HORMONE THERAPY AND RISK OF FRACTURES AND MORTALITY IN POST-MENOPAUSAL WOMEN: 20 YEARS FOLLOW UP OF OSTPRE COHORT STUDY

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Osteoporosis increases the lifetime risk for wrist, hip or vertebral fractures. Out of all the fractures, hip fractures cause highest morbidity and mortality, and cost the highest to the health care system. Hormone therapy (HT) is one of the options to prevent the osteoporosis and it may consist of estrogens only or may be in combination with progestin.

This research work was a part of the OSTPRE cohort study. Aim of this study is to investigate the link between use of hormone therapy with risk of fractures and mortality in post-menopausal women. Study specifically looks into life-style features, which act as risk factors for fracture and associated mortality. Study includes the baseline data collected in 1989 and additionally the incidence data of fractures and mortality until 2009. At the baseline, data included all 14,220 peri and post-menopausal women, aged 47 to 56, who were inhabitants of Kuopio region, Eastern Finland at that time. Out of these 14,220 women, 13,100 replied to the baseline postal enquiry in 1989. For focusing on the main idea of the study plan, those cases were deleted from the study which were using the HT due to other reasons like; gynecological surgery, Hysterectomy and Oophorectomy. From the national registries, a total 278 hip fractures and 2587 deaths were reported. However, from the OSTPRE enquires of 1989 to 2009 (20 years), a total 3314 fractures were reported, of which 1799 were osteoporotic fractures.

OSTPRE data was collected by Kuopio University Hospital’s Committee, in which 12,399 participant’s physical parameters, life style features and fracture events were examined and recorded. In life-style features, patients’ practice of dietary calcium intake and smoking were explored. All fractures were recorded through self-reporting. For this study, participants were divided into two categories; users of HT and non-users of HT. Selected variables for this study are; age, weight, height, smoking, fracture types, dairy calcium intake, hormone use.

This longitudinal population-based study of 20 years predicts that use of HT prevents from osteoporotic fracture and premature death in post-menopausal women, however HT therapy does not have any protective effect in overall fracture and hip fracture. This study shows that intake of dietary calcium and an increase in BMI have a positive association with bone health, which reduces the risk of fracture. Study also reports that smoking leads towards premature death.
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## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BMD</td>
<td>Bone mineral density</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>Cm</td>
<td>Centimeters</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>DXA</td>
<td>Dual x-ray absorptiometry.</td>
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<tr>
<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>HT</td>
<td>Hormone therapy</td>
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<tr>
<td>IOF</td>
<td>International osteoporosis foundation</td>
</tr>
<tr>
<td>Kg</td>
<td>Kilograms</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NAMS</td>
<td>North American Menopause Society</td>
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<tr>
<td>OSTPRE</td>
<td>Osteoporosis risk factor and prevention</td>
</tr>
<tr>
<td>PMMA</td>
<td>Poly methyl methacrylate</td>
</tr>
<tr>
<td>PTH</td>
<td>Parathyroid hormone</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SERMs</td>
<td>Selective estrogen receptor modulators</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical package for social sciences</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
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<tr>
<td>WHI</td>
<td>Women health initiative</td>
</tr>
<tr>
<td>WHO</td>
<td>World health organization</td>
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1. INTRODUCTION

Statistics from 2015 reported that there are about 900 million people over the age of 60 around the world. These numbers are expected to double, around 2 billion, till 2050 (WHO 2015a). This demographic pressure raises many health issues like osteoarthritis, osteoporosis and falls associated with that, and many other different types of health disorders like depressive disorders, diabetes, and dementia (WHO 2015b).

Globally, more than 8.9 million major and minor fractures recorded annually due to osteoporosis, from which more than 4.5 million happen in the America and Europe (WHO 2014). The lifetime threat for an osteoporotic wrist, hip or vertebral fracture has been projected to be in the order of 30% to 40% in developed countries which is very similar to the coronary heart disease. (WHO 2004). In various areas of the world, the risks in women is doubled as compared to the men. The residual lifetime probability of osteoporotic fractures in women at the age of 50 years surpasses 40% in developed countries. Out of all the fractures, hip fractures cause highest morbidity and mortality and also cost the highest to the health care system. The residual lifetime possibility of hip fracture in women at the age of 50 years exceeds 20% in these countries. (WHO 2004). However, studies show that some severe osteoporotic fractures are linked with the surplus mortality rate and risk increases twice after a fracture event (Vestergaard et al. 2007).

Hormone therapy (HT) is one of the options to prevent the osteoporosis and it may consist of estrogens only or may be in combination with progestin. This therapy reduces bone turnover and rises BMD at all skeletal positions in postmenopausal women (Szulc et al. 2003). However, HT is not considered as the first line treatment. Several risks are associated with the use of HT, withdrawal or discontinuation is often an option in clinical practice. This withdrawal itself may cause an increased risk of fractures, including osteoporotic fractures, as reported by different studies (Roksana et al. 2011). But later on, Global Consensus Statement on Menopausal Hormone Therapy clearly presented that HT is operative and suitable preventive option, but before the age of 60 years or within 10 years after start of menopause (Gambacciani & Levancin 2014). So, the aim of this study is to check preventive effect of hormone therapy and risk of fractures and mortality in post-menopausal women in Kuopio region of Eastern Finland.
2. LITERATURE REVIEW

Literature review encompasses osteoporosis, its treatment, hormonal therapy and the withdrawal, and fracture risk. Search strategy involves use of PubMed and exploring studies from year 1990 onwards.

2.1 Geriatric syndromes

All over the world, the percentage of people aged over 60 years is rapidly increasing more than any other age group, which shows an increase in life expectancy. It is a challenge for the societies to maximize the fitness and functional ability of older people. Despite the fact that life expectancy is on the rise, more in the developed world, but the population growth rate is increasing in developing world too. It is estimated that by 2050, 80% of older people population will live in low- and middle-income countries. This will bring additional pressure on the health care system and its costs more, as old age is generally associated with an increased need for health care (WHO 2015a).

Geriatricians explain the term “geriatric syndrome”, a condition in which symptoms are not due to one distinct diseases, but also from collected impairments in various systems. It is a condition in which various anomalies run together to cause a single health condition (Flacker 2003). According to the Sharon et al. 2007 the definition of geriatric syndrome is “multifactorial health conditions that occur when the accumulated effects of impairments in multiple systems render [an older] person vulnerable to situational challenges”. So, several risk factors and organs are tangled in and contribute to one particular condition. Among many, there are five conditions which often point towards geriatric syndromes i.e. pressure ulcers, incontinence, falls, functional decline, and delirium (Sharon et al. 2007).

Along with geriatric syndromes, fall and fall-associated fractures are one of the main reason of the elderly's need for long-term medical and social attention. Hip fractures are the emblematic cases in the aged population. Almost 424,000 fatal falls occur annually, creating it the second foremost reason of injury related deaths, after road traffic injuries (WHO 2016a). Sarcopenia, the decline of muscle mass with age, is a vital factor of the frailty syndrome and it places older people at threat of fragility fractures. It disturbs the musculoskeletal and non-musculoskeletal systems in older people and is thus linked with a susceptibility of fractures events. Hip fractures are turn out to be a hallmark case condition in the analysis of frailty (Milte & Crotty 2014).
Research shows that women are more prone towards the disabilities due to geriatric syndrome. Those women who are suffering from more than five geriatric syndromes have six times more risk of incident disability as compared to women with no geriatric syndrome (Andrea et al. 2013).

2.2 Menopause and bone

Menopause is a normal biological process which is outlined as period of 12 months after the last menstrual period and sign of the end of menstrual cycles. Menopause commonly happens between age 50 and 53 years in women from Europe and North America, and it is slightly different in Asia and Latin America which is 42 years. According to the report of IOF on the world osteoporosis day, the bone mass rapidly decreases after the onset on menopause which shown in figure 3 (IOF 2013).

![Bone mass loss is at peak after the onset of menopause](image)

Figure 1. Bone mass loss is at peak after the onset of menopause (IOF 2013).

In post-menopausal women, the bone turnover rate is high and bone reabsorption rate is so high as compared to the bone formation rate, which leads towards the low bone mass. Seventy percent of bone strength is regulated by the bone mineral density and then remaining is explained by bone turnover rate, matrix proteins, micro fracture and calcification (Yoshiko 2015).
Although BMD is the most common predictor of the osteoporosis and low BMD increases the fracture risk, but studies show that most fractures occur in postmenopausal women at moderate risk. Osteoporosis is the reason of 8.9 million fractures annually throughout the world. Which is causing an osteoporotic fracture in every three seconds. It gives immense load on health care systems globally, and the incidence of osteoporosis is multiplying every year and fractures are the third highest cause of bedbound complications. In 2010, the costs of osteoporosis-interventions, which includes pharmacological intervention too, was estimated to be €37 billion. Out of it, the costs of handling incident fractures, pharmacological interventions and long-term fracture care share 66%, 5% and 29% respectively (IOF 2016).

2.3 Osteoporosis

The term osteoporosis exactly means “porous bone” and states to a condition in which bone is generally mineralized and trimmed down in quantity. So, due to low bone mineral density, fractures are the health outcomes of osteoporosis (Compston & Rosen 2009). According to the WHO, osteoporosis is defined as a “BMD (bone mineral density) that lies 2.5 standard deviations or more below the average value for young healthy women (a T-score of < -2.5 SD)” (WHO 2004). The genetic and environmental factors both contributes towards the bone health. Some essentials of bone health are decided by the genes and simple faults by these genes cause the deprived bone health but they are mainly birth defects. Some other external factors like diet, physical activity and lifestyle are critically important for bone health too and they contribute throughout the life. There are multiple pathophysiological factors of fracture which are shown in figure 2.

