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HANDS-ON OSTEOPOROSIS SCREENING WITH
DIGITAL X-RAY RADIOGRAMMETRY

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To my dear parents Henryk and Brigitte, and last but not least, to my beloved Jana.

"I always get to where I'm going by walking away from where I have been."

Winnie-the-Pooh

ABSTRACT

According to epidemiological studies about one third of women and one fifth of men over 50 years will experience a fragility fracture. These fractures account for substantial mortality, morbidity and health care cost. Osteoporosis is a silent disease and thus often goes undiagnosed for a long time. Second to trauma it is considered to be the main cause of fractures among elderly. Several methods to reduce fracture risk have been developed. Identifying individuals with high fracture risk who would most benefit from such measures is of utmost importance for cost-efficient fracture prevention. Dual-energy X-ray absorptiometry (DXA) is widely considered to be the gold standard for assessing bone mass, diagnosing osteoporosis and estimating fracture risk. However, access to DXA is limited and not everyone in need of an examination is able to have one. Other fracture risk prediction models have therefore been developed, e.g. questionnaire-based tools. Different bone mass measuring devices have also been invented, e.g. qualitative ultrasound, peripheral DXA and digital X-ray radiogrammetry (DXR). None of these methods has been investigated nor validated as much as DXA. The aim of this study was to investigate the clinical use of DXR, which uses hand radiographs to determine bone mass.

In paper I, we retrospectively analyzed already obtained radiographs from 8,257 patients with DXR and found that DXR was highly predictive for hip fractures in both women and men.

Later we recruited study participants from the Swedish mammography screening program and sampled a prospective, population-based cohort, the so-called STOP cohort. In paper II, the cohort was described, and it was shown that self-reported information about established clinical risk factors for osteoporosis were significantly associated with DXR T-score.

A subset of the STOP cohort based on those with the lowest bone mass for their age (Z-score) was studied in paper III. In this subset we found a high prevalence of DXA-verified osteoporosis. Underlying causes for secondary osteoporosis and risk factors for primary osteoporosis were also overrepresented.

In paper IV the STOP cohort was matched with fracture data from the Swedish National Inpatient Register and fracture prediction with DXR-BMD with and without clinical risk factors was examined. DXR T-score was significantly associated with hip, major osteoporotic and any clinical fracture.

In summary DXR derived bone mass was associated with fracture risk and known clinical risk factors for osteoporosis. Further research should focus on longer follow-up of the STOP cohort and health economical assessments concerning potential clinical implementation of the method.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Ungefär varannan kvinna och var femte man över 50 år väntas drabbas av en benskörhetsrelaterad fraktur (benbrott). Sådana frakturer är förknippade med avsevärd dödlighet, sjuklighet och samhällsekonomisk börda. Osteoporos, dvs benskörhet, är en tyst sjukdom som ofta går oupptäckt. Förutom trauma är osteoporos är den starkast bidragande orsaken till frakturer bland åldringar. Tillståndet diagnosticeras med hjälp av en röntgenmetod som kallas för Dual-energy X-ray absorptiometry (DXA). Tillgången till DXA-apparatur är dock begränsad, vilket gör att inte alla som behöver en undersökning kan genomgå den. Riskskattningsverktyg, exempelvis i form av frågeformulär, har därför utvecklats. Andra tekniker för att mäta bentätheten har också tagits fram, till exempel kvantitativt ultraljud, perifer DXA eller digital röntgenradiogrammetri (DXR). Ingen av dessa metoder har dock utvärderats lika mycket som DXA. Syftet med denna avhandling var att undersöka den kliniska nyttan av DXR, en metod som använder vanliga röntgenbilder av handen för att bedöma bentätheten.

I delarbete I gjorde vi en retrospektiv analys av redan utförda röntgenundersökningar från 8257 patienter. Vi fann att DXR hade en god prediktionsförmåga för höftfrakturer hos både kvinnor och män.

Senare rekryterade vi studiedeltagare från den svenska mammografiscreeningen och skapade således en prospektiv, populationsbaserad kohort, den så kallade STOP-kohorten. I delarbete II gjordes en deskriptiv analys av STOP-kohorten och egenrapporterade uppgifter om kliniska riskfaktorer för osteoporos visades vara korrelerade med benmassa enligt DXR.

I delarbete III studerades ett urval av STOP-kohorten där de studiedeltagare som hade lägst bentäthet för sin åldersgrupp valts ut. I denna grupp fann vi en hög förekomst av DXA-verifierad osteoporos. Bakomliggande orsaker till sekundär osteoporos och riskfaktorer för primär osteoporos var överrepresenterade i den studerade gruppen.

I delarbete IV matchades STOP kohorten med det nationella slutenvårdsregistret och DXRs frakturprediktiva förmåga utvärderades. Bentäthet mätt med DXR korrelerade med höftfrakturer, huvudsakliga osteoporosfrakturer och övriga frakturtyper.

Sammanfattningsvis korrelerade bentäthet mätt med DXR med frakturrisk och kända kliniska riskfaktorer för osteoporos. Framtida studier bör inrikta sig på längre uppföljning av STOP-kohorten och innefatta hälsoekonomiska utvärderingar rörande eventuell klinisk användning av DXR.

LIST OF SCIENTIFIC PAPERS

I. Wilczek ML, Kälvesten J, Algulin J, Beiki O, Brismar TB Digital X-ray radiogrammetry of hand or wrist radiographs can predict hip fracture risk--a study in 5,420 women and 2,837 men. Eur Radiol. 2013 May;23(5):1383-91. doi: 10.1007/s00330-012-2706-9.

II. Wilczek ML, Nielsen C, Kälvesten J, Algulin J, Brismar TB. Mammography and osteoporosis screening--clinical risk factors and their association with digital X-ray radiogrammetry bone mineral density. J Clin Densitom. 2015 Jan-Mar;18(1):22-9. doi: 10.1016/j.jocd.2014.07.007. Epub 2014 Oct 5.

III. Wilczek ML, Kälvesten J, Bergström I, Pernow Y, Sääf M, Freyschuss B, Brismar TB. Can secondary osteoporosis be identified when screening for osteoporosis with digital X-ray radiogrammetry? Initial results from the Stockholm Osteoporosis Project (STOP). Maturitas. 2017 Jul;101:31-36. doi: 10.1016/j.maturitas.2017.04.006. Epub 2017 Apr 12.

IV. Wilczek ML, Bhatta L, Brumpton BM, Freyschuss B, Brismar TB. Screening for fragility fractures in a general female population using digital X-ray radiogrammetry (DXR). Submitted 2020.

CONTENTS

LIST OF ABBREVIATIONS

AUC	Area under curve
BMD	Bone mineral density
CI	Confidence interval
CT	Computed tomography
DXA	Dual-energy X-ray absorptiometry
DXR	Digital X-ray radiogrammetry
FRAX®	Fracture Risk Assessment Tool
HR	Hazard ratio
ICD	International Statistical Classification of Diseases and Related Health Problems
NPV	Negative predictive value
PPV	Positive predictive value
QUS	Quantitative ultrasound
STOP	Stockholm Osteoporosis Project
T-score	Standard deviation of bone mineral density compared to young normal mean
WHO	World Health Organization
Z-score	Standard deviation of bone mineral density compared to age-matched normal mean

1 INTRODUCTION

1.1 SCREENING

Within a medical context the term screening refers to a strategy of identifying a possible condition or disease in individuals who have not yet presented with clinical signs or symptoms [1]. The objective is to identify the condition as early as possible in hope of optimizing the effect of preventive measures and/or treatments. Screening programs vary regarding populations and methods being used and healthcare organizations around the globe offer different screening programs.

