias since these studies have been conducted on women with low bone BMD at initiation. The use of these agents on a frailer population may result in a greater fracture risk reduction than if the intervention
was implemented in a younger less frail population. Additional long-term studies are needed in younger, community dwelling postmenopausal women.

Initiation of the interventions evaluated were at either 50 or 65 years of age. The rationale for initiating therapy at 50 years was because this is the age at which women typically transition into the menopause and this is the time that they may seek symptomatic relief. As a result of this event women may be more willing to initiate therapy for menopausal symptom relief, and be persuaded by health care professionals to continue therapy long-term for HRT’s benefits in preventing CHD events and hip fractures. The 65 year old time point was chosen to coincide with two significant events in a woman’s life: entry to the pension/seniors category and generally a change in coverage for the woman’s drug plan (provincially funded primarily). The data for both CaVD and HRT interventions provided a more compelling economic argument for delaying the initiation of therapy. This finding raises the question at which age does the optimal osteoporosis intervention exist (ie most cost-effective/cost-saving). The thesis did not address this issue, however it should be noted that a delay in therapy initiation may result in a more compelling economic argument (and a much lower cost to the drug plan budget). However, the trade-off is that a larger number of hip fractures and cardiovascular events will occur as initiation of therapy is delayed.
9.7 Implementation of Strategies

9.7.1 Implementing Calcium/Vitamin D Therapy

Calcium and vitamin D therapy in the form of an oral supplement is widely available at reasonable cost. The evaluation of the CaVD50 and CaVD65 strategies demonstrated that although the CaVD50 strategy was not as cost-effective as any of the HRT strategies, the benefits of this intervention (i.e., hip fractures prevented) are greater than the NI arm. Unlike HRT, the CaVD strategies were assumed not to have CHD protective effects, however they lack the increased risk of development and death from breast cancer associated with HRT.

Calcium is required through the diet, the largest proportion of which is needed to support skeletal function. As discussed in chapter 2 of the thesis, considerable controversy exists surrounding the current level of calcium intake in Canadians by age and sex. The task of identifying the requirement or intake distribution for this mineral is monumental, with considerable activity in this area being expended in the last twenty years (Heaney, 1996; Poliquin et al, 1997). The lack of requirement and intake information make it difficult to estimate the prevalence of inadequacy in Canadian postmenopausal women (Beaton, 1994). Issues surrounding the calcium requirement in this group include the definition of basal requirements versus normative requirements for calcium. The basal requirements are defined as those that are adequate to maintain all demonstrable functions of the nutrient; normative requirements are those that are sufficient to maintain tissue stores (Beaton, 1996).

A number of organizations have recently suggested an increase in intake to optimal levels which are above the current RNIs. The Osteoporosis Society of Canada
recommended that the optimal intake in women \( \geq 50 \) years should be 1,500 mg of elemental calcium (OSC Advisory panel, 1996). Recently a report released by a combined United States and Canadian panel recommended dietary reference intakes (DRI) for calcium of 1,200 mg (Institute of Medicine, 1997). Since mean calcium intake (571 mg +/- 286; CSFII, 1994) is generally below the RNI in postmenopausal women, the issue becomes how does one achieve the DRIs? Similarly vitamin D status has been discussed to some length in chapter 2 of the thesis, with acknowledgement that vitamin D deficiency is a greater issue in older postmenopausal women due to a combination of reduced sunlight exposure and potentially impaired conversion of vitamin D to its active metabolite.

Implementation of the CaVD strategies suggested in the osteoporosis model (750 mg calcium, and 400 IU vitamin D\(_3\)), would result in higher total intakes in this target population. The population approach to supplementation taken in this thesis can result in issues related to toxicity. This is a potential concern since it has recently been documented that users of any supplement type, tend to have higher intakes of calcium than non-users (Slesinski et al, 1996). The three areas of concern are interference with absorption of iron, formation of kidney stones, and hypercalcemia.

It is currently thought that high calcium intakes via supplements or fortified foods may contribute to decreased bioavailability of minerals including iron, magnesium and zinc. Reduced absorption is believed to occur by a competitive mechanism in the gut (Whiting and Wood, 1997). Reduced bioavailability of iron may be sufficient especially in older institutionalized women to lead to anemia. It is suggested, although not formally studied, that an iron supplement be included in calcium supplemented women, to
minimize the probability of iron deficiency. In order to minimize the potential for this occurrence, a multiple vitamin was sought that provides elemental iron (9mg), and calcium (200mg) (Spectrum Select*, Life Brands). This multivitamin preparation can be supplemented with a 500 mg calcium tablet. The cost of this combination of products is greater ($0.1405) than the base case of $0.1166. The higher cost of the calcium/vitaminD/iron supplement is within the threshold value established in the sensitivity analysis of $0.1183 for the CaVD50 arm, and did not change the expected value ranking of this intervention. This threshold however ($0.1183) is close to the base case cost of calcium/vitamin D ($0.1166), and implementation of this new supplement regimen at its higher cost ($0.1405) would result in the loss of the weak dominance of the CaVD65 management strategy, and impact on the ranking of expected cost in the CaVD65 strategy. Although it could be argued that implementation of this strategy may shift the summary results, it is also possible that this intervention may reduce the prevalence of anemia in this segment of the population.