![Diagram of osteoporosis related fracture](image)

Figure 2. Pathophysiology of osteoporosis related fracture (Gambacciani & Levancini 2014).
Osteoporosis is a skeletal disorder which reduces the bone depth and leads towards the chance of fracture. The most common is “primary osteoporosis” which is chiefly a disease of the elderly, in which the bone loss and decay of bone structure occurs. While it occurs in both genders, it is thrice times more common in women. May be the reason being that women have two stages of age associated bone loss, one phase is at the beginning of menopause and it lasts for four to eight years and other phase is a slower constant phase which lasts through out the life. While men experience a different pattern and face only the slower continuous phase. Women in their post-menopausal state are at a greater risk of primary osteoporosis and this type is rarely seen in young and adults. It is also referred as age-related osteoporosis. However, bone loss triggered by peculiar diseases or medications is called “secondary osteoporosis” (Sarah et al. 2008).

The major determinants of bone strength are composition of mineral and matrix of bone, fine assembly of trabecular bone and presence of porosity of cortical bone. The structure of trabecular bone plays an essential role because on the sites of osteoporotic fracture, the trabecular bone is predominant e.g. spine, wrist and hip. This bone consists of well-connected plates that provide strength but osteoporotic individual has disrupted and poorly connected bone structure (Rockville 2004).

![Figure 3. Electron micrograph scan from the biopsies of normal and osteoporotic patient (Rockville2004).](image)

Clearly shows that the normal bone has the strong connection as compared to the other one. In osteoporotic bone, half of bone is already lost and remaining is having weaker rod-like structure while some of them are completely disconnected, which is the cause of poor bone strength.
2.4 Osteoporosis and co-morbidities

Co-morbidity is a condition in which two or more chronic conditions exist simultaneously within an individual and it is an emergent phenomenon in ageing humanities and is especially dominant in older age groups. The studies show that women who are suffering from osteoporosis are more prevalent to the other chronic diseases like hypertension, asthma, bronchitis, gout, cardiovascular disease, glaucoma and chronic kidney diseases and so on. Women with osteoporosis have nearly two times more risk of suffering bronchiectasis than women without osteoporosis (Roberto et al. 2014). In 1980, Baastrup et al. explained that schizophrenic patients which were using neuroleptic drugs suffer from low bone mineral content especially in their both forearms. They propose that schizophrenics have osteoporosis maybe due to the disease or the treatment given. After the introduction of second generation antipsychotic drugs, which affect prolactin level less as compared to the first-generation high potency drugs, different studies show almost the same phenomena that the antipsychotics drugs contribute to a small rise in the possibility of fractures (Taishiro et al. 2012).

Generally, diabetes is not measured as a risk factor for fractures, but some studies shows the significant association between the two conditions. Diabetic neuropathy or extreme risk for hypoglycemia may rise the chance of falls in post-menopausal women which ultimately raise the possibility of fractures and especially the hip fracture (Kristin and Aaron 2001). Another study shows that old women who are suffering from the diabetes are considered at risk for particular types of fractures. However, on average they have the high bone mineral density. May be the possible reason is that diabetes is related with a decline in bone strength that is not replicated in the measurement of BMD. Women who are using insulin as a treatment are linked with a high risk of foot fracture (Ann et al. 2001).

Numerous finding shows that women suffering from depression are diagnosed by depleted bone mineral density which increase the fracture risk. One aspect that may be the source of bone loss in depression is increased production of cortisol by the adrenal stress gland (Rockville 2004). On average BMD of women with depression is 6 percent lower in the spine and 10-14 percent lower in hip as compared to the normal women (David et al. 1996).

2.5 Osteoporotic fractures

The description of an osteoporotic fracture is not very definite or clear-cut. Regardless of the approaches used, ideas differ regarding the addition or omission of diverse sites of fracture.
The most widely accepted one points to a fracture which occurs due to low energy trauma. Low energy is defined as a fall from a standing height or less (WHO 2007). Fractures of the vertebrae (spine), proximal femur (hip), and distal forearm (wrist) have been observed as the typical osteoporotic fractures (Figure 4).

![Figure 4. Osteoporosis sites of fractures (Rockville 2004).](image)

In white women, the chances of hip fractures are more as compared to the breast cancer. In fact, they are having one in six life-time-risk of facing the hip fracture, which is larger than the one in nine risks of acquiring breast cancer (Steven and Joseph 2002). In US and Europe, 30% of postmenopausal women have osteoporosis and 40% of these women will have a chance of one or more fragility fractures in their residual lifespan (IOF 2016b). Different studies show that fracture history is a risk factor for further fracture, and risk increases to 86% for those who have fracture history (Kanis et al. 2004). Another study reveals that the patients with previous vertebral fracture have 2.3 times increased risk of hip fracture and 1.4 times increased risk of forearm fracture (Melton et al. 1999).

There are some strong predictors of osteoporotic fracture like the low BMD, fracture history and falls. According to WHO’s report on falls, in United States of America, 20–30% of older people, face rational to serious damages such as injuries, hip fractures, or head traumas after the fall event. Older women and younger children are predominantly prone to falls and increased injury severity (WHO 2016). Bone mineral density (BMD) and fracture tolls differ among women of different societies. Many studies propose that BMD is highest in African-American women as compared to Asian who have the lowest BMD values, while Caucasians
are at the intermediate level. However, an interesting fact is that the Asians have the lower fracture rates as compared to the Caucasians (Joel et al. 2002). There are some silent spine fractures, which do not produce the obvious symptoms, but they may involve in compression of the vertebrae, and can result in kyphosis, and severe back pain which may increase the morbidity (Rockville 2004).

2.5.1 Vertebral fracture

Approximately 60% of vertebral fractures are clinically silent, mostly diagnosed when a patient visits a doctor for a routine chest X-rays, other than back pain. A 50-year-old white woman has a 16% lifetime risk of suffering a vertebral fracture as compared to man of the same age which is 5%. In Europe, the prevalence of vertebral fracture is demarcated by radiological criteria. The incidence clearly increases by the age. In Europe, after age standardization occurrence of morphometric fracture is 10.7 in women while 5.7 in men per 1000 person-years (IOF 2016).

Vertebral fractures are one of the most difficult fractures to define as compared to other osteoporotic fracture. They are categorized on the base morphology of the vertebral body. The abnormalities that happen due to vertebral fracture are typically categorized as crush fracture in which the entire vertebral body is compressed. A wedge fracture is associated with the anterior height loss, and biconcavity is associated with the central compression of the end plate region. A commonly used scientific system to categorize the vertebral fractures is based on this height loss and it is classified as mild, moderate and severe, and the percentages of height loss are 20-25%, >25%-40% and more than 40% respectively (WHO 2007). The morbidities associated with the vertebral fracture are back pain, loss of height, abnormality in spine, immovability, more bed rest, and even reduced pulmonary function (Lips et al. 1999). When the vertebral body loses its height, it adopts a wedge type shape and in the result of this wedge type appearance, spine loses its normal shape and assumes a quite kyphotic posture which commonly called as hunchback. In cases of silent fracture, the fractured bone heals itself but heals in a malformed state which is permanent. This distorted shape puts more pressure on the spine, which gives rise to yet another fracture (Sarah et al. 2008). According to International Osteoporosis foundation, women who have a vertebral fracture are at considerable risk for further fracture within the next 1-2 years (IOF 2016). A patient who suffers from a compression fracture, mostly complains about the sudden increase in back pain. Mostly, chances of clinically silent compression fractures are in the upper thoracic spine as
compared to the lumbar spine. Because at upper thoracic spine the vertebral body is small and has relatively less amount of vertebral body weight. X-rays, magnetic resonance imaging (MRI) and Computerized tomography (CT) scan are the tools for diagnosis of vertebral compression fracture. If the patient has a pace maker and cannot tolerate the MRI than total body bone scan can be helpful for detecting the age of fracture (Sarah et al. 2008). In the recent past years, very efficient techniques are introduced in the field of treatment of vertebral fracture like Vertebroplasty and Kyphoplasty. These treatments are considered “gold standard” option for the treatment of acute vertebral fracture cases. The main purpose of these treatments is to strengthen the vertebral body immediately. The intraosseous injection of methyl methacrylate is introduced into the vertebral body which is commonly called as bone cement. After few minutes, the polymer settles and reinforce the fractured vertebral body is permanently. Another treatment which is used for vertebral fracture is Kyphoplasty which is somehow similar to the Vertebroplasty but it is introduced to overcome the limitation of Vertebroplasty which is leakage of bone cement. Kyphoplasty involves invasion of balloon into the broken vertebral body and then the balloon creates some space in the broken bone and then slowly release the PMMA liquid after the removal of balloon under high pressure. Once the bone cement settles the procedure is complete and it strength the vertebral body and restore the height of vertebral body too (Ravishankr 2009).

2.5.2 Hip fracture

Hip fracture is one of the most critical osteoporotic fractures. The long-lasting outcomes of any osteoporotic fracture can be shocking, and approximately 20% of patients who were suffering from hip fracture die within 6 months, even those who live, they struggle for life and face extensive and complex rehabilitation (Compston & Rosen 2009). Annually 1.6 million hip fractures are reported globally, and it is prediction that this value will increase up to 4.7 million to 6.3 million by 2050 (IOF 2016). Almost 75% of hip fracture cases occur in women and 90% of the patients are over 50-year-old. A study shows that a white woman of 50 year has 2.8% risk of death associated to hip fracture in her residual lifespan, which is four time higher than the endometrial cancer (Cumming et al. 1989). Different studies reveal that the Scandinavian countries have the highest reported cases of hip fractures and 5-10 % of patients face a recurring hip fracture within the three-year interval (Kanis et al. 2002). Hip fracture is linked with acute infirmity and high chances of death. Those women who have suffered from a hip fracture have a 10-20% higher mortality than expected for their age. There are many risk factors of hip fracture but falls is one of them and studies show that urban women face more
hip fracture as compared to the rural areas. This may be due to less physical activity or more chances of falls due to urbanization (Steven and Joseph 2002).

A hip fracture is associated with fracture of the proximal femur, also over the femoral cervix (sub-capital or trans-cervical: intra-capsular fracture) or by way the trochanteric region (intra-trochanteric: extra-capsular fracture). There are different types of hip fractures. Which are shown in figure 5.