Though the main idea behind screening (identifying individuals at risk of disease) may have existed earlier, the current concept of screening seems to have arisen in the early 20th century. The reason for this is most likely due to the rapid medical development of that time leading to four key factors required for screening to be of relevance. These are:

1. Simple and valid diagnostic tests.
2. Effective treatments or measures.
3. Large scale access to health care.
4. Establishment of a theory regarding risk factors and early, preclinical detection of a condition or disease.

One of the first described programs which in retrospect may be viewed as screening is the United States army's mental evaluation tests used among those eligible to join the army. The testing was introduced in 1917 and was supposed to identify and thereby enable exclusion of individuals with psychological disorders from enlisting [2]. The assessment methods were designed to be fast and reliable in order to evaluate large number of individuals quickly. Other historical and current examples include screening for syphilis, diabetes, cervix cancer, PKU, breast cancer [1]. Screening does not have to be diagnostic in itself but is intended to identify subjects who merit further investigation. Screening may target an entire population, such as newborn screening or selected populations due to e.g. age, sex or known risk factors. In 1968 guidelines regarding the principles and practice of screening for disease were published by the World Health Organization (WHO) [3]. These principles are more commonly referred to as the Wilson and Jungner Criteria and include 10 principles listed in Box 1.

1. The condition should be an important health problem.
2. There should be a treatment for the condition.
3. Facilities for diagnosis and treatment should be available.
4. There should be a latent stage of the disease.
5. There should be a test or examination for the condition.
6. The test should be acceptable to the population.
7. The natural history of the disease should be adequately understood.
8. There should be an agreed policy on whom to treat.
9. The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole.
10. Case-finding should be a continuous process, not just a "once and for all" project.

Box 1. Wilson and Jungner criteria

Though still mostly applicable, the Wilson and Jungner principles were adjusted about 40 years later in 2008 [4]. The revision contained a synthesis of points having been brought up and recognized since the publication of the Wilson and Jungner criteria. These aspects mostly emphasize quality assurance. The current WHO guiding principles of screening for disease are listed in Box 2.

- The screening program should respond to a recognized need.
- The objectives of screening should be defined at the outset.
- There should be a defined target population.
- There should be scientific evidence of screening program effectiveness.
- The program should integrate education, testing, clinical services and program management.
- There should be quality assurance, with mechanisms to minimize potential risks of screening.
- The program should ensure informed choice, confidentiality and respect for autonomy.
- The program should promote equity and access to screening for the entire target population.
- evaluation should be planned from the outset.
- The overall benefits of screening should outweigh the harm.

Box 2. Synthesis of emerging screening criteria proposed between 1968 and 2008.

Today most western countries operate several screening programs for e.g. phenylketonuria (PKU) [5], cervical cancer and breast cancer [6]. However, many prevalent conditions and diseases for which there are available treatments are not necessarily subject for mass screening. Examples of such include aortic aneurysm [7] and osteoporosis [8, 9].

Screening is often a subject of great debate for various medical, psychological as well as economic reasons [6, 10]. In order to understand the nature of these concerns it is important to first know what testing implies as well as potential pitfalls of tests being used.

1.2   WHAT MAKES A GOOD TEST?

When we do studies and perform measurements it is important that we measure the right thing in a consistent way. The two most important elements of a test are its reliability and validity. These define the quality and usefulness of the test. A third, important feature is test standardization.

1. **Reliability** points to the overall consistency of a measure. It means that the test does not change in nature over time reflecting the quality of measurement. The term usually refers to the "consistency" or "repeatability" of ones measures and it is a marker of how well a test measures that what it should. Thus, a test has high reliability if it generates comparable outcomes under consistent conditions, indicating that if it was to be repeated by others they would come to the same result. Various kinds of reliability coefficients are used to indicate the amount of error in the scores. Cronbach's alpha (coefficient alpha) is the most widely used internal-consistency

coefficient. The reliability coefficient defines the precision of the test by a given value between 0.00 and 1.00, where the former indicates much error and weak reliability and the latter minimal or no error and strong reliability. However, one must understand that a test measuring something consistently, does not signify that it also provides a correct prediction regarding the specific objective that is set to be measured. Good tests demonstrate reliability coefficients of about 0.70 to >0.90 [11].

2. **Validity** is about a test's relevance within its context. While reliability refers to doing measurements in a reliable way, validity is fundamentally about the relevance of measurements, i. e. the degree to which a test really measures what one wants to measure. Simply put, validity is about using the right thing at the right time. Validity provides an estimate of the test's usefulness. No valid conclusions can be drawn from a test score unless one has made sure that the test is reliable. It must be emphasized that reliability does not presuppose validity, meaning that even if a test is reliable it may not give a valid measure. Three main validity categories exist. Content validity evaluates if the tool used satisfactorily takes into account all relevant content with respect to the studied variable. Construct validity answers whether you can deduce conclusions from the test scores of what is being studied. Criterion validity gives a measure on the extent to which an investigational tool relates to other tools studying the same variable. Like reliability, the validity can be mathematically expressed by a coefficient showing the strength of the relationship between a test score and the variable studied. The value of the validity coefficient lies within the same range as for other correlation coefficients (0 to 1), but it is unusual to find high values. Usually, the value lies between 0 and 0.50 (0 showing no or weak validity and 0.50 moderate validity) [11, 12].

3. **Standardization** denotes the mathematical procedure of making various variable measurements homogenous and comparable. In science, it is a procedure aiming to increase the validity and reliability of research. The mathematical operations assign a score to each variable placing all of them on the same scale, permitting scores of different variables to be compared. Simply explained the procedure is typically done by calculating the mean and standard deviation (SD) for a variable after which one subtracts the mean and divides by the SD for each observed value of the variable. The operation yields standard scores that represent the number of SD above or below the mean that a specific observation falls. To exemplify, a standardized value of 1 implies that the observation falls 1 SD above the mean, and a SD of -1 that the observation falls 1 SD below the mean. This will be valid for every type of standardized variable.

In addition to the above-mentioned elements, it is also important to take into consideration the following test characteristics:

(a) the sensitivity

(b) the specificity

(c) the positive predictive value (PPV) and

(d) the negative predictive value (NPV) of the test when determining its value.

The sensitivity and specificity define the test characteristics and evaluate the usefulness of a test. The PPV and NPV express the clinical relevance of the test. One should note that sensitivity and specificity are both independent of the prevalence of the disorder studied, in contrast to PPV and NPV that depend on the population being tested and use the prevalence of the disorder to determine (e) the likelihood of the test recognizing the condition studied.

a. The sensitivity of a test is the proportion of individuals who test positive among all those who actually have the condition studied. A sensitive test helps <u>excluding</u> a disorder when the test is negative. Mathematical sensitivity expresses the following way:

$$Sensitivity = \frac{True\ positive}{True\ positive + false\ negative}$$

A test with 100% sensitivity will correctly identify all individuals with the disorder

b. The specificity of a test is the proportion of individuals who test negative among all those who actually do not have the condition studied. Positive specificity of a test helps including a disorder. Mathematically specificity expresses as follows:

$$Specificity = \frac{True\ negative}{True\ negative + false\ positive}$$

A test with 100% specificity will accurately identify all individuals without the disorder.

c. Positive predictive value is the probability that following a positive test the individual will truly have that specific disease.

$$PPV = \frac{True\ positive}{True\ positive + false\ positive}$$

d. Negative predictive value is the probability that following a negative test, the individual will truly not have that specific disease.

$$NPV = \frac{True\ negative}{True\ negative + false\ negative}$$

e. Lastly, the term likelihood ratio deserves to be mentioned, because it can sometimes also be used to evaluate the usefulness of a test. The likelihood

ratio is a gauge, obtained by using both a test's sensitivity and specificity. A positive likelihood ratio tells you how much more likely it is that an individual who tests positive has a disorder compared with someone who tests negative. When negative, the likelihood ratio gives information on how much the odds of the disorder are reduced. Mathematically likelihood ratios are expressed as follows:

$$Positive\ likelihood\ ratio = \frac{Sensitivity}{1 - Specificity}$$

$$Negative\ likelihood\ ratio = \frac{1 - Sensitivity}{Specificity}$$

2 OSTEOPOROSIS

For many years, scientists have known that loss of bone tissue, a condition medically named osteoporosis/osteopenia, constitutes a major health concern that affects millions of individuals all over the world [13, 14]. The risk of osteoporosis varies between countries, being highest in the western European countries and in North America. The condition is widespread and comes with a high price. In the United States, for example, it was estimated that in 2005, 10 million women and men were affected with direct costs of $17 billion [15-17]. In a European analysis from 2013 the total economic burden was estimated to €37 billion and a 25% increase by 2025 was expected [18]. Analyses indicate that at least 30% of all postmenopausal women and about 25% of Caucasian men older than 60 years will incur at least one osteoporotic fracture in their lifetime [19-21]. Twenty percent of the individuals affected by hip fractures will die within one year and 20% will need permanent nursing home care [17, 22].