Two other issues related to excessive intake of calcium which may lead to high blood calcium levels are severe renal damage, and milk-alkali syndrome. Typically intakes greater than 2,900 mg are required for this type of toxicity (Food Directorate, 1997), and is unlikely to occur if the patient is compliant with therapy, is routinely monitored by their physician, and is counselled on the need to control their intake of calcium.
9.7.2 Implementing HRT Therapy

The output from the economic model strongly suggests that a preventative intervention is better than a no intervention approach in order to prevent osteoporosis-related hip fractures. The HRT65 intervention has been shown to be dominant in the base case as well as the majority of sensitivity analyses evaluated in the thesis. The HRT50 strategy was not dominant in any of the scenarios however it was also found to have a favourable profile in preventing hip fractures and CHD related deaths. However, the increased number of breast cancer deaths with HRT50 resulted in this strategy looking less favourable. The incremental cost-effectiveness ratios of the HRT50 strategy however under the base case and optimistic scenarios, were reasonable ($10,969/LYG, and $2,810/LYG respectively) and justify this intervention if no suitable alternatives were available (Table 9.1). Currently HRT (generically available HRT), is listed in all provincial drug formularies in Canada. These formularies typically cover older Canadians (>65 years of age), and the indigent. Generally these provincial formularies do not cover women in the early menopausal period (age 50-65), however private plans, which cover approximately 70% of this population (Canadian Health and Life Insurance Association, 1996) have some form of coverage and almost all of these third party insurer plans reimburse the generically available HRT as a minimum. This suggests that coverage for HRT is relatively universal and available to the patient at minimal cost. Those menopausal women without any form of insurance would have to pay out of pocket approximately $120.00 per year up until age 65 if they obtain the generically available HRT.
Data from surveys conducted on HRT use vary substantially, however it is believed that about 15% of Canadian postmenopausal women are currently taking HRT on a long-term basis (IMS, 1997). A study conducted in the United States found that only 15-25% of women eligible for hormone replacement make use of the therapy (Ravnikar, 1987). Other data sources indicate that approximately 40% of women between the ages of 50-64 have taken HRT at some point during the past one year. Compliance issues also surround the use of HRT with women never filling their first prescription (20-30%), and (70%) not continuing to take their long term therapy at one year post initiation (Witt et al, 1997).

The survey data and the reimbursement status of HRT imply that although this agent is beneficial in preventing hip fractures and CHD there are other valid reasons why more women are not initiating this treatment, or taking this agent for the longer term. The concern over an increased risk of breast cancer may be one of the important reasons.

9.8 Compliance To Management Strategy

The economic evaluation on the management strategies of CaVD and HRT in the prevention of hip fractures has provided an overview of the relative roles of each intervention. This evaluation assumed that the cohort of women who initiated therapy were compliant with their therapy. It is evident that long-term compliance with these therapies is critical if these women are to realize the benefits of the management strategies. In diseases where the patient physically feels ill if they are not compliant, like diabetes or epilepsy, compliance is typically very high. In this case, women at age 50 or 65 are being encouraged to initiate a long-term therapy, with the benefits of hip fracture
prevention occurring approximately 15 years later. In some regards preventative strategies for osteoporosis are similar to cholesterol lowering recommendations, where the patient does not feel particularly different when they do not take the medication, however in the future, events will occur that could have been avoided if compliance to therapy was maintained. Coombs et al (1995) have suggested that four conditions must be met before compliance strategies can be employed. These are: “1) an accurate diagnosis, 2) establishment of treatment efficacy, 3) patient consent, and 4) establishment of intervention strategy efficacy”. Consequently, if the objective is to ensure compliance in these “silent” diseases then these four conditions need to be met to ensure the benefits of long-term therapy. Unfortunately data are lacking on the impact of partial compliance to each of the management strategies evaluated in the osteoporosis model.