Figure 5. Types of hip fracture (a) intertrochanteric hip fracture (possible sites); (b) basilar femoral neck fracture (un displaced); (c) sub capital fracture (un displaced) (Compston & Rosen 2009).

The two hip fracture types, cervical or trochanteric, trochanteric fractures are more typically osteoporotic fractures, and age-exclusive and sex-peculiar risks for hip fractures are higher for trochanteric than for cervical fractures (WHO 2007). Hip fracture patient feels severe pain in the hip, swelling, bruising, stiffness in the hip area and sometime they are not capable to tolerate weight on the affected side. The X-ray, CT scan and MRI are the best diagnostic tools for the patient complaining of severe pain at hip site. Different studies show that the MRI is better tool for identification of hip fracture as compared to the CT-scan. Bone scan is also an effective way of identification but then it should be done within 48 hours after the injury. When the hip fracture is diagnosed than the surgery is one of the common way of treatment (Sarah et al. 2008).
2.5.3 Wrist fracture

Wrist fracture is more prevalent in women and only 15% men face the wrist fracture and contrary to women, the rate does not increase much with the age in men. In women, the rate increases with age and more prevalent wrist fracture age is 45 to 60 years. In Europe, the annual incidence rate of wrist fracture in male is 1.7 per 1000 person and 7.3 per 1000 person in female (IOF 2016). Different studies show that in Finland the incidence of age specific distal radius fracture in elderly women has increased as compared to the previous years. A research preformed in 2011 by Flinkkila et al., in a Finnish city, reported a total wrist fracture incidence for over 80 years age, as 258 per 100,000 person-years. The incidence rates in male and female were reported as 466 per 100,000 persons -year and 1,107/100,000 person- year respectively. The fracture number was increased 2.5 time more in the winter slippery days as compared to the summers. The fracture rate was only 1.4 times more in non-slippery winter days to the normal days (Flinkkila et al. 2011).

The wrist joint is consisted of two lengthy bones in the forearm, the radius and the ulna, which are further linking to numerous smaller bones in the hand, known as carpal bones. If a patient suffers with the wrist fracture it often includes both radius and ulna. Mainly there are two type of wrist fracture one is Colles’ fracture and another one is Smith’s fracture. If it is a dorsal angulation of distal fragments it is called as Colles’ fracture but if it is causing a volar angulation, then it is termed as Smith’s fracture. Colles’ fracture which is more common in postmenopausal women. The x-ray technique is commonly used to confirm the wrist fracture (US News and World Report 2006).

The wrist fracture treatment is not as extensive as in the hip or vertebral fracture. The main concern is to immobilize the fractured bones. If the fractured bones are properly aligned, then the splint and cast are the best treatment option but if they are not aligned properly then the reduction is the treatment option which mainly composed of internal fixation and external fixation by the percutaneous pinning and the main purpose of these procedure is first to realign the bones and then immobilize it till its recovery which are mostly removed after 3-6 weeks (Sarah et al. 2008).

2.6 Osteoporosis related mortality

Recent studies revealed that excess mortality rate is coupled due to some severe osteoporotic fractures, out of which spine and hip fractures are causing more death risks. Hip fracture is
thought to be a complicated fracture because it can either cause permanent disability, loss of self-control and all of above increases mortality rate (Caliri et al. 2007, Leboime et al. 2010). Some studies reveal that osteoporosis is called “silent disease”. Because patient does not feel any symptoms before fracture. After event, it effects both the patient and the health care system in form of huge cost of treatment and poor quality of life (Caliri et al. 2007).

A Danish research shows that mortality increases twice after an osteoporotic fracture as compared to the control group. Researches divide the mortality into two categories; an excess mortality within one year of fracture and excess of mortality after every additional year and the percentages of risk of death are 19% and 1.8% respectively. However, 70.8% risk of death increases due to the complication which arises within the 30 days of fracture event (Vestergaard et al. 2007). Abrahamsen et al. also described that the risk of mortality was at its peak during the first three to six months and then mortality decreased after one year, but continued to be high for several years. Mortality rate ranges between 8.4% to 36% in the first year after the onset fracture (Abrahamsen et al. 2009). Friesendorff’s study states that mortality rate for older women was 52% at first five years of fracture and then increases to 77% at 10 years (Friesendorff et al. 2008).

Most patients require surgery as a treatment of hip fracture, but the timing of the operation remains crucial. Mostly, surgery within twenty-four hours after admission has been suggested. Several analyses stated that delay in hip fracture surgery is linked to the higher risk of premature death. A study reported that the thirty-day mortality after a surgery of hip fracture was 9%. Some patients who are delayed the surgical event due to co-morbidities have 2.5 times more risk of mortality as compared to those who delay surgery without any co-morbidity. Patients who are medically fit but delay the surgical event up-to four days have less chances of risk of death as compared to those who delayed more than four days (Moran et al. 2005). Several studies agreed upon this finding that a delay in fixation following hip fracture, increases the morbidity and mortality. A 5-year retrospective review of elderly patients shows that survival rate significantly reduces after the late fixation. May be the patients who arephysiologically fit and are operated late have more chances of infectious morbidities, which causes longer stay in hospital and ultimately more costs as compared to those who are fixed early (Rogers et al. 1995).

A research quantified that from all the clinical fractures, hip fracture and vertebral fracture have the highest mortality risk by 6.68 and 8.64 respectively. Studies reveal that mortality rate
did not increase following forearm or any other clinical fracture among healthy older women (Cauley et al. 2000). No single factor is claimed to be as a risk factor for premature death after a fracture. Insistent treatment for a group of populations who have already suffered from a fracture may lessen the morbidities and mortality related to osteoporosis and may alter the course towards a long-term survival. Future research would help to better illustrate interpreters of mortality and to plan cost-effective strategies with the goal to decrease short and long-term morbidity and mortality in patients with supreme risk.

2.7 Therapeutics options for fractures

Osteoporosis is avertible and curable disease. Physical activity and proper nutrition intake are among the factors that can reduce the risk of osteoporosis. There are four major goals of osteoporosis treatment which include preventing the fracture, increasing the bone mass, relieving the symptoms of disability and most important one is to maximize the mobility and physical function. US surgeons have suggested a pyramidal approach which is composed of three levels, in order to treat the osteoporosis (Rockville 2004). These levels are given below:

- First level is to change the life style by adding more nutritious diet in their daily life like consumption of proper calcium and vitamin D.
- Second one is to eliminate the secondary causes of osteoporosis, which includes adverse effects of drug therapy, endocrine disorders, immobilization, cancer, disorders of the gastrointestinal and renal disease.
- Pharmacological intervention comes at the third level to intensify bone mass and decrease the fracture risk.

Use of antiresorptive and anabolic agents are the two drug therapy approaches to cure osteoporosis. Antiresorptive agents are used for reducing the bone loss while some anabolic agents are used to rebuild the bone structure. At the end, both approaches lead towards the decrease of fracture risk. Antiresorptive agents are bisphosphonates, estrogen, selective estrogen receptor modulators (SERMs) and calcitonin, while anabolic agents include the parathyroid hormone therapy (PTH). As a first line therapy bisphosphonate are used for the treatment of osteoporosis but it is more effective with the combination of life style modifications and adequate doses of calcium and vitamin D. They have less reported adverse effects and they have the capacity to sustain the stomach hydrolysis as compared to their
patent compounds like inorganic pyrophosphates. They inhibit the action of osteoclast and increase the BMD (Crandall 2001).

2.8 Hormonal therapy

Bone loss is the major core cause of postmenopausal osteoporosis which occurs due to the deficiency of estrogen. HT is the most widely used approach to cure osteoporosis in postmenopausal women. The word HT is used to define two kinds of formulation:

- Estrogen-only (unopposed) therapy
- Combined estrogen and progestogen (opposed or combined) therapy

Main purpose of HT, either unopposed or opposed, is to inhibit menopausal bone loss from spine, femur and radius (Compston & Rosen 2009). The founder of this theory was Reifenstein and Albright. First time they recognized the link between estrogen lacking state in the menopausal women in their original publications in the 1940s. Calcium absorption and serum 1,25-dihydroxyvitamin D [1,25-(OH)2D] decreases in osteoporotic women and they suffer from negative calcium balance. Estrogen therapy improves calcium balance in patients with postmenopausal osteoporosis. Different studies indicated estrogen therapy increase the calcium absorption and serum 1,25(OH)2D level in women suffering from postmenopausal osteoporosis (Gallagher et al 1980). Another study shows that hormone therapy significantly reduces the fracture incidence ratio. The relative ratio dose does not show any significant difference either if estrogen is used alone or in combined form (Stovall 2013). Estrogen therapy not only increases the bone mineral density but also inhibits the bone loss by binding the estrogen receptors on the bone and blocking the production of cytokines that increase the number of osteoclast. After the menopause, the ovarian secretion of estrogen varies and falls at variable rate. Women with intact uterus should use estrogen or combined therapy with progesterone to prevent themselves from endometrial hyperplasia which may lead to the endometrial cancer. Favorable impact of estrogen and progesterone combined therapy on BMD of post-menopausal women were revealed from several randomized and placebo-controlled trials (Sarah et al. 2008). Several observational studies describe that coronary heart disease risks reduce after the estrogen therapy in post-menopausal women. Nevertheless, there is no strong association with the prevention of stroke (Grodstein et al. 1996).

Meta-analysis conducted by Well et al. in 2002, showed that HT had a consistent and positive impact on the BMD of post-menopausal women at forearm 3%-4.5%, spine 3.5% -7 % and
hip 2%-4%. Other meta-analysis studies explain that hormone therapy reduced non-vertebral fracture and vertebral fracture by 27% and 33 % respectively (Torgersen & bell 2001). The long-term use of this therapy is reserved for the women who cannot tolerate the non-estrogen therapies. After several studies, researchers reach at a point that may be the low dose of estrogen and combined therapy reduced the side effects but maintained the BMD. Women’s HOPE study shows that if the dose of estrogen or combined therapy decreases up to 0.3mg daily, it still increases the hip and spine BMD within two years of treatment (Lindsay et al. 2002). Other studies also show the same evidence of low dose estrogen therapy effect. They reveal that post-menopausal women taking 0.25mg dose of 17-estradiol for three years have positive effect on BMD of hip, spine and total body and it also reduces the bone turn over (Prestwood et al. 2003).