In Sweden, similar figures have been found with approximately 33% of women age 70-79 suffering from osteoporosis when bone density in the hip is assessed. It is estimated that roughly 1 of 2 Swedish women and 1 of 4 Swedish men will suffer an osteoporosis related fracture in their lifetime. The annual incidence of osteoporosis-related fractures in Sweden has been estimated to approximately 70,000, of which 18,000 are hip fractures, with an estimated total cost of 3-4 billion SEK. Furthermore, mortality in the first year after the fracture is 10-15% higher compared with a sex and age-matched population with no hip fracture Also, the quality of life is worsened for many of the patients [23-26]. Thus, besides having severe negative effects for many of the affected individuals osteoporosis imposes a heavy societal burden making it a major public health issue. Because of this, identifying individuals affected by osteoporosis is essential if one is to decide proper therapeutic intervention measures and reduce the number of fragility related fractures.

Unfortunately, there are no reliable blood sample biomarkers for the diagnosis of osteoporosis. A feasible option is to obtain imaging biomarkers by performing and analyzing radiographic examinations. Bone mineral density (BMD) is the major criterion used for the diagnosis and monitoring of osteoporosis. It presents a quantitative estimate of bone mass per unit area, expressed in g/cm^2. According to the definition by WHO, osteoporosis exist if BMD lies ≥2.5 SD below that of a normal young healthy female (T score of ≤ −2.5 SD) for postmenopausal women and men >50 years as measured by dual-energy X-ray absorptiometry (DXA) at the femoral neck [27]. In a statement from 2015, the International society for Clinical Densitometry (ISCD) claims that a BMD DXA T-score of ≤ −2.5 at the lumbar spine (LS), total hip (TH), femoral neck (FN), or one-third radius may be used to diagnose osteoporosis in postmenopausal women and in men over 50 years old [28]. Studies have shown that BMD is strongly associated with fracture risk [29-33] and that low BMD is a major risk factor for fragility fracture. Thus, evaluating BMD in the skeleton plays a salient role for the diagnosis of osteoporosis and in assessing fracture risk and it points to the need of finding simplified and effective diagnostic methods to counter-act this devastating ailment.

Several techniques are available to measure BMD, but DXA of the hip, femoral neck or spine has hitherto been generally acknowledged as the gold standard examination for the assessment of osteoporosis [31, 32, 34]. The drawback with the DXA technique is its relatively high cost in addition to it not being available everywhere resulting in many osteoporosis patients not being offered this examination [35-40]. Other techniques for measuring BMD, such as quantitative computed tomography (QCT) [41], quantitative ultrasound (QUS) [42], peripheral DXA (pDXA) [43] and Digital X-ray radiogrammetry (DXR) [44] have been proposed but so far not gained general recognition in osteoporosis

care [45]. DXR is a peripheral measurement method which uses a standard radiograph of the hand to derive a computed BMD equivalent measurement. Digital radiography equipment is fast, cheap and requires minimal radiation exposure. It is also widely accessible. This makes DXR an interesting and potentially cost-effective candidate for osteoporosis detection at a larger scale.

2.1   PRINCIPLE BEHIND DIGITAL X-RAY RADIOGRAMMETRY IN SUMMARY

Analyzing cortical bone width at the metacarpals for the quantification of BMD was considered already 60 years ago [46]. Unfortunately, this early technique was quite time-consuming and the introduction of single-photon absorptiometry in the 1970s and DXA in the 1980s led to it disappearing from clinical use. However, modern improvements in digital imaging and advanced computerization of the labor-demanding analysis process has caused a renewed interest in the technique. This modus operandi named Digital X-ray radiogrammetry (DXR), is an easier and less costly software technique to analyze BMD. It evaluates the geometry and texture of the metacarpal bones from a standard radiograph of the hand by means of an automated image analysis of a standard radiograph of the hand (Figure 1 and 2). An important advantage with DXR is that it can easily be realized at all medical facilities that provide radiological services. Described in simplified terms, the underlying peripheral analysis technique applied in DXR is based on a combination of an average geometrical measure of the cortical thickness of metacarpals II-IV and structural analysis of cortical bone porosity [44, 47]. The procedure returns a calculated areal BMD value, a T-score and a Z-score that can be used to evaluate the individual's state of osteoporosis and the risk of bone fracture with a precision error <1% [44]. The effective radiation dose of a DXR examination is <0.001 mSv [48], similar or lower than a DXA examination and generally considered unimportant [49]. Correlation coefficients between
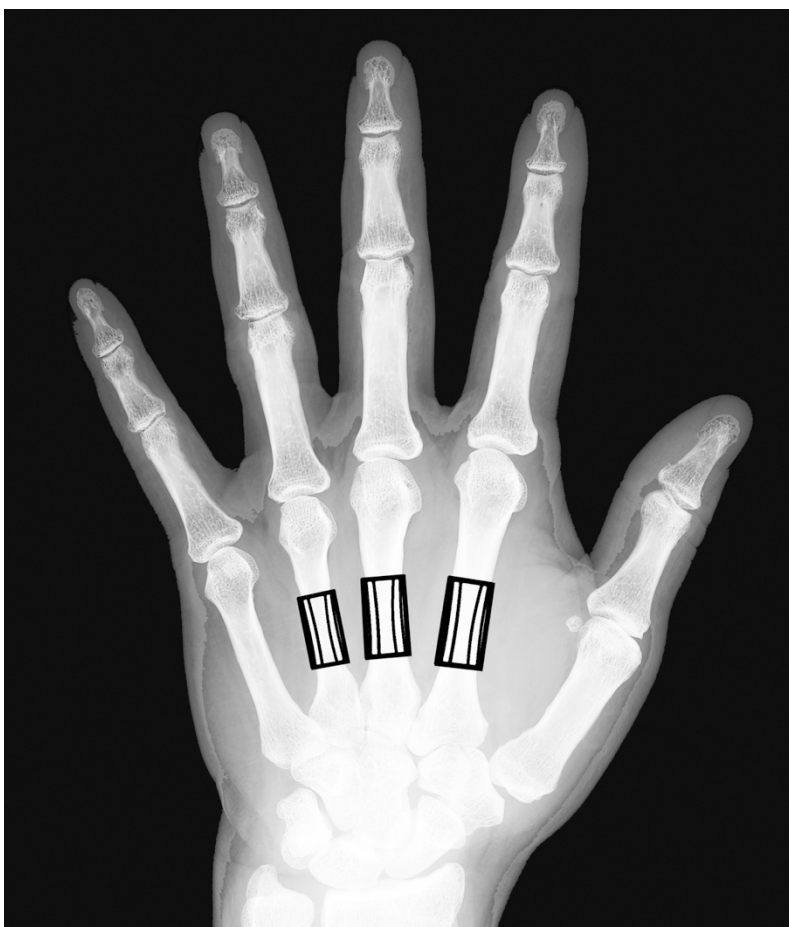

Figure 1. Hand radiograph with measurement regions for digital X-ray radiogrammetry on metacarpals II-IV marked. Image used with permission from Sectra AB.