9.9 Education

A Gallup survey of 45-60 year old women found that only 44% of women were satisfied with the information they received from their doctors on menopause (Utian et al, 1994). The Canadian peri-menopausal woman today is more educated, and highly interested in her health than women of her age twenty years ago. The availability of treatment options, publicity surrounding the menopause and osteoporosis in print and the media, have helped make peri-menopausal women aware of their treatment choices. Unfortunately some physicians are not comfortable with counselling women on the options available to them. Similarly women consult their physician on therapies for long-term bone health, however issues surrounding long-term therapy with HRT is intimidating due to the anxiety surrounding the possible risk of cancer (Coyle et al, 1998).
A study of 2,500 women revealed that 50% of the non-compliant patients either discontinued or sporadically took their HRT because of the fear of cancer (Sagraves, 1995). Educating patients about the relatively small risk of breast cancer, and the benefits of HRT's CHD protective effects has had a positive impact in women who were contemplating the use of estrogen (Robinson, 1997).

Compliance with a CaVD strategy can also be maximized via education of its benefits. Currently 6-35% of women aged of 50 years or older are supplementing their diet with a form of calcium, at any given time (Table 2.4) (NHANES II, 1996). In contrast 0-15% are currently taking a vitamin D Supplement (NHANES II, 1996). This suggests that education is necessary, especially to this large proportion of women who are already adding a calcium supplement to their diet, on the value of adding vitamin D to their regimen since it would enhance the benefits being afforded to them with calcium supplementation alone.

Enhancement of compliance can also be achieved by frequent physician follow-up and periodic (every two years) BMD testing, for those patients who are currently on an osteoporosis prevention strategy. The results of these scans are likely to demonstrate to the patient the impact of the therapy and to confirm that clinically this is the optimal strategy for them. Mass BMD screening is not considered as a cost-effective option.

Affordability of an intervention may also provide a barrier to compliance. The evolution of third-party drug plans over the past ten years, in which a co-pay was introduced, resulted in a significant drop in utilization of pharmaceuticals, and was linked to the magnitude of the co-pay (LeLorier et al, 1998). Calcium and vitamin D supplements are currently not reimbursed by the majority of third party and government
plans, consequently the purchase of these agents (although the retail monthly acquisition cost from a pharmacy of less than $10 per month) may result in non-compliance or poor compliance based on personal affordability and motivation for taking these agents over the long-term.

Compliance is likely to be enhanced if one considers interventions from a side-effect profile since the CaVD strategies do not have the cancer risk element associated with HRT.

9.10 Policy Implications

Osteoporosis is another disease of the elderly that has a high burden of illness (Goeree et al, 1996). As the Canadian baby boomer population ages, it is estimated that the Canadian health care system will have to deal with approximately four times the current annual number of hip fractures in the year 2041 (Papadimitropoulos et al, 1997).

The economic evaluation in this thesis has demonstrated that calcium/vitamin D management strategy initiated at age 65 exhibited weak dominance. HRT therapy initiated at age 65 is the dominant strategy compared to the do nothing (NI) strategy under the base case assumptions. The NI approach was not the least expensive option under the treatment scenarios evaluated in the thesis and will result in more hip fractures. HRT therapy initiated at age 50 was cost-effective ($10,969/LYG), and the most effective in reducing the number of hip fractures and CHD deaths than any intervention evaluated, however the increased number of deaths due to breast cancer, may result in slower adoption of this strategy. Calcium/vitamin D therapy initiated at age 50 under the base
case assumptions was not as cost-effective as HRT initiated at 50 years, however this strategy resulted in fewer hip fractures than the CaVD strategy initiated at 65 years.

Barriers to initiation of preventative therapy include poor education on the impact of osteoporosis on postmenopausal health, compliance to therapy, the fear of breast cancer, and lack of funding for effective preventative strategies (calcium/vitamin D) by provincial formularies. Each of these issues were covered in detail in the discussion section, however they are re-emphasized here, since successful implementation of population supplementation programs will require that each of these issues is addressed. Enhancement of the cost-effectiveness of these interventions, may require screening and targeting of therapy (shift from population to individual focus) to only those at high risk for osteoporosis, or those at risk of osteoporosis and high risk for breast cancer. This analysis did not evaluate screen and treat scenarios.

### 9.11 Conclusions

Supplementation of postmenopausal women with calcium/vitamin D or HRT from age 50 until age 90 years resulted in fewer hip fractures with the CaVD arm, and fewer hip fractures and CHD deaths, but more breast cancer deaths with the HRT arm, compared to the no intervention strategy.

Delaying supplementation to age 65 with calcium/vitamin D resulted in fewer hip fractures than the no intervention strategy, and the intervention exhibited weak dominance, however more hip fractures resulted than when this strategy was initiated at age 50.
Initiation of HRT at age 65 resulted in fewer hip fractures and CHD deaths, but more breast cancer deaths, than the no intervention arm. This strategy was considered the dominant intervention, however there were more hip fractures and CHD events, but fewer breast cancer deaths than HRT therapy initiated at age 50.