There is another medication Raloxifene which belongs to the class called as SERMs (selective estrogen receptor modulators). Their mechanism is that they bind to the estrogen receptors and behave like estrogen, so they prevent the bone loss and increase the BMD and improve the lipid profile too. They avoid the potential side effects of estrogen which lead towards the risk of breast and endometrial cancer. The standard dose for prevention of osteoporosis in post-menopausal women is 60 mg/day. After constant use of three years it increases BMD 2.3 % at spine and 2.5 % at hip site. different studies show that it can reduce half of the vertebral fracture but it is not effective in case of hip and other non-vertebral fractures (Cranney et al. 2002). Raloxifene shows more hot flushes and leg cramping as compared to placebo but less vaginal bleeding than the estrogen and combined therapy (Sarah et al. 2008).

In addition to the conventional hormone therapy, there is another option for treatment which is called as bioidentical hormone which is often termed as Natural hormone therapy. These compounds share the same molecular formula of human hormones. They are derived from the plants and identical to endogenous hormones. They are either extracted from the soybean plant and Mexican wild yam root. They are prescribed and formulated under the licensed health care provider to treat the symptoms of perimenopause and hormonal unbalancing (Sarah et al. 2008).

2.9 Withdrawal of hormone therapy and risk of fracture

Special intensive care is required for those women who withdrew the HT to prevent them from fracture risk. Some studies show that proliferated risk of fracture occurs after discontinuation of estrogen therapy. Research also shows that the defensive connection of HT
with the reference to hip fracture disappeared within two years of termination of HT. Women who withdrew the hormone therapy had a 55% more chance to get hip fracture in comparison to those who continued their therapy. Cessation of HT not only increase the fracture risk but also decreases the BMD (Roksana et al. 2011). Another study explains the drastic surge of occurrence of hip fracture which is 65% higher in women who terminated HT from last five years as compared to those who never used HT (Miriam 2006). Specifically, bone loss is greatly enhanced, consequentially reduction of BMD at the lumbar spine and hip up to 4.5% and 3.3% respectively in the first 12 months of cessation of hormone therapy (Miriam 2006).

The study reported the 3.7% increase in bone mineral content during first three-year treatment, whereas it decreased by 5.7% in women who were not on HT. Current users of HT had 40% low prevalence of hip fractures in comparison to the non-users of HT. However, the risk of hip fracture is almost same for those who ceased HT from last five years to those who never used it (Yates et al. 2004). Still there have been conflicting findings as well. A study reported by Christiansen et al. in 1981 reveals that bone loss rate was similar for those who discontinued HT from a year to the placebo group. It also shows that after cessation of HT the bone loss was same as compare to normal bone loss (Christiansen et al. 1981). This research is also confirmed by Greendale and his colleagues in late 2002, that also recorded that the withdrawal of hormone therapy did not lead to an accelerated bone loss. Specially, HT for almost 7 years did not provide any further bone mineral density advantage as compared to what it provided during first three years (Greendale et al. 2002).

Numerous studies revealed the useful impacts of HT on BMD and bone turnover but either its withdrawal causes accelerated bone loss or not is still controversial and debatable. However, some studies still show that rate of bone loss increased after termination of HT in postmenopausal women as compared to non-users of hormone therapy. One study reveals that annual rate of bone loss is between -0.7 to -1.6% at radius area which is 2.2 to 2.8 times higher after withdrawal of HT. Furthermore, it explains that termination of therapy brings out a prompt rise of bone turnover in postmenopausal women who undergoing HT from at least 6 years (Elisabeth et al. 2003).

As the withdrawal effects are still controversial, another research raises a point about the residual beneficial effect of the hormone therapy. Study divulges that on an average after 3 years of termination of HT there was increase in mean vertebral BMD then the baseline
values, before the HT treatment started, which points to the lasting valuable effect on bone mass (Trémollières et al. 2001).

2.10 Reasons of withdrawal of hormone therapy

Increased risk of cardiovascular disease and breast cancer are the main reason of withdrawal of this therapy, but it can be controlled by reducing the standard dose of estrogen therapy. Different studies show that women started to discontinue the treatment after 6-8 months of publication of women health initiative (WHI) report and half of them did not have the exact knowledge of the WHI report’s findings (Ettinger et al. 2003).

As different studies explain that the reasons of withdrawal of hormone therapy are an increased risk of cardiovascular event, breast cancer, vaginal bleeding and weight gain. Research shows that 52% older women have stopped taking HT due to vaginal bleeding which is one of the most frequent reason of withdrawal of HT (Ettinger et al. 1999). Using the estrogen alone gives rise to the chance of endometrial cancer. In fact, for controlling this issue a combined regime is adopted which is using estrogen with the progestin, but the progestin gives adverse effects on the serum lipids level and an elevated risk of coronary heart disease as compared to the estrogen therapy (Bruce et al. 1994).

Then later on, the advance studies showed that women using combine hormone therapy have had more chances of breast cancer in comparison to those who had unopposed estrogen therapy. The risk is increased in the women who are using combined hormone therapy for more than 5 years. They have 1.7 times more risk of breast cancer and 2.7 times more risk of invasive lobular carcinoma as compared to those who are using unopposed estrogen therapy (Li et al. 2003). Another UK based research reveals that women who undergo estrogen therapy for 10 years added 7 additional breast cancer cases per 1000 users but 19 cases in case of combined therapy (Beral 2003).

The reduction of risk is depending on the dosage of the progesterone, and if it is added only 10 days in the standard regimen of HT then the occurrence of endometrial hyperplasia is 5.3% and atypical hyperplasia is 0.7%. However, constant combined HT is not related with an enhanced threat of hyperplasia, in fact it will alter the endometrium to normal in those who are suffering from complex hyperplasia due to prior HT (Sturdee et al. 2000). One study explains that continuous use of nine months of combined therapy may recover from the hyperplasia which occurred due to prior HT. It not only recovers but it also prevents from the
reoccurrence of hyperplasia in the women who went through treatment for five years. The outcomes of this treatment provide the assurance of the long-term safety of endometrium (Michael et al. 2002).

The linkage between the hormone use and weight gain is still unknown. Maybe it is due to aging or the genetic factors. A study shows that women who were using HT increased 1.0 kg less weight at the end of three years as compared to the non-users. As well as they show significant 1.2 cm less increase in waist girth and 0.3 cm less increase in hip girth as compared to non-users. Still these values are not statically significant because there are number of other factors which are associated with the weight gain and loss e.g. ethnicity, smoking status, physical activity and the hip work activity (Espeland et al. 1997). Ian and his colleagues describe that after 2 years use of conjugated estrogen and progesterone does not affect the body composition but in the placebo group weight gain is clearly visible because menopause is the reason of weight gain (Ian et al. 2007). In 2003, a Danish randomized controlled clinical trial study reveals that women who used HT for 5 years had less increase in body weight in contrast to those who never used HT. The key element of the weight gain was a decrease in physical fitness (Jensen et al. 2003). Another study accepted this statement and explains that postmenopausal women who were not treated had increased in total fat mass and serum leptin level after one year of study (Di Carlo et al. 2004). Some studies contradict this effect of HT and explain that HT which was used during the initial years of menopause does not show an important role in gaining muscle strength, lean muscle mass, or the reduction in total body or abdominal fat (Maddolozzo et al. 2004).

Women having less estrogen dosage in comparison to typical dosage levels are having less undesirable side effects like vaginal bleeding or breast tenderness, which are some of the foremost explanations for the termination of HRT (Gambacciani & Levancin 2014). A study claims that specific low dosage of continuous combined hormone replacement therapy which is 0.5 mg 17β-estradiol and 2.5 mg dydrogesterone protects the endometrium of postmenopausal women and it is also well accepted by majority of women (Bergeron et al. 2010).

Another way of preventing the side effects of HT is by changing the route of administration, it means changing the oral route to the transdermal route and the main point is to avoid the “First pass effect”. In comparison to oral estrogen therapy, transdermal estrogen therapy is associated with less risk of venous thromboembolism and stroke (Stovall 2013).
2.11 Other risk factors for fractures in post-menopausal women

After the onset of menopause in women the low level of estrogen in the body is not the only reason of bone loss, there are some other predictors of bone loss and fracture’s risk such as low or high body weight, low calcium and vitamin D level, less physical activity, genetics, age, fracture history and parity and excess alcohol and tobacco use. Some studies show that women who did some kind of physical exercise suffered 55% less hip fractures than women who were not involved in any physical activity. Less than 7 alcoholic drinks per week may not give any adverse effect to the bones but the excessive alcohol consumption has adverse effects on bone (Miriam 2006). Another study claims that one hour per week of walk at an average rate reduces 6% risk of fracture in post-menopausal women. Different researches show diverse results but past prospective studies reported a 25% to 39% lower risk of hip fracture in physically active group as compared to non-active. Change in a lifestyle behavior also protects from the risk of fracture. Women who were not inactive in the past but started physical activity 4 hours in a week, have less fracture risk as compared to those who remain sedentary (Diana et al. 2002). However, Hoidrup and his colleagues reported that women who were inactive in their past 6 years, but currently moderately active have more risk of fracture as compared to the active group which maintained their physical activity throughout the 6 years (Hoidrup et al. 2001). Several studies describe that in clinical research, women who were taking estrogen supplement with being moderately physically active had less fractures and had more bone mineral density in trabecular bone as compared to those who were just doing exercise (Kohrt et al. 1998).