DXR-BMD and DXA-BMD vary between 0.5–0.77 for central DXA (hip and spine) [44, 50-53] and 0.55–0.90 for peripheral DXA (distal forearm) [50, 51, 53, 54]. In a comparison based on the Study of Osteoporotic Fractures (SOF) cohort, DXR-BMD has been found to be of similar predictive value for non-hip major osteoporotic fractures as central DXA-BMD (AUC 0.65 versus 0.65-0.68). The prediction of hip fractures was slightly better (AUC 0.69), although weaker than that of DXA of the femoral neck (AUC 0.75) [55].
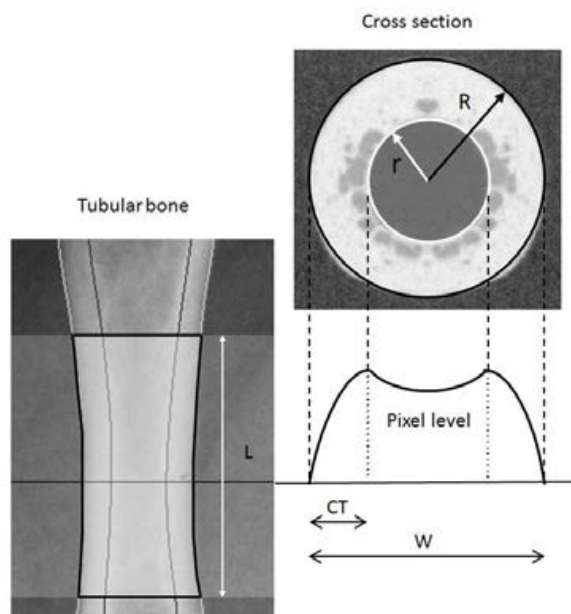

Figure 2. Illustration of the principle of digital X-ray radiogrammetry in a single measurement region. L: length of measurement region; R: periosteal radius; r: endosteal radius; CT: cortical thickness; W: width of the measured bone. Image used with permission from Sectra AB.

2.2 USING THE FRACTURE RISK ASSESSMENT TOOL (FRAX®) TO DETERMINE FRACTURE RISK

Clinical management of osteoporosis has as its end goal to minimize fracture incidence in risk individuals. It is traditionally done by assessing the skeleton's strength via BMD measurements usually done by DXA. This combined with clinical experience and judgement has formed the basis whether to incur pharmacological treatment [8]. Unfortunately, with regard to fracture likelihood, BMD measurement is only one piece of the puzzle due to the multi-factorial nature of the osteoporotic condition. Earlier studies have shown that intervention thresholds based on BMD alone have a poor sensitivity leading to a low detection rate, and that adding other clinical risk factors into the assessment calculation improves the sensitivity [56].

FRAX is a software tool, specifically created for the assessment of fracture risk by using multiple risk factors in the equation. It is a computer-based algorithm aimed at analyzing an individual's 10-year probability to suffer hip fracture and major osteoporotic fracture defined as a clinical spine fracture, forearm fracture, hip fracture or shoulder fracture [57-59]. In order to make an assessment of the fracture risk, a number of easily obtained clinical risk parameters can be introduced into the FRAX instrument (Box 3).

The FRAX models originated from the analyses of large population-based cohorts from Europe, North America, Asia and Australia [33, 60-63]. The algorithm also accounts for life expectancy [64]. By allowing for multiple risk factors in the calculation, the algorithm can produce a more accurate estimate of an individual's fracture risk than earlier techniques. Because different regions of the world demonstrate different fracture probabilities, the

FRAX tool is calibrated to those countries where the epidemiology of fracture and death is known[64, 65]. FRAX has been incorporated into many national guidelines around the world, some of which are Belgium, Canada, Japan, Netherlands, Poland, Sweden, Switzerland, the UK, and the US [66]. FRAX estimates are intended to provide guidance for determining access to treatment in healthcare systems. Country-specific FRAX is recommended for assessing fracture probability in postmenopausal women demonstrating risk factors for fracture. In individuals showing intermediate risk, BMD measurement using

- Sex
- Age
- Weight
- Height
- Smoking
- Previous fracture
- Family history of hip fracture
- Steroids
- Rheumatoid arthritis
- Femoral neck bone mineral density (BMD) (optional parameter that may be used to enhance fracture risk prediction. Including BMD increases the sensitivity without decreasing the specificity of the fracture risk assessment)
- Secondary osteoporosis
- Alcohol intake (≥3 standard drinks per day)

Box 3. Clinical risk parameters included in FRAX.

DXA plus recomputed FRAX fracture probability is considered sufficient [59, 67]. It should be emphasized that FRAX is not to be considered as a standard benchmark in patient assessment, but more of an auxiliary reference platform that can be deepened [66]. One limitation with the FRAX evaluation is that it does not take into account dose-responses for several risk factors e.g. like in patients medicating with steroids, smoking, alcohol intake or a patient who has had two prior fractures compared to a patient who has had only one. The FRAX tool should theoretically improve the doctor's decision-making regarding the need of preventive pharmacological treatment, help to avoid needless treatment interventions and may ultimately also lead to cost-savings by heightened efficiency [68]. Nevertheless, since in practice it is impossible to meet all conceivable situations, physicians are advised not to rely on FRAX solely but to apply sound clinical judgement when deciding whether preventive treatment intervention is needed [59]. The FRAX instrument is accessible online free of charge but can also be purchased as a desktop application.

2.3 SCREENING FOR OSTEOPOROSIS

Screening for osteoporosis aims at identifying individuals who have not yet developed clinical signs of osteoporosis but nevertheless run a high risk of fragility fractures. Apart from being responsible for considerable morbidity and mortality [17, 19, 20, 22], fractures in osteoporotic individuals are socio-economically extremely costly [15-18]. Thus, early identification of osteoporotic individuals is of vital importance and, screening is the first and probably most important step with regard to the prevention of fragility fractures. By early identification of individuals afflicted with secondary osteoporosis early and appropriate preventive treatment can be instituted.

Therefore, in some countries screening for osteoporosis with DXA is recommended. In the US postmenopausal women younger than 65 and women older than 65 are considered to be risk groups where screening is advocated [69, 70], though this strategy has been a controversial issue because of lack of compelling evidence and therefore not adopted everywhere [71-73]. Population-based screening for osteoporosis is not recommended in neither Sweden nor in the UK [26, 74, 75], despite reportedly higher fracture incidence in both these countries than in the US [65]. More recent studies of screening interventions have been conducted [76, 77] and newer meta-analyses and cost-efficiency studies provide some support for population-based screening [78, 79], though results have been questioned [80]. However, there are alternatives to population-based screening with regard to osteoporosis, e.g. opportunistic screening, screening in selected populations or fracture-liaison services.

2.3.1 Opportunistic screening
One strategy for identifying individuals with osteoporosis is opportunistic screening. Opportunistic screening suggests taking opportunity of useful data already collected for another reason, e.g. re-examining CT scans obtained for other indications with quantitative CT BMD assessment [45, 81-83]. Thus, data can retrospectively be used for further diagnostic investigation without additional patient time, radiation exposure, equipment or significant cost [84]. Another implementation of opportunistic screening might be using DXR on routine hand radiograph controls in rheumatoid arthritis's patients or on trauma radiographs depicting the metacarpals.

2.3.2 Fracture liaison service
A strategy for osteoporosis detection and fracture prevention which has rapidly gained recognition are fracture liaison services which identify patients who present with fractures and refer them for further investigation and subsequent actions to prevent additional fractures [85-87]. DXR might be a useful tool improve existing fracture liaison services as it provides an automated bone mass analysis using hand/or wrist radiographs obtained in routine fracture examination.