Calcium/vitamin D initiated at age 65 demonstrated weak dominance under base case assumptions. The results of this analysis suggest that the use of CaVD at age 65, is a viable alternative to HRT for the prevention of osteoporosis. Despite its CHD protective limitations the CaVD management strategy is an ideal alternative for women who would not take HRT either because of predisposition to developing breast cancer, or the level of anxiety surrounding the potential development of breast cancer.

Implementation of these preventative strategies will be limited if successful and cost-effective awareness and education programs are not instituted. Perimenopausal women today are more educated, and more interested in their health than their counterparts of twenty years ago. The task of implementing these screening and implementation programs is more likely to succeed today, since these efforts can be supported by a number of women’s health initiatives at governmental and publicly-supported organizations such as the Osteoporosis Society of Canada, and the Heart and Stroke Foundation of Canada.
REFERENCES


Supplement A: Tables used in the CHIMP model

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Dear Dr. Papadimitropoulos:

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Professional Development
Current and projected rates of hip fracture in Canada

Emmanuel A. Papadimitropoulos, BSP, MSc(Phm); Peter C. Coyte, MA, PhD; Robert G. Josse, MB, BS; Carol E. Greenwood, PhD

Abstract

Objective: To determine the current values and estimate the projected values (to the year 2041) for annual number of proximal femoral fractures (PFFs), age-adjusted rates of fracture, rates of death in the acute care setting, associated length of stay (LOS) in hospital, and seasonal variation by sex and age in elderly Canadians.

Design: Hospital discharge data for fiscal year 1993–94 from the Canadian Institute for Health Information were used to determine PFF incidence, and Statistics Canada population projections were used to estimate the rate and number of PFFs to 2041.

Setting: Canada.

Participants: Canadian patients 65 years of age or older who underwent hip arthroplasty.

Outcome measures: PFF rates, death rates and LOS by age, sex and province.

Results: In 1993–94 the incidence of PFF increased exponentially with increasing age. The age-adjusted rates were 479 per 100 000 for women and 187 per 100 000 for men. The number of PFFs was estimated at 23 375 (17 823 in women and 5552 in men), with a projected increase to 88 124 in 2041. The rate of death during the acute care stay increased exponentially with increasing age. The death rates for men were twice those for women. In 1993–94 an estimated 1570 deaths occurred in the acute care setting, and 7000 deaths were projected for 2041. LOS in the acute care setting increased with advancing age, as did variability in LOS, which suggests a more heterogeneous case mix with advancing age. The LOS for 1993–94 and 2041 was estimated at 465 000 and 1.8 million patient-days respectively. Seasonal variability in the incidence of PFFs by sex was not significant. Significant season–province interactions were seen (p < 0.05); however, the differences in incidence were small (on the order of 2% to 3%) and were not considered to have a large effect on resource use in the acute care setting.

Conclusions: On the assumption that current conditions contributing to hip fractures will remain constant, the number of PFFs will rise exponentially over the next 40 years. The results of this study highlight the serious implications for Canadians if incidence rates are not reduced by some form of intervention.

Résumé

Objectif: Déterminer les valeurs actuelles et évaluer les valeurs prévues (jusqu’en l’an 2041) des éléments suivants : nombre annuel de fractures fémorales proximales (FFP), taux comparatifs de fractures selon l’âge, taux de mortalité en milieu de soins de courte durée, durée du séjour (DS) connexe à l’hôpital et écarts saisonniers par sexe et par âge chez les personnes âgées au Canada.


Contexte: Canada.

Participants : Patients canadiens âgés de 65 ans ou plus ayant subi une arthroplastie de la hanche.

Mesures des résultats : Taux de FFP, taux de mortalité et DS par âge, sexe et province.

Résultats : Il y a eu en 1993–1994 une croissance exponentielle de l’incidence des FFP avec l’âge. Les taux comparatifs selon l’âge sont de 479/100 000 chez les...
Osteoporosis is an important public health problem, especially in postmenopausal women. Fractures of the wrist, vertebra and hip are attributed to this disease. Osteoporosis is also very costly: in 1988 the cost associated with its treatment in Canada was $280 million. Recently Goeree and colleagues estimated the cost of treating this disease in Canada at $1.3 billion for 1993. Similar estimates of the annual costs for the treatment of osteoporosis in the United States range from US$5.2 billion to US$7.2 billion (Can$7 billion to Can$10 billion), a difference that reflects to some extent the larger population base. Decreasing budgets for publicly funded programs have prompted a re-evaluation of expenditures in all areas of health care, particularly the costly treatment of proximal femoral fractures (PFFs, also known as hip fractures) in "aging" industrialized countries.