Numerous researches explain that walking is one of the best physical activity for the older women. It is safe and effective way of exercise and it has beneficial effect on BMD. According to a study, if an older woman walks four hours per week or more, she has 41 % less risk of hip fracture (Krall & Dawson 1994). A Danish research describes that increasing physical activity did not give any fracture protective effect, however it gives a clue that moderate levels of physical activity may provide a shield from later hip fracture (Hoidrup et al. 2001). Less physical activity is a vital risk aspect for hip fracture, that is why health professionals should recommend regular and maintained physical activity during the aging process. It should also be a vital part of policies, designed for controlling the frightening increase in hip fractures globally (Sievänen & Kannus 2007).
Alcoholism is a threat for low bone density and osteoporotic fractures, but the effects of limited alcohol use on bone are still debatable. A systematic review shows that modest drinker who is consuming half to one drink per day has lower risk of hip fracture as compared to the person who is consuming more than two drinks per day (Karina et al. 2008). A study in France depicts that moderate alcohol use which is 11-29g/day is linked with a substantial increase in trochanteric bone mineral density in aged women. Though this trend is not visible in non-users and in heavy users which is more than 30g/day. The results propose that the positive effect on bone mineral density happened only with the sensible alcohol intake (Olivier et al. 2000).

Another study explains the positive effect of modest alcohol consumption >28g/week which is lower from the previous study. They observed that this amount of alcohol usage decreases the serum PTH concentration, which could be the cause of reduced bone reabsorption. Alcohol increases calcitonin production, which surges the vertebral BMD but it did not give any result on femoral sites (Prema et al. 2000).

Several researchers concluded that a decreased BMI is related to higher risk of developing fractures at an older age. A large worldwide prospective population base cohort study reports that low BMI is a risk factor of all fractures but it also depends on bone mineral density values. A person with BMI of 20 kg/m² has twice more risk of hip fracture than that of BMI of 25 kg/m². Whereas, when BMI 30 kg/m² is equated by BMI 25 kg/m² it shows only 17% decrease in risk of hip fracture (De Laet et al. 2005). Another prospective cohort study describes 10% weight loss of women in middle age (50-64 years) as a strong indicator for hip fracture risk (Langolis et al. 2001). As the word “thin“ do not have any proper definition but different studies explain it differently, Ravn and his colleagues defined thinness as “low percentage of body fat, low body mass index or low body weight” (Ravn et al. 1999). A United States based clinical research explains that even an intended weight loss in older women leads towards the hip fracture risk. Older women who lost their weight loss in later years have double risk of bone loss at hip site and hip fracture, regardless of their current weight (Ensrud et al. 2003).

The main ingredients of cigarette, nicotine and cadmium have a harmful effect on bone cells. Several studies linked smoking with the fracture risk. A research reveals that smoking increases the lifetime risk of 13% vertebral and 31% hip fracture in women while 32% vertebral and 40% hip fracture in men. It also shows that smoking count has direct effect on
bone loss and increases fracture risk, which may be moderately overturned by quitting smoking (Kenneth & Robert 2001). According to the WHO report “Tobacco and osteoporosis”, in every eight hip fractures one is due to cigarette smoking. In comparison, current smoker loses bone mass faster than a nonsmoker. In addition, hip fracture risk among smokers is always more but it reaches to 17% more at age of 60 and 71% at age of 80, and it further increases up to 108% at age of 90 (WHO 2016b).

In postmenopausal women suffering from calcium deficiency calcium supplementation can help in preventing osteoporotic fractures. Several studies conclude different range of effective dose of calcium intake, a French research found that women who were taking 1200mg/day calcium and 800units/day of vitamin D have 43% and 32% less risk of hip fracture and non-vertebral fracture respectively (Chapuy et al. 1992). On the other hand, some research shows positive trend towards the risk reduction of vertebral fracture but the values for the risk reduction for non-vertebral fractures was unclear. A meta-analysis of 15 assessments found that calcium intake can cause positive BMD alter from baseline of 2.05% for total body bone density, 1.66% at the lumbar spine, 1.6% at the hip, and 1.9% at the distal radius (Shea et al. 2004). Another research found that if calcium is used alone or with the combination of vitamin D, it reduces 24% risk of all types of fracture and the most effective dose is 1200mg/day and 800 units of vitamin D daily for people more than 50-year-old (Tang et al. 2007). A study exposes that vitamin D supplements along with calcium, give more valuable effects in slip falls events and increases bone density in elderly women who have experienced a hip fracture (Harwood et al. 2004).

Age is also one of the risk factor for fracture because with time the bone gets weak due to co-morbidities or due to poor age related nutritional habits. The statistics reveal that globally, one in three women while one in five men above the age of 50 will face osteoporotic fractures (IOF 2016). Researchers have also looked at association with pregnancies, however, different researches claim that there is no association between the multiple pregnancies and subsequent osteoporosis. But, one study found that each pregnancy reduces 5-10 percent chance of hip fracture (Michaelsson et al. 2001).
2.12 Logical frame work of the study

Based on the literature review, Figure 6 depicts the protective effect of HT in the post-menopausal women. It shows that the protective effect decreases after some time of cessation of HT and it leads to low bone mineral density, which causes a higher risk of fractures.

Figure 6. Aging, menopause and resulting osteoporosis
3. AIMS OF STUDY

General aim is to explore the link between the usage of hormone therapy (HT) and risk of fracture and mortality in post-menopausal women.

Specific aims are to:

- To inspect the preventive effect of hormone therapy to risk of overall fracture, osteoporotic fracture, hip fracture and mortality in post-menopausal women.
- To investigate the duration of hormone therapy and risk of fracture and mortality.
- To look into the other life style related features which act as a risk factor for a fracture and mortality.
4. METHODOLOGY

4.1 Study design

This research work is part of Kuopio Osteoporosis Risk Factor and Prevention (OSTPRE), which is a population based prospective cohort study.

4.2 Study setting and subjects

OSTPRE study started in 1989 and included all 14,220 peri and post-menopausal women aged 47 to 56, who were inhabitants of Kuopio province, Eastern Finland during that time period. The baseline cohort has been monitored with postal reviews at 5-year interims and this study data is allied with national registries. Out of 14,220 women, 13100 replied to the baseline postal enquiry in 1989. For focusing on main idea of the study plan, those cases were deleted from the study which were using the HT due to other reasons like; gynecological surgery, Hysterectomy and Oophorectomy. At the baseline, postal enquiry a total of 703 cases were reported these surgical operations. A total 617 were stated the hysterectomy and 86 were reported the oophorectomy. The sum of 703 cases were separated from the study to control the confounding. Remaining 12399 participants were first divided into two categories users and Non-users. The user’s category is subdivided into two classes, users up to five years and users more than five years.

From the national registries, total of 2587 deaths and 278 hip fractures were recorded. In addition, from the postal enquires between 1989 to 2009 (20 years), total 3314 fractures were reported from which 1799 were osteoporotic.
Figure 7. The study process

OSTPRE population base cohort: Women age 47-56 in 1989. Kuopio Finland n=14220

National Registry Data

Responded in 1989 n=13100

Case dropped on the bases of gynecological operations n=703
Hysterectomy n=617
Oophorectomy n=86

Final cohort study cases n=12399

Any fracture N= 3314
Osteoporotic fracture N=1799
Hip fracture N=278
Deaths N=2587

Hormone Therapy

Dichotomous Hormone Use
Non-Users n=5419
Users n=6980

Non-users
Any Fracture n=1462
Osteoporotic Fracture n=807
Hip Fracture n=128
Deaths n=1347

Users
Any Fracture n=1888
Osteoporotic Fracture n=992
Hip Fracture n=150
Deaths n=1240

Durational Hormone Use
Non-Users n=4519
Up to 5 years n=5401
More than 5 years n=1579

Non-users
Any Fracture n=1462
Osteoporotic Fracture n=807
Hip Fracture n=128
Deaths n=1347

Users Up to 5 Years
Any Fracture n=1445
Osteoporotic Fracture n=762
Hip Fracture n=108
Deaths n= 973

More than 5 years
Any Fracture n= 443
Osteoporotic Fracture n= 230
Hip Fracture n= 42
Deaths n=267
4.3 Data collection

The data was collected by postal questionnaire, which inquired about health disorders like incidence of fractures, medications, lifestyle factors and use of HT. Selected variables for this study are; age, weight, height, smoking, fracture types, milk and cheese intake, Hormone use. BMI was calculated by self-reported weight (in Kg) and height (in Cm). Current smoking status was categorized as YES or NO. Fracture types were recorded at each postal questionnaire. Calcium intake was calculated by self-reported intake of milk and cheese products. The period of intake of HT was determined based on following question in self-reports: For how long you used female hormone in total? Questionnaire used at the Baseline is given as Appendix 9.

A postal inquiry was mailed to the participants in 1989, 1994, 1999, 2004 and 2009. This study analyses the data at baseline (1989) and includes fracture history up to 2009.
4.4 Data analysis

IBM Statistical Package for Social Sciences (SPSS) version 23 was used for the statistical examination of the data. Association of fracture risk and mortality with the use of HT were estimated as hazard ratios by using cox regression model. Categorical variables were quantified using frequency distribution while mean, standard deviation and percentiles have been concluded for the continuous variables. In order to predict the fractures, univariates analysis, cross-tabulation and chi square tests were carried out for categorical data while continuous data was analyzed using T-test. Both the One-Way ANOVA and the Independent Samples T- Test are used to compare the means for the two groups.

Lastly, for evaluation of adjusted relative risks of fracture and mortality, all covariates are added into the cox regression model one by one and those are selected which are statistically significant. The Kaplan-Meier test which estimates the cumulative hazard for each type of fracture, indicated the differences among the treatment group and non-users. The results are reported as mean SD, standard errors or 95% confidence interval and p value is set at 0.05. Results are presented in tables and graphs.

4.5 Ethical Considerations

The OSTPRE study was approved by the Ethics committee of Kuopio university Hospital for the entire study period, with protocols set for the informed consent, confidentiality and other ethical requirements.
5. RESULTS

5.1 Description of study population

Baseline features (Age, weight, height, Ca intake, fractures, mortality, smoking) of the study population (n=12399) are shown in Table 1. Mean and Standard Deviations are given for the continuous variables. Numbers and proportions (%) are given for categorical variables.