3   AIM

The objective of this thesis was to evaluate whether DXR analysis can predict osteoporotic fracture risks by using standard clinical hand or wrist radiographs in the hospital healthcare setting. The aims of the individual papers were to:

3.1   PAPER I

assess DXR as a fracture predictor using retrospectively collected hand and wrist radiographs from hospital settings.

3.2   PAPER II

investigate the association between clinical risk factors for osteoporosis and DXR-BMD measurements as well as assess the feasibility of a combined osteoporosis and general mammography screening program using DXR.

3.3   PAPER III

study the occurrence of causes for secondary osteoporosis among the individuals with the lowest bone mineral density in the cohort from paper III.

3.4   PAPER IV

investigate the predictive value of DXR prospectively in a normal female population.

4 MATERIAL AND METHODS

4.1 STUDY POPULATIONS

Patients who had had a radiograph of either their hand or wrist obtained at any of the three major hospitals in Stockholm, Sweden (Södersjukhuset, Karolinska University Hospital Solna or Huddinge between) 2000-2008 constituted the cohort used for **Paper I**.

Women participating in the general mammography screening program who attended screening center (Unilabs Tumba, Stockholm County) between March 2010 and June 2012 were invited to participate in the study and make up the so-called STOP (Stockholm Osteoporosis Project) cohort and the general study population used for **Papers II-IV**. For **Paper III** a subset of the STOP-cohort was used, including only the 2 percent of participants with the lowest bone density for their age (Z-score).

4.2 METHODS

4.2.1 Paper I

All radiographic examinations coded as hand or wrist radiographs obtained between 2000 and 2008 at Södersjukhuset, Karolinska University Hospital Huddinge or Solna were collected and assessed regarding image quality during 2009-2010. Only radiographs depicting metacarpals II-IV and deemed appropriate for assessment with DXR were included for analysis. These radiographs were then analyzed with DXR. Figure 3 provides examples of such images and analyses. These patients were matched with National Patient and Death registries from the Swedish National Board of Health and Welfare. Only individuals over 40 years of age, without previous hip fractures and with an observation time >7 days were included in subsequent analyses. The patient selection process is illustrated in Figure 4. The outcome measure was hip fracture, which was defined as having an ICD code for femur fracture (S72.0, S72.1, S72.2) as well as an ICD-code for surgical treatment (NFJ and NFB) or dying within 3 days of fracture. Comparisons of individuals with fractures (cases) and those without (controls) regarding age and DXR-BMD where made. Age-adjusted ROC curves were plotted, and the AUC calculated.
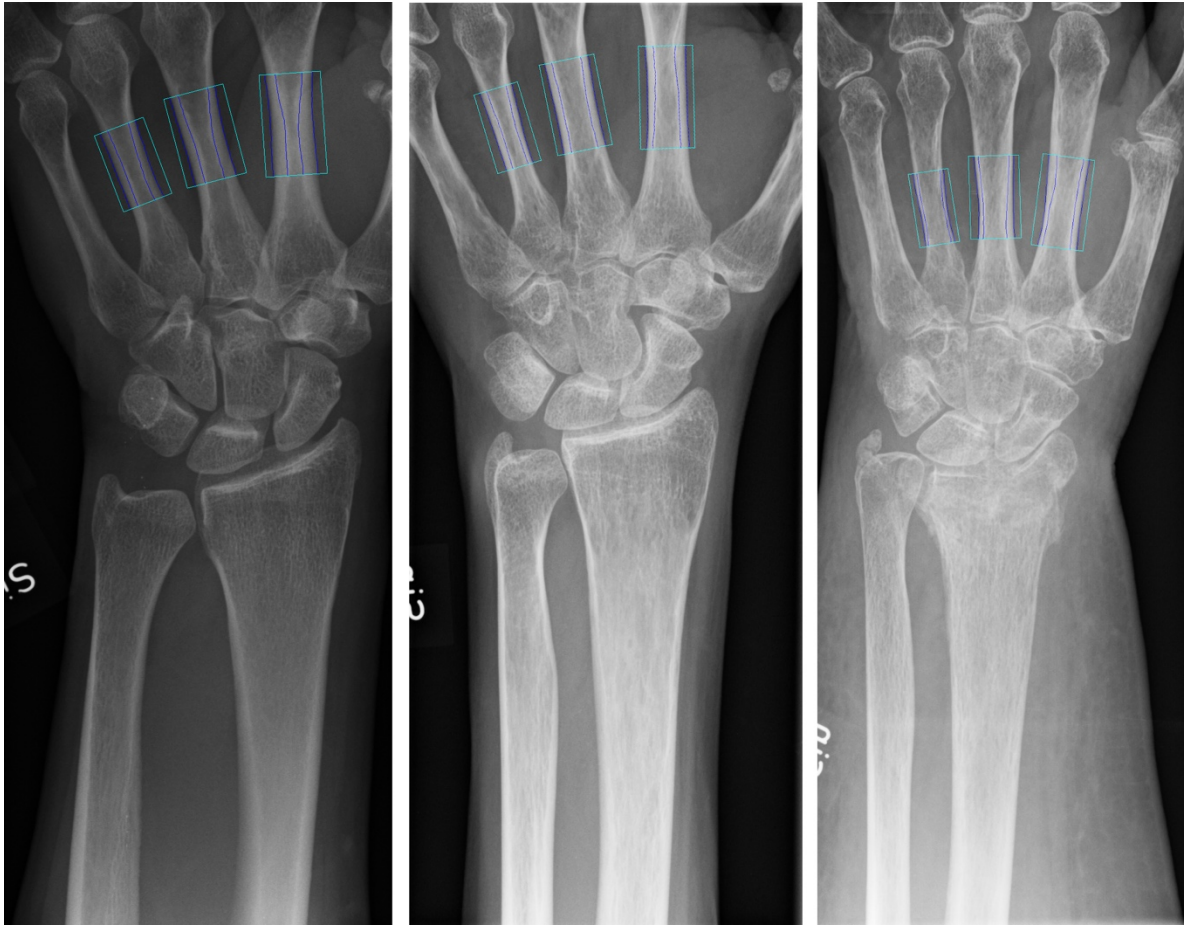
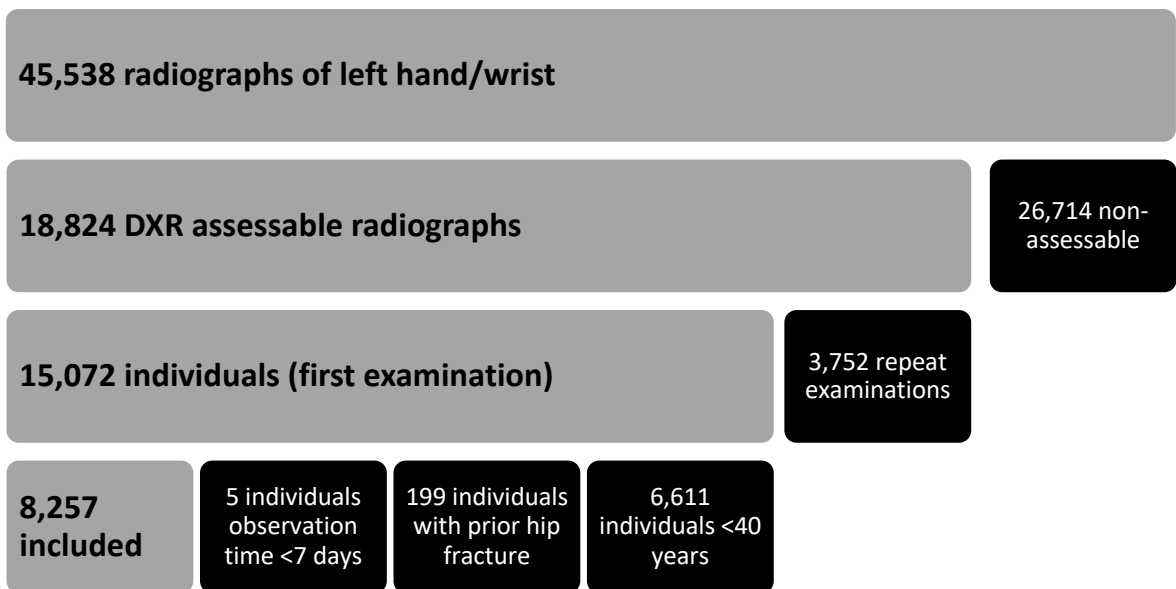*Figure 3. Radiographs included for DXR analysis in paper I.*

Figure 4. Flowchart of how radiographs and patients were selected for paper I (gray = inclusion, black = exclusion).