A greater understanding of the pathophysiology of osteoporosis has led to the development of treatment regimens. The use of hormone replacement therapy has resulted in an arrest of the osteoporotic process in most postmenopausal women receiving this treatment. Other treatment strategies include therapy with calcium, vitamin D, bisphosphonates, calcitonin or fluoride and load-bearing exercise as well as other treatments that are still investigational, such as therapy with selective estrogen receptor modulators or parathyroid hormone.

Published projections of the number of PFFs in Canada, we hypothesize, have underestimated their occurrence. The previously reported age-adjusted incidence rates of PFFs for Canada are lower than those for other industrialized countries; however, the reason for this difference is not clear. Since these earlier projections a more comprehensive hospital discharge database has evolved (Canadian Institute for Health Information [CIHI], Ottawa, Ont.). The development of the CIHI's database as well as recent population projections by Statistics Canada prompted a re-evaluation of this issue. The purpose of this study was to determine current PFF rates and to estimate the projected number of such fractures in elderly Canadians (those 65 years of age or older) to the year 2041.

Methods

We obtained data on all hospital discharges for femoral fracture that were reported to the CIHI for fiscal year 1993-94. Four provinces and the 2 territories in Canada currently provide full discharge reporting to the CIHI. We extracted these data from the master database using ICD-9 codes 820 (fracture of neck of femur [PFF]) and 821 (fracture of other and unspecified parts of the femur) for patients aged 65 years or older. A recent analysis of the CIHI database covering acute care discharges for Ontario between 1981 and 1992 showed that there was no change in the rate of PFF over this period.

The incidence of PFF was determined for the 3 largest provinces that fully report to the CIHI (Ontario, British Columbia and Alberta). Other provinces, including Quebec, Manitoba, Saskatchewan and some of the Atlantic provinces, do not provide full reporting; consequently their reported PFF data were not used in this analysis. To project national PFF rates we estimated weighted (by population) PFF incidence rates for Canada on the basis of the rates for Ontario, British Columbia and Alberta. We assumed that these provinces are generally represen-
ative of the country, since in the 1991 census 58% of the Canadian population was regionally and multiculturally distributed in them.\textsuperscript{22}

We used the annual PFF data for each of the 3 provinces to evaluate the relation between age and PFF rate and to describe this relation mathematically. These data were then collapsed to 5-year age groups (i.e., 65–69 years, 70–74 years, etc.) by sex and by province for further analysis and comparison, since PFF rates are generally discussed this way in the literature. We calculated the average number of PFFs in each of the 5-year groups at the corresponding median age (i.e., 67.5, 72.5, etc.). Equations were then generated that described PFF rates, by age and sex, on the basis of a weighted PFF rate. We calculated the weighted rates by adjusting the provincial PFF rate for each 5-year age group by the population of the province.\textsuperscript{23} Variability in the weighted PFF rate was calculated on the assumption that the 3 provinces used as a base were “randomly” selected. We also calculated projections of all femoral fractures for Canada using the same weighting procedure outlined above.

We obtained demographic information and population projections to 2041 from Statistics Canada and 1991 census data for Canada.\textsuperscript{2,23} Four demographic projections were produced by Statistics Canada on the basis of a number of assumptions relating to rates of birth, immigration and death. We chose the median projection (Statistics Canada projection 2) as the baseline projection for our analysis since it provided an estimate based on current trends and since it assumes a constant fertility rate of 1.7 births per woman and a constant immigration rate of 250 000 combined with a low life-expectancy assumption of 78.5 years for men and 84 years for women by 2016.\textsuperscript{24} Other projections (low-growth assumption [projection 1] and high-growth assumption [projection 4]) were included in our sensitivity analysis of the projected number of PFFs.

We calculated the age-adjusted PFF rate for Ontario for comparison with rates reported for Rochester, Minn.\textsuperscript{4} Age-adjusted PFF rates reported in the literature are based on data for men and women 50 years of age or older. Since the CIHI database provided information for Canadians 65 years of age or older, we obtained the femoral fracture rate reported by Statistics Canada for people aged 45 to 64 years\textsuperscript{25} and used this rate in calculating the rate for people aged 50 to 64 years.

Inpatient death rates and length of stay (LOS) while in the acute care setting, as well as seasonality of fractures, were also evaluated from the CIHI data. We multiplied the average LOS for each of the 5-year age groups by the estimated number of patients with PFFs in each group to calculate the total projected LOS (in patient-days). Seasonality was defined as the number of PFFs that occurred during a season (e.g., the number of PFFs that occurred during the summer was calculated by adding together one-fourth of the fractures that occurred in June, all those in July and August, and three-fourths of those in September). All the seasons were compared simultaneously to evaluate differences in PFF incidence. We also evaluated these variables for each of the 3 provinces and used the data as a basis for the projection to the rest of Canada.