Table 1: Baseline characteristics of study population for fracture analysis and mortality (n=12399).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Non-HT N=4519</th>
<th>HT Users N=6980</th>
<th>Categories of HT Use ≤ 5 years HT N=5401</th>
<th>&gt;5 Years HT N=1579</th>
<th>Total N=12399</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous Variables Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>52.6 (2.9)</td>
<td>51.9 (2.8)</td>
<td>51.8 (2.8)</td>
<td>52.0 (2.9)</td>
<td>52.3 (2.9)</td>
</tr>
<tr>
<td>weight (kg)</td>
<td>69.4 (12.7)</td>
<td>27.3 (11.2)</td>
<td>67.6 (11.3)</td>
<td>66.3 (10.8)</td>
<td>68.2 (11.9)</td>
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<tr>
<td>Height (cm)</td>
<td>160.8 (5.4)</td>
<td>161.4 (5.1)</td>
<td>161.4 (5.1)</td>
<td>161.3 (5.0)</td>
<td>161.1 (5.2)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.8 (4.6)</td>
<td>25.8 (4.0)</td>
<td>25.9 (4.1)</td>
<td>25.4 (3.9)</td>
<td>26.2 (4.3)</td>
</tr>
<tr>
<td>Calcium intake (mg/day)</td>
<td>840.1 (423.5)</td>
<td>800.1 (385.4)</td>
<td>803.2 (383.4)</td>
<td>799.4 (392.0)</td>
<td>817.5 (402.9)</td>
</tr>
<tr>
<td>Categorical Variables N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any fracture</td>
<td>1426 (11.5%)</td>
<td>1888 (15.2%)</td>
<td>1445 (11.7%)</td>
<td>443 (3.6%)</td>
<td>3314 (26.7%)</td>
</tr>
<tr>
<td>Osteoporotic Fracture</td>
<td>807 (6.5%)</td>
<td>992 (8.0%)</td>
<td>762 (6.1%)</td>
<td>230 (1.9%)</td>
<td>1799 (14.5%)</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>128 (1.0%)</td>
<td>150 (1.2%)</td>
<td>108 (0.9%)</td>
<td>42 (0.3%)</td>
<td>278 (2.2%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>1347 (10.9%)</td>
<td>1240 (10.0%)</td>
<td>973 (7.8%)</td>
<td>267 (2.2%)</td>
<td>2587 (20.9%)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>5.2%</td>
<td>6.8%</td>
<td>5.0%</td>
<td>1.8%</td>
<td>11.9%</td>
</tr>
</tbody>
</table>
5.2 Hormone use and fracture analysis

Altogether, there are 56.2% (n=6980) women who had use hormone therapy whereas 36.4% (n=4519) were non-users of hormone therapy. The association of number of fracture events and use of hormone therapy was studied by chi-square. Cox regression analysis’s results are explained in form of hazard ratio and 95% confidence interval in the final multivariate model.

5.2.1 Overall fracture analysis and HT

Total n=3314 overall fractures were recorded in 20 years from which n=1426 were occurred in the non-HT group whereas rest of n=1888 were in the HT user’s groups. After comparison with the users, it was found that the risk of overall fracture increased in women who were not using the hormone therapy.

Table 2: Adjusted risk of overall fracture related to the hormone therapy (n= 12399).

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio (HR)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HT users</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Non-HT</td>
<td>1.06</td>
<td>0.98-1.13</td>
<td>0.103</td>
</tr>
<tr>
<td>Age</td>
<td>1.03</td>
<td>1.01-1.04</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>0.98</td>
<td>0.97-0.99</td>
<td>0.0001</td>
</tr>
<tr>
<td>Calcium intake(mg/day)</td>
<td>1.00</td>
<td>1.00-1.00</td>
<td>0.036</td>
</tr>
</tbody>
</table>

Table 2 shows that hormone therapy does not have any association with the risk of overall fracture. One-way ANOVA test indicated that women who had less BMI and calcium intake are more likely to have a fracture as compared to high BMI and calcium intake. (Data not shown). However, trends are almost same in the durational hormone use and risk of overall fracture. Hence results are not significant but the hazard ratio value is less in group of women who were used hormone therapy for up to 5 years as compared to non-users. Which is well presented in table 3.
Table 3: Adjusted risk of overall fracture related to the duration of hormone therapy (n=12399).

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio (HR)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5-year users</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≤ 5-year users</td>
<td>0.96</td>
<td>0.87-1.07</td>
<td>0.567</td>
</tr>
<tr>
<td>Non-HT</td>
<td>1.03</td>
<td>0.92-1.15</td>
<td>0.532</td>
</tr>
<tr>
<td>Age, year</td>
<td>1.03</td>
<td>1.01-1.04</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.98</td>
<td>0.97-0.99</td>
<td>0.0001</td>
</tr>
<tr>
<td>Calcium intake (mg/day)</td>
<td>1.00</td>
<td>1.00-1.00</td>
<td>0.036</td>
</tr>
</tbody>
</table>

The overall fracture risk associating with the hormone use is not substantial. However, the graph indicates users having slightly lower hazard of cumulative fractures as compared to non-users (fig 9).

Figure 9. 20-year follow up, hazard ratio trend for overall fracture with the dichotomous hormone use (y/n). (Blue line shows the non-users and green depicts the users).
5.2.2 Osteoporotic fracture analysis and HT

Out of 3314 overall fractures, 1799 are recorded as osteoporotic fractures. Those osteoporotic fractures are categorized into wrist fracture, vertebral fracture and hip fractures. Same covariates were used for osteoporotic fracture models to check the hypothesis, whether use of hormone therapy have protective effect or not. The cox regression analysis shows that women who were not using HT have a 14% increased annual risk of osteoporotic fracture over the follow-up period of 20 years. The P-value is less than 0.05 shows the preventive effect of HT towards the fracture risk. Table 4 illustrate the risk of fracture among the non-users of HT.

Table 4: Adjusted risk of osteoporotic fracture related to the hormone therapy (n= 12399).

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Users HT</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Non-HT</td>
<td>1.14</td>
<td>1.04-1.25</td>
<td>0.005</td>
</tr>
<tr>
<td>BMI(kg/m²)</td>
<td>0.96</td>
<td>0.95-0.98</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>1.06</td>
<td>1.05-1.08</td>
<td>0.0001</td>
</tr>
<tr>
<td>Calcium intake(mg/day)</td>
<td>1.00</td>
<td>1.00-1.00</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Table 5 shows that risk of osteoporotic fracture increased up to 15% among non-users and remained the same in group of women who were using up to 5 years as compared to the users of more than 5 years. However, the p value is not significant in case of up to 5-year users but the hazard ratio indicates some plausible preventive effect of HT among the users. However, analysis suggests that decrease in calcium intake leads towards the fracture risk and the risk continued to decrease with increasing BMI. Whereas, the predictor age has a coefficient of 1.06, which means the hazard rate increases by 1.06 with each unit increase (year) in age. It means rise in each unit of age increases the risk of osteoporotic fracture by 6 %.
Table 5: Adjusted risk of osteoporotic fracture related to the duration of hormone therapy (n=12399).

<table>
<thead>
<tr>
<th>Hazard Ratio (HR)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5-year users</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≤ 5-year users</td>
<td>1.01</td>
<td>0.87-1.17</td>
</tr>
<tr>
<td>Non-HT</td>
<td>1.15</td>
<td>0.99-1.33</td>
</tr>
<tr>
<td>Age</td>
<td>1.06</td>
<td>1.05-1.08</td>
</tr>
<tr>
<td>BMI</td>
<td>0.96</td>
<td>0.95-0.98</td>
</tr>
<tr>
<td>Calcium intake</td>
<td>1.00</td>
<td>1.00-1.00</td>
</tr>
</tbody>
</table>

The graph shows that users have lower risk of osteoporotic fractures as compared to non-users (Fig 10).

Figure 10. 20-year follow up trend of hazard ratio of osteoporotic fracture with the dichotomous hormone use (y/n). (Blue line shows the non-users and green depicts the users).
5.2.3 Hip fracture analysis and HT

Total 128 cases of hip fracture were self-reported. Same covariates were used for hip fracture to analyze whether use of hormone therapy protects from the fracture risk or not. The results are quite different from the osteoporotic fractures and the model shows that there is no association between the hormone use and risk of fracture. In hip fracture analysis, all covariates are non-significant except the age which shows that the hazard rate increases by 1.17 times (17%) with each unit increase in age.

Table 6: Adjusted risk of hip fracture related to the hormone therapy (n= 12399).

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio (HR)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Users HT</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Non-HT</td>
<td>0.96</td>
<td>0.75-1.22</td>
<td>0.740</td>
</tr>
<tr>
<td>Age</td>
<td>1.17</td>
<td>1.12-1.22</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI(kg/m²)</td>
<td>0.99</td>
<td>0.96-1.02</td>
<td>0.622</td>
</tr>
<tr>
<td>Calcium</td>
<td>1.00</td>
<td>1.00-1.00</td>
<td>0.413</td>
</tr>
<tr>
<td>intake(mg/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Situation is almost same in a case of durational hormone therapy. In addition, by increase in each unit of age it showed 17% more risk of hip fracture. The hazard ratio is almost the same among all groups and it shows that hormone therapy did not protect from the risk of hip fracture. Even the figure 11 shows that the hazard rate among the non-users of HT and users of HT is almost same and lines are overlapping each other.

Table 7: Adjusted risk of hip fracture and the duration of hormone therapy use (n= 12399).

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio (HR)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5-year users</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≤ 5-year users</td>
<td>0.77</td>
<td>0.54-1.11</td>
<td>0.171</td>
</tr>
<tr>
<td>Non-HT</td>
<td>0.79</td>
<td>0.56-1.13</td>
<td>0.208</td>
</tr>
<tr>
<td>Age</td>
<td>1.16</td>
<td>1.12-1.22</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI(kg/m²)</td>
<td>0.99</td>
<td>0.96-1.02</td>
<td>0.668</td>
</tr>
<tr>
<td>Calcium</td>
<td>1.00</td>
<td>1.00-1.00</td>
<td>0.408</td>
</tr>
<tr>
<td>intake(mg/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 11. 20-year follow up trend of hazard ratio of hip fracture with the dichotomous hormone use (y/n). (Blue line shows the non-users and green depicts the users).