4.2.2 Paper II

Between March 2010 and June 2012 women attending general mammography screening were invited to participate in the study. The study was conducted two days per week, Monday and Wednesday, at a single mammography-screening center (Unilabs AB, Tumba, Stockholm County, Sweden). Inclusion in the STOP cohort implied having a radiograph of the non-dominant hand obtained in conjunction with mammography (Figure 5) and filling

out a questionnaire regarding clinical risk factors for osteoporosis (Box 3). Univariate associations between the questionnaire and DXR T- and Z-scores were examined. A generalized linear regression model was fitted to independent variables with univariate associations of P<0.05. A multivariable model was reduced through manual backward elimination, with P<0.1 as the exclusion criterion.

Figure 5. Hand radiograph obtained for DXR use with mammography equipment (Sectra OneScreen). Image used with permission from Sectra AB.

4.2.3 Paper III
DXR analysis reports from the STOP cohort were reviewed each month. Ranked by Z-score the lowest scoring 2 percent (rounded-up) of study participants were referred for DXA (left and right hip and lumbar spine) and a clinical consultation including blood sample analyses at an osteoporosis clinic. Initially all referred participants were offered clinical consultations but in 2012 consultations had to be restricted due to staff shortage at the department in question. From that point on selected women were referred for DXA as well as pre-specified blood samples (blood status, serum electrolytes including calcium, PTH, TSH and T4) without clinical consultation. Invitations were sent via mail without reminders. A clinical appointment was offered if participants had DXA T-scores equal to or below -2.0 at any site or laboratory test results outside reference intervals. Figure 6 illustrates the selection process. Women with PTH ≥5.0 pmol/L and ionized calcium ≥1.3 (mmol/L) were considered to have primary hyperparathyroidism. Those with a high PTH (>6.9 pmol/L) in absence of hypercalcemia (<1.33 mmol/L) or with low 25OHD3 (<25 nmol/L) and evidence of renal failure were considered to have secondary hyperparathyroidism. Fisher's exact test or χ2 test were used to compare binary variables between those selected for DXA and those only examined with DXR. Variables with cell values of less than 5 were analyzed with Fisher's exact test. Data that did not fulfill the

criteria of normality were analyzed with Mann-Whitney U-test for differences in distribution.
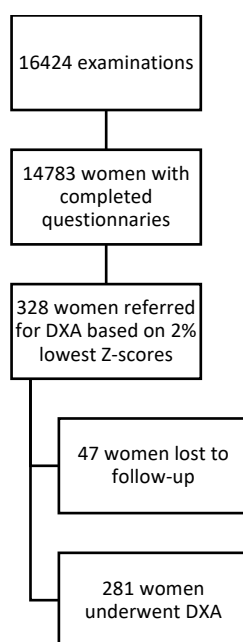

Figure 6. Selection process for participants in paper III.

4.2.4 Paper IV

Participants from the STOP cohort were matched with National Patient and Death registries from the Swedish National Board of Health and Welfare. Individuals with hip fractures, major osteoporotic (hip, spine, humerus and forearm) fractures and all fractures (except skull, fingers and toes) were identified using ICD-10 codes in the patient registries. Individuals who suffered fractures before their DXR exam were excluded from analysis of subsequent hip fractures. For those with major osteoporotic fractures after DXR, individuals with fractures of the same type occurring within 6 months were excluded from analysis in that group. Study subjects with fractures after DXR (cases) were compared to the remaining study population (controls) with regard to DXR-BMD and clinical information provided in the questionnaire. Hazard ratios were calculated, and ROC curves were plotted.

4.3 RESULTS AND DISCUSSION

4.3.1 Paper I

Radiographs from 8,257 patients (65.6% women; 34.4% men) were considered acceptable for analysis. The mean age was 59.6 years (SD 12) and the average follow-up time was 3 years and 3 months. 122 patients with hip fractures were identified (89 women and 33 men) Patients who suffered hip fractures were older at the time of examination and had significantly lower DXR-BMD, DXR T-score and Z-score than patients without fracture (Table 1). Age-adjusted hazard ratios and ROC-curves were calculated and plotted for the entire study population and for an age-restricted group between 55 to 85 years. Restriction, based on ages 55-85, was chosen considering the age group most likely to be candidates for pharmaceutical treatment. Hazard ratios among all participants per standard deviation in DXR T-score decrease were 2.08 for women and 2.52 for men (Figure 7). In the age-restricted group the equivalent values were 2.33 and 2.00 respectively. The age-adjusted area under the curve was 0.89 for women and 0.84 for men in the entire cohort. Among those between 55-85 years the AUC was 0.83 (women) and 0.80 (men) (Figure 8-9).

	Number	Age at examination (years)	DXR-BMD (g/cm²)	T-score	Z-score
Female					
Fracture	89	78 (10)	0.419 (0.05)	-3.5 (1.1)	-0.565 (0.988)
Non-fracture	5331	60 (12)	0.528 (0.08)	-1.2 (1.6)	0.009 (0.997)
Male					
Fracture	33	70 (16)	0.538 (0.09)	-2.2 (1.4)	-0.900 (1.110)
Non-fracture	2804	58 (12)	0.630 (0.07)	-0.7 (1.1)	0.030 (0.994)