We used regression analysis to define best-fit relations, based on greatest $R^2$, and conducted one-way and two-way analysis of variance for each of these variables by province and sex to examine whether significant main effects existed. We determined differences among means using Tukey’s honestly significant difference test ($\alpha = 0.05$).

The CIHI discharge abstract data were transferred to a personal computer, and Statistical Application Software (SAS–Windows version 6.08, SAS Institute Inc., Cary, NC) was used for the analysis.

Results

Current incidence

We found an exponential increase in PFFs with increasing age and a significant effect of age for both women ($F_{1,76} = 1638, p < 0.0001$) and men ($F_{1,76} = 868, p < 0.0001$). There was no significant interaction with province for women ($F_{3,76} = 0.84, p = 0.4367$); however, a significant interaction was noted for men ($F_{3,76} = 4.14, p < 0.02$), lower PFF rates with increasing age being noted in British Columbia than in Ontario and Alberta. The weighted PFF rates for Canada, by age and sex, are shown in Fig. 1. The total number of PFFs in people aged 65 years or older in 1993–94 was calculated as 17 823 for women and 5552 for men.

Age-adjusted rates

The age-adjusted PFF rate for Ontario in 1993–94 was 479 per 100 000 for women and 187 per 100 000 for men (Table 1). These rates are higher than those previously reported for Ontario\textsuperscript{4} but similar to those from elsewhere.\textsuperscript{28}

Projected incidence

Currently 12% and 1% of Canada’s population is aged 65 years or older and 85 years or older respectively. Demographic projections by Statistics Canada indicate that by 2041 the corresponding proportions will be 25% and 4% respectively.\textsuperscript{25} Using weighted current PFF rates (as described in the methods section), we estimated the total number of PFFs in older Canadians in 2041 at 88 124 (projection 2), with a range of 78 649 (projection 1) to 103 954 (projection 4). The projected incidence reflects
changes in both population size and projected mean survival. Our results indicate that previous Canadian projections have underestimated the number of PFFs (Fig. 2).

Mortality

The CIHI data for 1993–94 indicated that death rates for older inpatients increased exponentially with increasing age. We used logistic regression to model the probability of inpatient death after a fracture, with effects for sex, age, and province. There were no significant interactions between these explanatory variables. Men were at significantly higher risk for death after PFF than women (p < 0.001) (Fig. 3). We estimated that there were 1370 deaths (999 in women and 571 in men) in the acute care setting after PFF in 1993–94, and we project that the number of deaths will increase to 7000 (4404 in women and 2596 in men) by 2041.

Length of stay in acute care setting

LOS increased with increasing age until age 85 to 89 years for women and 80 to 84 years for men (Fig. 4). Of interest was the finding that variability in LOS also increased with increasing age. An estimated 465 000 patient-days were used in 1993–94 to treat these PFF patients (estimate based on current mean LOS by age and sex). The projected LOS for patients with PFFs in 2041 was estimated at 1.8 million patient-days.

Seasonality

Analysis of the data for Ontario, British Columbia and Alberta did not demonstrate a significant main effect of season on the incidence of PFFs for women ($F_{1,2} = 3.20$, $p = 0.0947$) or men ($F_{1,2} = 2.82$, $p = 0.1196$). We did find significant season–province interactions for both women ($F_{1,2} = 12.38$, $p = 0.0125$) and men ($F_{1,2} = 7.28$, $p = 0.0356$); however, the differences in incidence were on the order of 2% to 3% and were not considered to have had a large effect on resource use in the acute care setting.

Table 1: Reported age-adjusted rates of proximal femoral fracture for people 50 years of age or older

<table>
<thead>
<tr>
<th>Region</th>
<th>Year</th>
<th>Women</th>
<th>Men</th>
<th>Female: male ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oslo, Norway</td>
<td>1978–79</td>
<td>766.6</td>
<td>299.3</td>
<td>2.56</td>
</tr>
<tr>
<td>Funen, Denmark</td>
<td>1973–79</td>
<td>511.1</td>
<td>191.0</td>
<td>2.68</td>
</tr>
<tr>
<td>Rochester, Minn</td>
<td>1979</td>
<td>487.4</td>
<td>175.5</td>
<td>2.78</td>
</tr>
<tr>
<td>Picardy, France</td>
<td>1987</td>
<td>305.3</td>
<td>126.6</td>
<td>2.41</td>
</tr>
<tr>
<td>Ontario</td>
<td>1981</td>
<td>413</td>
<td>133</td>
<td>3.10</td>
</tr>
<tr>
<td>Ontario (current study)</td>
<td>1993–94</td>
<td>478.7</td>
<td>187.1</td>
<td>2.56</td>
</tr>
</tbody>
</table>