5.3 Hormone use and mortality analysis

Out of total 12399 participants, n=1347 deaths occurred. In mortality analysis, current smoking status, age and BMI are used as a covariate. Cox regression model is used to check the association between the hormone use and risk of mortality. Table 8 shows that risk of death increased by 30% in non-user group as compared to the users and the smokers had 45% increased risk of death as compared to nonsmokers. The risk of death is increased by 10% with each unit of age. However, the hazard rate of mortality increases by 1.04 with each unit increase in BMI.
Table 8: Adjusted Cox regression analysis of mortality risk related to the hormone therapy (n=12399).

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio (HR)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Users HT</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Non-HT</td>
<td>1.30</td>
<td>1.20-1.40</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>1.10</td>
<td>1.08-1.11</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.04</td>
<td>1.03-1.05</td>
<td>0.0001</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.45</td>
<td>1.38-1.52</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

The hazard ratio shows that risk is less among those who used the therapy up to 5 years as compared to non-users. Rest of all covariates shows the significant results. The risk of death increases by 1.45 among smokers, meaning around 45% higher risk of premature death as compared to the non-smokers. Whereas risk increased up-to 10% with each year of age. Non-users had 39% increased risk of death as compared to the group which were using HT more than 5 years.

Table 9: Adjusted risk of mortality related to the duration of hormone therapy (n=12399).

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio (HR)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5-year users</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≤5-year users</td>
<td>1.09</td>
<td>0.95-1.25</td>
<td>0.206</td>
</tr>
<tr>
<td>Non-HT</td>
<td>1.39</td>
<td>1.21-1.59</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>1.10</td>
<td>1.08-1.11</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>1.04</td>
<td>1.03-1.05</td>
<td>0.0001</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.09</td>
<td>1.38-1.52</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

The analysis graph clearly shows that hormone therapy has a strong association with the premature death. The users of HT have lower chance of mortality as compared to non-users which shown in figure 12.
Figure 12. 20-year follow up trend of hazard ratio of mortality with the dichotomous (y/n) hormone use. (Blue line shows the non-users and green depicts the users).
6. DISCUSSION

The aim of this research was to examine associations between hormone use and risk of fracture and mortality. The data was collected by committee of Kuopio university Hospital and study called as OSTPRE study in which 12399 participants physical parameters, life style and fracture events were examined. Patients attitude towards calcium intake and smoking status were investigated, all fractures were recorded through self-reports. Main findings of this study are presented, following discussions on the found associations. The strengths and limitation are discussed. As a final step, suggestions regarding future studies and implications of findings are presented.

6.1 Main findings

The main findings of this study are that the use of hormone therapy is associated with both the risk of osteoporotic fracture and mortality in postmenopausal women. Result showed that risk of fracture and mortality varied by the use of hormone therapy and lifestyle factors. Women who were using more calcium containing product like cheese and milk are facing less risk of fracture. Specifically, the hormone therapy is more effective in preventing the osteoporotic fracture as compared to the overall fracture. Increase in age, continued the risk of fracture and chances of death. The founded reasons of risk of fracture and death were; smoking status, change in BMI, aging and less use of calcium containing products. The discussion will focus on the below mentioned major findings and co-relate them with previous studies.

6.1.1 Risk of fracture and mortality associated with hormone therapy

This study reports that hormone therapy protects from osteoporotic fractures, but does not apply to other fractures which are not osteoporotic. Previous studies show the positive relation between the osteoporotic fracture, not between all kinds of fracture (Watarai 2007). HT is not only a single factor which contributes towards the prevention of these fractures, the physical fitness, fitness education and training and many other factors involved in diagnosis and management of such events (Sterling et al. 1992). Several researches describe that there is no particular evidence of protective effect of HT in premenopausal women athletes (Carolina et al. 2016). Several studies demonstrate that HT increase the BMD while reducing the risk of osteoporotic fracture among healthy post-menopausal women (Cauley et al. 2003). Studies based on Women’s Health Initiative, Women’s Interventional Study of long Duration
Estrogen after Menopause (WISDOM) reveals that HT decreases risk of fragility fracture by 20-35% (IOF 2016).

In this study, age, dietary calcium and BMI were taken as covariates to study the association between HT and risk of fracture. The result showed that HT gives protective effect towards the osteoporotic fracture. The hazard ratio for overall fracture and hip fracture is not significant which predicts that for the prevention of hip fracture and overall fracture, which may consist of stress fracture, cannot be prevented by only one intervention like HT.

As the previous research demonstrates that mortality among the HT users is lower than the non-users but the survival benefits reduces with long duration of use (Grodstein et al. 1997). Various studies support clinical discussion about the role of HT in the care of symptomatic postmenopausal women (Benkhadra et al. 2015). This present study also accepts this approach and result shows that women who were using the HT therapy has less risk of premature death as compared to the non-users.

6.1.2 Risk of fracture and mortality associated with BMI

Several studies suggest that increase in BMI contributes as a protective factor for a risk of fracture. Even though the prevalence and the pathogenesis of fracture in obese individuals has not still explained. Some studies explore that it is connected with the BMD. When BMD is adjusted, low BMI prevents from osteoporotic fracture but remained as a risk factor for hip fracture (Johansson et al. 2014). Numerous meta-analysis studies accepted that high BMI or overweight is certainly a protective factor of hip fracture in adults (Xianye et al. 2013).

Our present study is also in the line of previous studies and shows that each unit increase in BMI, protects from the risk of overall fracture and osteoporotic fracture. The findings regarding the hip fracture are different from previous studies and explain that increase in BMI also increase the risk of hip fracture. In this study it does not act as a protective factor for hip fracture analysis.

6.1.3 Risk of fracture and mortality associated with age

Increasing age results to skeletal fragility by bone loss and structural harm which is usually exhibited by low bone mass and deformity of bone geometry. Most of the research agreed that the old aged people are at higher risk of fracture (Ensrud 2013). The Study of Osteoporotic Fractures (SOF) also stated that risk increases by every passing year after the age of fifty. And
it is used as an evaluation tool for forecasting fracture risk in postmenopausal women (Black et al. 2001).

This study also believed that age is risk factor for fracture. Specially in case of osteoporotic fracture which shows that hazard rate increases by 1.06 with each unit increase in age. Several meta-analysis studies stated that during first three months of hip fracture risk for all-cause mortality increases up to 8 times in older adults (Patrick et al. 2010). Some researches stated that hip fractures increase mortality rate but other fractures (non-hip, non-wrist, non-vertebral fracture) did not contribute as much as hip fracture did, but in some cases, there may be a substantial increase in mortality after an osteoporotic fracture among older women. (Cauley at al. 2010). This study also explains the same ideology and shows that risk of death increased up-to 10% with increase in each unit of age.

6.1.4 Risk of fracture associated with dietary calcium

Most research suggests that calcium intake excess than the median value have no effect on lowering the risk of any type of fracture either it is hip fracture or any other osteoporotic fracture. Low dietary calcium intake increases risk of osteoporosis and other fractures. Moreover, increased intake of calcium above first quintile did not further reduce the fracture risk. (Eva et al. 2011). After reviewing statistical results of randomized controlled trials and observational studies for dietary calcium intake it is concluded that fracture risk is not proportional to dietary calcium intake. However, there is some plausible evidence that calcium supplements prevent fractures (Mark et al. 2015). This study also shows a weak protective effect of dietary calcium and risk of overall and osteoporotic fracture, although it did not prevent from hip fractures.

6.1.5 Risk of mortality associated with smoking

Several researches found a harmful association between smoking habit and overall mortality, as smoking triggers estrogen depletion in women with menopause. The North American Menopause Society (NAMS) stated that women who currently use to smoke and are experiencing early menopause will die 2.6 years earlier (NAMS 2015). Whereas a study shows that the obese women who were smokers were at higher risk of ischemic stroke mortality (Sang et al. 2009). This study also stated that post-menopausal women who were smokers have 45% more chances of premature death as compare to the non-smokers.
6.2 Strength and limitations of study

This study includes large group of homogenous cohorts participating in a long-term population based follow-up. Mixed model statistical method is able to take into account for time-varying covariates. There were several covariates that were dropped from the final analysis, since they didn’t have any contribution to the risk analysis. Self-reported fractures were cross-verified by reviewing patient records. All outcomes of this study related to the duration and use of HT can be considered reliable as the postal inquiry considered as a reliable method of recording long-term use of therapy (Joshua and Adena 2012).

The limitations of the study were that bone mineral density (BMD) values were not available to be considered in this study which is one of the key predictors in fracture’s risk. Also, there may exist some errors due to self-reports that bias the outcome. For simplicity only self-reported HT duration, not dosage or source of HT, was employed in the risk analysis. In Finland, HT regimens contained estradiol 1–2 mg as the estrogen component. Even after considering age, BMI, dietary calcium intake and smoking status, some other potential confounding factors like previous fracture history, age of menopause, physical activity and intake of calcium and vitamin D supplements exist.

6.3 Implication for future research

The possible implication of our findings would be to further expand and improve the existing results by adding the BMD, muscle strength and functional capacity into the final model as muscle weakness is related to both higher fracture risk and lower bone mineral density. High muscle strength is also linked with a lower frequency of fall-related limb fractures and may reduce the injury risk in case of a fall. Thus, muscle strength should also be considered in final model, since it is shown to be independent risk factor for post-fracture mortality (Hanh et al. 2017). The risk of fracture is partly associated with early menopause (Sullivan et al. 2017). Therefore, adding age of onset of menopause could improve the accuracy of fracture prediction along with other risk factors in the future.
7. CONCLUSION

This longitudinal population-based study of 20 years showed that use of HT prevents from osteoporotic fracture and premature death in post-menopausal women. Whereas HT therapy did not have any preventive effect in overall fracture and hip fracture risk. However, increasing age, low dietary calcium intake and low BMI in post-menopausal women are known to have an association with higher fracture risk. Furthermore, this study confirmed that smoking by post-menopausal woman is associated with increased mortality. Therefore, policies, interventions and practice should be guided accordingly.
8. REFERENCES


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https://www.iofbonehealth.org/hormone-replacement-therapy-hrt


Kristin K. Nicodemus and Aaron R. Folsom. Type 1 and Type 2 Diabetes and Incident Hip Fractures in Postmenopausal Women. Diabetes care 2001:24(7);1192-1197.