Table 1. Characteristics for fracture and non-fracture groups by sex. One standard deviation is given within parenthesis. All differences were statistically significant at the p<0.01 level.
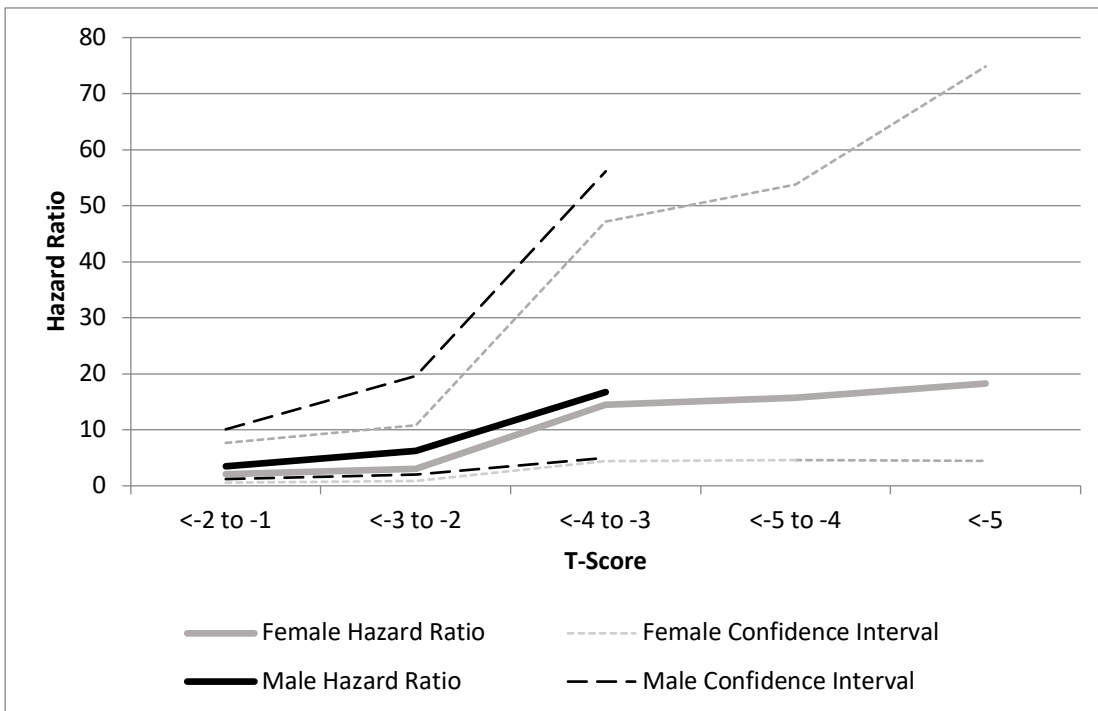
Figure 7. Hazard ratio by various T-scores for female and male subjects. No data shown for male subjects at T-score <-4 due to insufficient number of subjects.
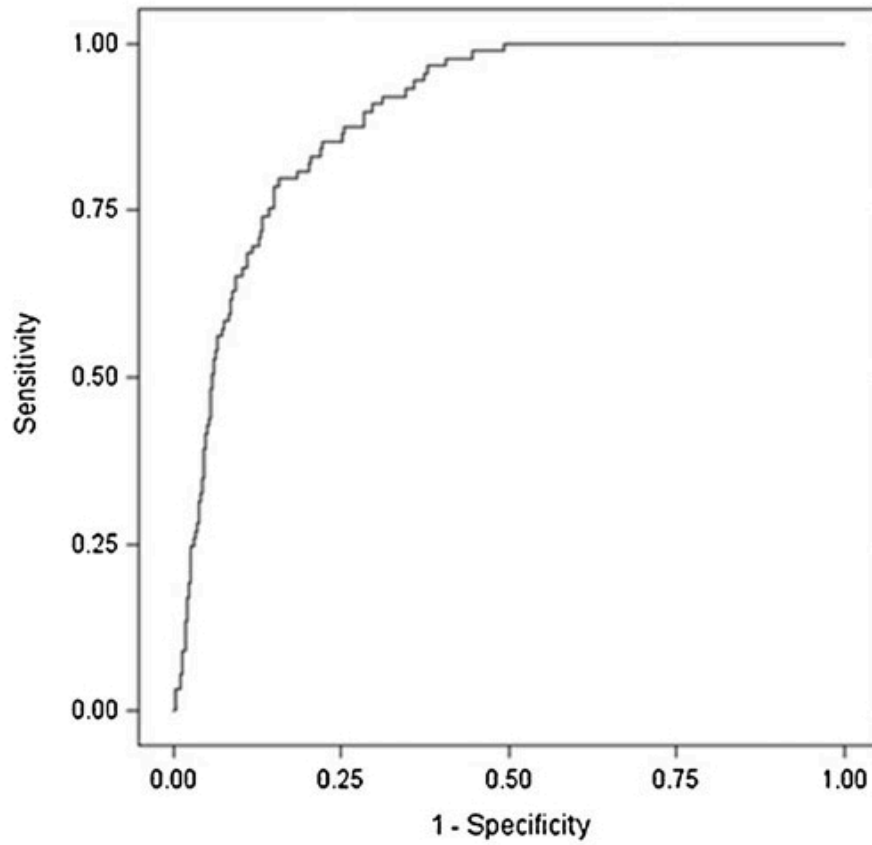
Age-adjusted ROC curve

Figure 8. Age-adjusted ROC curve for DXR T-score and hip fracture in women. **AUC 0.89**.
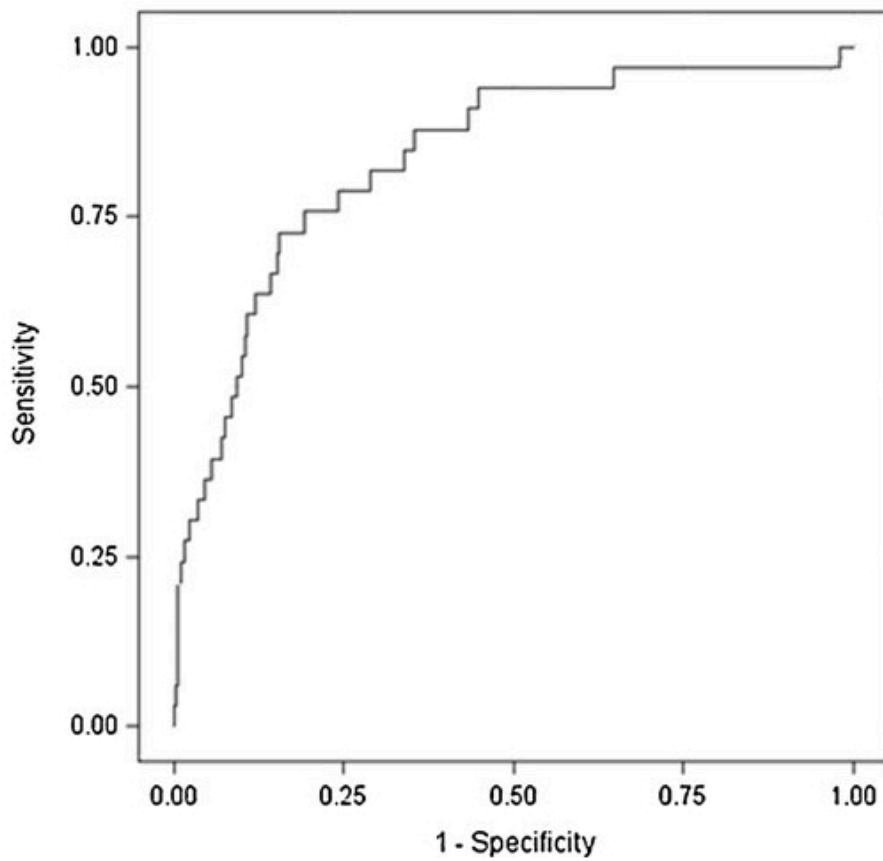
Age-adjusted ROC curve

Figure 9. ROC curve for DXR T-score and hip fracture in men. **AUC 0.84**

Strengths of the study include the large cohort, including both men and women, and a small loss to follow-up due to high-quality national registries. Weaknesses include selection bias of the cohort and not knowing the indications for the radiographs performed. Based on clinical experience we presumed that most radiographs were obtained as part of trauma investigations to exclude fractures in hand or wrist. A smaller, but still significant portion might be due to rheumatic arthritis or osteoarthritis or post-operative controls. From a clinical perspective however, the study selection is probably not a weakness as it rather mimics how opportunistic screening might be conducted in practice. Our results indicate that DXR-analysis of radiographs obtained for any reason provides valuable information without additional examinations or radiation exposure.

In this study we also only looked at hip fractures. The reasons for this were to minimize the risk for misclassified fractures and to look at the fracture type most strongly with excess morbidity and mortality. Further studies ought to look into refining the predictability of DXR based on different indications for radiographs and various fracture types.

4.3.2 Paper II

At the interim analysis, 8,810 women attending the standard mammography screening program had had DXR examination of the non-dominant hand and had returned questionnaires. This population constitutes 75.5% of all women attending mammography screening at the study center during the study period. All risk factors asked for in the questionnaire were found to be statistically significant in a univariate analysis. In a multivariate analysis however, season of examination and family history of fracture were no longer significant and thus excluded in the final model. Smoking alone was not significant but an interaction term with smoking status and age was found to be significant ($p = 0.009$). The coefficient of determination of the multivariate model was 0.37. No evidence of collinearity was found. Well-established risk factors for osteoporosis, such as age, weight, age at menopause, use of glucocorticoids and rheumatic disease were influential risk factors in our final model, i.e. they were associated with DXR-BMD in this study population. The prevalence of risk factors (Table 2) was similar to epidemiological data of the same region, indicating that the STOP cohort was representative of the general population in the county.