Discussion

Previous Canadian projections of PFF incidence have suggested a lower rate than that for the United States and other industrialized countries. However, we found that these projections underestimated the incidence of PFF. A comparison of the provincial incidence of PFF for Ontario, British Columbia and Alberta, as recorded in the CIHI database, revealed an exponential increase in fracture rates with age. Differences between provincial rates of PFF were not significant for women; however, there was a significant different in fracture rates between men in Ontario and Alberta and those in British Columbia. Fracture rates in older British Columbia men were lower than for the men in the other 2 provinces. The use of the weighted provincial PFF rate as representative of the

Fig. 1: Weighted rate of proximal femoral fracture (PFF), with 95% confidence intervals (dotted lines), for Canadian women (solid line) and men (dashed line) 65 years of age or older by age group, based on full reporting from Ontario, British Columbia and Alberta for fiscal year 1993–94.

Fig. 2: New and previously projected (a) number of PFFs in Canadians 65 years of age or older from 1993 to 2041, under 3 assumptions of population growth (maximum [●], median [▲] and minimal [□]).
Canadian population yielded exponential equations that were in good agreement with the interprovincial rates ($R^2 = 0.93-0.96$). Using the exponential equations, we calculated that there were 29,293 femoral fractures (23,375 PFFs and 5,918 fractures of other parts of the femur) among Canadians aged 65 years or older in 1993–94. We calculated the overall number of femoral fractures because Statistics Canada does not report these fractures by type. We estimated approximately 4,500 fractures more than Statistics Canada reported (24,687) for fiscal year 1992–93. The discrepancy is most likely due to the source of Statistics Canada's data (the CIHI database) and the potential for under-reporting.

Recently the Institute for Clinical Evaluative Sciences summarized a number of published and unpublished studies on the quality of health care administrative databases in Canada. The conclusion reached for hospital discharge summaries was that for primary procedures the levels of agreement were 90% or greater between the procedures recorded on the charts and those entered into the database. The CIHI database, however, does not have full reporting from several provinces, including Quebec, which accounts for 25% of the elderly Canadian population. It is likely that the number of hip fractures is underestimated in the data from Statistics Canada, since no adjustments for missing data are made to the CIHI database, in contrast to the adjustments that were made in the current study.

Reanalysis of the CIHI data, selecting for PFFs, allowed us to calculate the age-adjusted PFF rates for Ontario. The rates for both women and men compared favourably to the values reported for Rochester, Minn., and for Funen, Denmark. In our study approximately 70% and 85% of femoral fractures were PFFs in women 65 to 69 years of age and those 90 years of age or older respectively. Similar findings were observed for men. Elimination of the PFF rate for women 90 years of age or older from the regression shown in Fig. 1 resulted in an exponential relation with greater $R^2$, which indicates that in advanced age other mechanisms may be involved in modulating the incidence of PFF.

**Potential implications**

Our projections are greater than those of Narod and Spasoff and of Martin and associates because of differences in the assumptions used in the calculations. We believe that the more comprehensive database currently maintained by the CIHI and the demographic projections from Statistics Canada provide a more accurate basis for our projections. The rise in potential rates of PFFs as well as other diseases in older Canadians is intimidating and provides a strong impetus for establishing programs that will reverse the trend in this group. All demographic projections provided by Statistics Canada were used to calculate best-case and worst-case scenarios. The results indicate that 40 years from now the Canadian health care system will have to deal with approximately 4 times the current number of hip fractures. This number is conservative, since advances in medicine may increase longevity, which would lead to an increase in the number of hip fractures if acceptable treatment strategies to maintain bone mineral density are not implemented. Increasing longevity also has long-term implications for the use of health care resources in the treatment of other age-related conditions.

Fractures of the femur carry an increased risk of death, especially in men. Death rates in the acute care setting after PFF in Canada do not differ greatly from those in
other industrialized countries, and the risk of death for patients with PFFs by age and sex in this country has not changed since last reported for 1980–81. This finding is disturbing since clinical advances over the last decade should have led to decreases in the death rate for age- and sex-matched patients with hip fractures.

The reported average LOS in the acute care setting for patients with PFFs in Canada in 1981 was about 31 days. Our work suggests that the current average LOS is about 21 days and presumably will decrease further still. We found an increasingly variable LOS with increasing age (Fig. 4). It is possible that as people age the probability of concomitant conditions increases, which results in a longer and more variable hospital stay. A progressive reduction in LOS with age greater than 85 years was observed for men. Perhaps these patients were already living in nursing homes and were discharged sooner than younger patients still living independently, or death played a role, or both. For women, LOS increased with increasing age and then plateaued after age 89. The reduction in LOS by almost 10 days over a 10-year period may have influenced the reported death rate, since deaths during this 10-day period (when patients are no longer in hospital) are not captured in the current database.