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http://www.who.int/chp/topics/Osteoporosis.pdf


Roksana karim, Richard M. Dell, Denise F, Greene, Wendy J. Mack, J. Christopher Gallagher, and Howard N. Hodis. Hip fracture in postmenopausal women after cessation of


9. APPENDICES

APPENDIX I-A

POSTAL ENQUIRY FORM

Osteoporosis Prevention Study
Kuopio University Central Hospital &
University of Kuopio

To whom it may concern

The Kuopio University Central Hospital and University start this year a study about osteoporosis, its risk factors and prevention among menopausal women. This enquiry will be sent to all women aged 47-56 years resident in the Kuopio Province.

Osteoporosis is a remarkable health problem. It develops gradually with age, faster among women after menopause with decreasing hormonal function. Among the elderly it is often so severe that their bones are easily fractured.

This is a scientific study. All the information obtained will be handled absolutely confidentially. The results of this study will be published in statistics so that you will not be identified.

We thank you for participation. It will promote the prevention of this health problem.

Kuopio 05.05.1989

Seppo Saarikoski M.D.
Professor
Department of Gynaecology, KUH

Esa Ilhava M.D.
Associate professor
Department of surgery, KUH

Risto Hankarinen M.D.
Senior researchier
Academy of Finland
DIRECTIONS FOR FILLING THE QUESTIONNAIRE

Answer the questions by circling the appropriate alternative or by writing the information asked in the space reserved for it. Read the whole question before answering. If you do not remember exactly the asked information, an estimate is a satisfactory answer.

Example 1.

Do you have menopausal symptoms (like sweating or “hot flushes”)?
   1. No
   2. Yes

If there is a blank line after an alternative, write plainly the asked information on it.

Example 2.

Have you gone through gynaecological operations? Record causes and years of other operations on lines below caesarian sections and sterilizations.
   1. No [Move to question 9]
   2. Yes: caesarian sections 19__, 19__, 19__, 19__ sterilization ....................... 19__
      other causes ___________________________ 19__
      ___________________________ 19__

Answer ALL questions concerning you. Post the filled questionnaire in the enclosed envelope. Stamp is not required - the receiver will pay the postage. Keep the address and telephone number (on the big envelope) of the Osteoporosis Prevention Study for reference.
ANSWER SECTION BEGINS

If your name, address or social security number was not correct in the sticker on the first page, write corrections below.

Name ____________________________________________

Address ____________________________________________

Social security number ____________________________________________

GYNAECOLOGICAL QUESTIONS

1. Do you have menopausal symptoms (like sweating or "hot flushes")?
   1. No
   2. Yes

2. What was the starting date of your last menstruation?
   ___. ___. ___

3. How long have you used female hormones (including contraceptive pills) in total?
   1. I have never used (move to question 6)
   2. I have used less than one year in total
   3. I have used ___ years in total

4. For what purposes and how long have you used hormones?
   1. Contraception (regular pills) ......................... ___ years
   2. Contraception, mini-pills ................................. ___ years
   3. Menopausal symptoms .................................... ___ years
   4. Replacement therapy after ovariecotomy ............ ___ years
   5. Other purpose, what ........................................ ___ years

5. What are the names of the hormone tablets you have mostly used for your menopausal symptoms?
   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________
6. How many times have you been pregnant in total? _____ times raskikm
pregnancy ended in childbirth _____ times synlikm
pregnancy ended in abortion (spontaneous or legal) _____ times keslikm

7. Have you gone through GYNAECOLOGICAL OPERATIONS? Record the causes and years of operations on the lines below (caesarian sections and sterilizations)

1. No [move to question 9] leidkvm
2. Yes caesarian sections 19__, 19__, 19__, 19__ keisari
   sterilizations ......................................................... 19__ sterilv
   other causes __________________________ 19__ leiksvy1 & leiklvv
   __________________________ 19__ leiksvy2 & leiksvv
   __________________________ 19__ leiksvy3 & leiksvv3
   __________________________ 19__ leiksvy4 & leiksvv4

8. What was removed in these operations? (Record all alternatives concerning you with operation years):

1. Only uterus or main part of it ................. 19__ kohju
2. Uterus and one ovary ......................... 19__ kms
3. Uterus and both ovaries ....................... 19__ kmas
4. One ovary or its part ......................... 19__ ms
5. Both ovaries or the last ovary .............. 19__ molms
6. Part of uterine body (like myoma) ........... 19__ osa
7. Uterine cervix or its part ..................... 19__ kaula
8. Other parts of genitals ....................... 19__ muu
9. Nothing of the above-mentioned

9. Have you ever had radiotherapy to genitals?

1. No sadetys
2. Yes, why? _______________________________ 19__ sadetysy & sadetv4
BEHAVIORAL AND HEALTH QUESTIONS

10. How physically demanding has your work been DURING THE LAST 12 MONTHS on average? 
   1. I have not been at work  
   2. Sitting work  
   3. Light work  
   4. Medium heavy work  
   5. Heavy work

11. Do you take regular physical exercise during leisure? 
   1. No  
   2. Yes, ___ hours per week on average

12. Have you ever been smoking? 
   1. No (move to question 15)  
   2. Yes, tupakoin

13. Have you ever been smoking regularly (= almost every day at least for one year)? 
   1. No (move to question 15)  
   2. Yes, altogether ___ years

14. How much are you smoking presently?  
   1. I have stopped smoking in year 19 ___  
   2. I consume ___ cigarettes a day on average

15. How many decliters milk products (like milk, sour milk, yoghurt etc.) do you consume daily? 
   _____ decliters on average

16. How many slices of cheese do you consume daily? 
   _____ slices on average

17. Your length? _____ cm

18. Your weight? _____ kg
19. Have you sustained fractures since the age of 15?
   1. No (move to question 20)
   2. Yes, which bones? __________________________ 19__
   __________________________ 19__
   __________________________ 19__
   __________________________ 19__
   __________________________ 19__
   __________________________ 19__

20. How and in which years did you sustain these fractures?
   1. Falling on the same level .................... 19__, 19__, 19__
   2. Falling from one level .......................... 19__, 19__
   3. Bicycle accident ............................... 19__, 19__
   4. Car accident ................................. 19__, 19__
   5. Otherwise, how? _________________________ 19__, 19__
   Otherwise, how? _________________________ 19__, 19__

21. Has a PHYSICIAN EVER DIAGNOSED following diseases in you? (Circle all diseases concerning you)
   1. Hypertension requiring treatment
   2. Hypercholesterolemia
   3. Coronary disease (myocardial infarction or angina pectoris)
   4. Other heart disease like heart failure or valvular disease
   5. Cerebral stroke, haemorrhage or cerebral embolus
   6. Thrombophlebitis in lower extremity
   7. Pulmonary embolism
   8. Insulin-dependent diabetes
   9. Chronic kidney disease
   10. Chronic liver disease
   11. Rheumatoid arthritis
   12. Epilepsy
   13. Asthma or other chronic lung disease
   14. Lactose malabsorption
   15. Thyroid hyperfunction
   16. Parathyroid hyperfunction
   17. Alcoholism
   18. Chronic mental disease
   19. Osteoporosis
   20. Cancer, which?
   21. Other chronic diseases, what? __________________________
       __________________________

22. None of the above-mentioned diseases and no other diseases
22. Do you have urinary incontinence?
   1. No
   2. Yes

23. Do you regularly use prescribed drugs? If yes, record the purpose, the name of the drug and the duration of treatment.

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Name of drug</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>laaklaa1, &amp; kesto1</td>
<td>_____ years</td>
</tr>
<tr>
<td></td>
<td>laaklaa2 &amp; kesto2</td>
<td>_____ years</td>
</tr>
<tr>
<td></td>
<td>laaklaa3 &amp; kesto3 etc.</td>
<td>_____ years</td>
</tr>
<tr>
<td></td>
<td>laaklaa9 &amp; kesto9</td>
<td>_____ years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>_____ years</td>
</tr>
</tbody>
</table>

24. Do you use (without prescription) drugs or natural products containing calcium or vitamin D?

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Name of drug</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>muulaa1 &amp; annos1</td>
<td>_____</td>
</tr>
<tr>
<td></td>
<td>muulaa2 &amp; annos2</td>
<td>_____</td>
</tr>
<tr>
<td></td>
<td>muulaa3 &amp; annos3 etc.</td>
<td>_____</td>
</tr>
<tr>
<td></td>
<td>muulaa6 &amp; annos6</td>
<td>_____</td>
</tr>
</tbody>
</table>

25. Are you chronically unable to work?

   1. No
   2. Yes, why? ________________________________

26. Are you currently in hospital or in institutional care?

   1. No
   2. Yes, why? ________________________________
OTHER QUESTIONS

27. Are you willing to participate in free-of-charge bone density measurement (an X-ray examination without pain and side-effects) in KUH? (The trips you have to pay yourself).

1  Yes
2  No

28. Are you willing to participate in a 5-year prevention study, if you have incipient osteoporosis?

(The study will be conducted so that the willing persons will be randomly assigned in four groups. The first group receives hormonal therapy, the second hormonal therapy and vitamin D, the third vitamin D and the fourth group tablets which do not contain any effective drug. The examinees and personnel do not know which group each examinee belongs to. The members of each group will be followed annually in the outpatient department of the KUH. Examinations are free of charge. (You have to pay only trips and visit payments.)

1  Yes
2  No

29. Are you willing to participate in other enquiry studies concerning this subject?

1  Yes
2  No

30. Telephone number  home: 9_____
              work: 9_____

31. Date of answer:  ____ , 19____

THANKS FOR YOUR ANSWERS