The increased risk of fracture in inclement weather (when ice or snow is present) and during the winter months has been documented. We did not find any significant main effect of season on PFF rates in Ontario, British Columbia and Alberta. Jacobsen and collaborators reported that the incidence of hip fractures generally increases by about 15% in the winter months. Factors that have been implicated in increased fracture rates during the winter season in the northern hemisphere include poor vitamin D status and a number of environmental hazards (such as increased slipping due to ice and snow, and tripping). According to the Ontario Weather Office, the winter of 1993–94 was typical, both in the number of millimetres of precipitation and in temperature. It would be prudent to re-evaluate the seasonal incidence of PFFs with the CIHI data from other fiscal periods to confirm our findings.

Limitations of analysis

The projections presented in this paper are based on the full reporting of 3 provinces on the assumptions that they are representative of Canada as a whole and that annual PFF incidence does not vary significantly. Seasonal, cultural, racial and demographic differences can influence the health of a population; consequently, our analysis is limited from this perspective. We assumed that the CIHI database is robust in terms of validity and reliability and that miscoding of fractures did not occur at the hospital level. Unlike databases in the United States, the CIHI does not collect racial or ethnic information. Our projections are therefore based on the assumption that the racial mix of Canadians will not change and hence that this factor will not alter PFF incidence and associated death rates and LOS in the acute care setting. Finally, since our projections assume the status quo with regard to dietary habits and supplementation, clinical treatment (e.g., LOS), lifestyle and longevity, we cannot comment on how changes in these variables would influence future projections.

Given that current conditions contributing to hip fractures remain constant, the number of PFFs will rise exponentially over the next 40 years. Our results highlight the serious implications for Canadians if incidence rates are not decreased by some form of intervention.

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References

19. Pak CYC, Zerwekh JE, Amich PP, Bell NH, Singer FR. Slow-release sodium...
20. Jaglal SB, Kreiger N, Darlington G. Past and recent physical activity and risk
M, et al.Raloxifene is a tissue-selective agonist/antagonist that functions
24. International classification of disease. 9th rev. Los Angeles: Practice Manage-
ment Information Corp; 1994.
25. Jaglal SB, Sherry PG, Schansker J. The impact and consequences of hip frac-
26. Lilienfeld AM, Lilienfeld DE. Foundations of epidemiology. 2nd ed. New York:
28. Bagur A, Mauataen C, Rubin Z. Epidemiology of hip fractures in an urban
29. Martin AD, Silverthorn KG, Houston CS, Bernhardt S, Wadja A, Roos
LL. The incidence of fracture of the proximal femur in two million Canadi-
30. Williams JL, Young W. A summary of studies on the quality of health care ad-
ministrative databases in Canada. In: Goel V, Williams JI, Anderson GM,
Blackstein-Hirsch P, Fooks C, Naylor CD, editors. Patterns of health care in
Ontario. The ICES practice atlas. 2nd ed. Ottawa: Canadian Medical Associa-
31. Cummings SR, Kelsey JL, Nevitt MC, O'Dowd K. Epidemiology of osteo-
32. Cooper C, Adakson EJ, Jacobson SJ, O'Fallon WM, Melton LJ III. Popula-
tion-based study of survival after osteoporotic fractures. Am J Epidemiol
1993;137:1001-5.
34. Kemsar JE, McCarthy RE, Lowell JD, Sledge CB. Hip fracture mortality:
relation to age, treatment, pre-operative illness, time of surgery, and compli-
CE, et al. Differences in mortality after fracture of the hip: the East Anglian
36. Jacobson SJ, Sargent DJ, Atkinson EJ, O'Fallon WM, Melton LJ. Population-
based study on the contribution of weather to hip fracture seasonality. Am J
Epidemiol 1993;141:79-83.
variation in the incidence of hip fracture among white persons age 65 and
38. Lewis LA, Laster LC. Frequency, distribution and measurement of injuries
39. Ralis ZA. Epidemics of fractures during periods of snow and ice. BMJ
1986;293:484.
40. Ralis ZA. Epidemics of fractures during period of snow and ice. BMJ 1981;
282:603-5.
41. Felson DT, Anderson JJ, Hannan MT, Milton FC, Wilson PW, Kiel DP.
1989;37:491-300.
Risk factors for falls as a cause of hip fracture in women. The Northeast Hip
1987;316(7):404-6.
al. Risk factors for hip fracture in white women. Study of Osteoporotic
and sex differences in mortality following fracture of the hip. Am J Public

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