Risk factor	N			
Continuous variables		**Mean (SD)**		
T-score, metacarpal bone	8810	-0.51 (1.25)		
Height (cm)	8606	165.2 (6.4)		
Categorical variables		*n*	**(%)[1]**	**T-score Mean (SD)**
Age (years)	8810			
< 50		4097	46.5	0.10 (1.00)
50 – 54		1211	13.8	-0.24 (1.04)
55 – 59		914	10.4	-0.81 (1.02)
60 – 64		1453	16.5	-1.27 (1.06)
≥ 65		1135	12.9	-1.74 (1.12)
Weight (kg)	8677			
36 – 54		561	6.5	-1.02 (1.23)
55 – 59		875	10.1	-0.73 (1.23)
60 – 64		1496	17.2	-0.58 (1.25)
65 – 69		1461	16.8	-0.51 (1.21)
70 – 74		1321	15.2	-0.47 (1.22)
75 – 79		942	10.9	-0.42 (1.22)
80 – 84		710	8.2	-0.35 (1.25)
85 – 89		480	5.5	-0.22 (1.15)
≥ 90		831	9.6	-0.17 (1.24)

Right-handed	8759		
Yes		8003	91.4	-0.52 (1.24)
No		756	8.6	-0.39 (1.33)
Menopause <45 years of age	8047		
Yes		1079	13.4	-1.01 (1.26)
No		6968	86.6	-0.47 (1.24)
Family history of hip fracture[2]	8626		
Yes		999	11.6	-0.76 (1.28)
No		7627	88.4	-0.47 (1.24)
Ever-smoker	8775		
Yes		2769	31.6	-0.57 (1.28)
No		6006	68.4	-0.48 (1.23)
Alcohol consumption	8690		
0		3253	37.4	-0.54 (1.29)
1		2526	29.1	-0.43 (1.19)
≥ 2		2911	33.5	-0.53 (1.23)
Cortisone treatment >3 months	8733		
Yes		655	7.5	-0.83 (1.37)
No		8078	92.5	-0.48 (1.23)
Angina pectoris or myocardial infarction	8709		
Yes		200	2.3	-1.38 (1.32)
No		8509	97.7	-0.48 (1.23)
Anorexia	8714		
Yes		22	0.3	-0.68 (0.90)
No		8692	99.7	-0.50 (1.24)
Diabetes (insulin-treated)	8697		
Yes		171	2.0	-1.03 (1.26)
No		8526	98.0	-0.49 (1.24)
Hemiplegia	8692		
Yes		45	0.5	-0.89 (1.42)
No		8647	99.5	-0.50 (1.24)
Hyperparathyroidism	8587		
Yes		141	1.6	-1.02 (1.33)
No		8446	98.4	-0.49 (1.24)
Malabsorption syndrome	8627		
Yes		31	0.4	-1.17 (1.50)
No		8596	99.6	-0.50 (1.24)
Rheumatic disease	8636		
Yes		464	5.4	-1.05 (1.47)
No		8172	94.6	-0.47 (1.22)
Substantial immobility[3]	8631		
Yes		205	2.4	-1.18 (1.43)
No		8426	97.6	-0.49 (1.23)
Other disease associated with osteoporosis	8280		
Yes		235	2.8	-0.97 (1.37)
No		8045	97.2	-0.47 (1.23)

[1]Within variable, percentages not summing to 100 are due to rounding.

[2] The patient's mother or father suffered a hip fracture.

[3]< 100 meters without support.

Table 2. Descriptive statistics of the 8810 women participating in the study.

The main strength of paper II lies in the recruitment and size of the cohort. Selection from a general population-based screening program with high attendance made it possible to sample a normal population. Using self-reported information without validation from clinical health records might constitute a limitation. However, this is the most likely way similar information will be gathered in clinical practice. This was a single-center study in which inclusion was only done on Mondays and Wednesdays, which might be considered a limitation. We received reports from on-site radiology technicians that some patients rescheduled their visit in order to be included. When looking at samples of the study vs non-study days however, we did not observe any difference regarding age distribution nor number of daily patients examined.

In conclusion we found that the STOP cohort was largely representative of the general population and that several known clinical risk factors for osteoporosis were significantly associated with DXR T-score.

4.3.3 Paper III

The final STOP cohort included a total of 16,424 DXR examinations done in connection with mammography screening of 14,841 women. Out of these 14,783 women had also partially completed questionnaires regarding risk factors for osteoporosis. 327 women were invited for further investigation due to low DXR Z-score and of those, 281 participated and had a follow-up DXA examination. A third (n=93) of those who underwent DXA had osteoporosis and in 84.9 % (n=79) women the diagnosis was previously unknown. Several self-reported clinical risk factors were significantly more prevalent among those selected for further investigation on the basis of DXR Z-score (Table 3). In one out of four of the selected women, the investigation led to a change in therapy, mainly by introduction of vitamin D and/or calcium supplements.

A potential underlying cause for secondary osteoporosis, e.g. hyperparathyroidism, was found in 32 women. One strength of the study is the use of the STOP cohort and a loss to follow-up for DXA of only 14%. One limitation of the study is that study participants were included in existing clinical workflows at two different hospital sites resulting in a variation in DXA equipment and follow-up protocols. This variability was minimized by adjustment of T- and Z-scores according to the NHANES III reference database [88]. Using self-reported data might be considered a limitation as it is prone to recall bias and misinformation. However, this is presumably the way information will be gathered in a clinical context and the STOP cohort has been found to be representative when compared to nationwide statistics (Paper II). Another limitation of the study was the lack of clinical consultation in all women due to staff shortage. This might have led to underestimation of causes of secondary osteoporosis and fewer therapy changes.

	Selected for DXA			DXR only			
	N	Mean (SD)	Median	N	Mean (SD)	Median	p-value
Age at DXR	281	54.8 (9.3)	58.0	14502	53.1 (9.6)	52	
Height (cm)	273	162 (6)	162	14188	165 (6)	165	<0.001
Weight (kg)	276	66 (12)	64	14301	71 (14)	70	<0.001
BMI	272	25.2 (4.5)	24.4	14135	26.1 (4.9)	25.3	0.001
	N (total)	N	%	Total	N	%	Significance
Ability to get up from seated position without using arms	278	259	93.2	14447	13669	94.6	0.29
Fallen last month	279	36	12.9	14471	1562	10.8	0.262
Smoking status	279	109	39.1	14443	4463	30.9	0.003
Right-handedness	280	261	93.2	14417	13197	91.5	0.317
History of low-energy fracture	278	77	27.7	14444	2154	14.9	<0.001
Parent with hip fracture	272	43	15.8	14186	1673	11.8	0.043
Height loss >3 cm	259	40	15.4	13886	1033	7.4	<0.001
Menopause <45 years	263	57	21.7	13279	1813	13.7	<0.001
Cortisone treatment >3 months	277	50	18.1	14376	1080	7.5	<0.001
Rheumatic disease	271	47	17.3	14245	733	5.1	<0.001
Insulin treated diabetes	273	12	4.4	14348	270	1.9	0.003
Any hyperparathyroidism	266	8	3.0	14156	254	1.8	0.142
Anorexia	274	0	0.0	14367	42	0.3	1
Malabsorption	271	4	1.5	14228	70	0.5	0.05

History of angina or myocardial infarction	273	11	4.0	14360	363	2.5	0.119
Other diseases that could cause osteoporosis	260	23	8.8	13685	389	2.8	<0.001
Hemiplegia	270	3	1.1	14330	72	0.5	0.162
Reduced mobility (<100 meters without support)	273	16	5.9	14256	352	2.5	<0.001
Alcohol consumption (days per week)	276			14308			<0.001
0		141	5.9		5451	38.1	
1		77	27.9			28.7	
≥2		58	21.0			33.2	
Alcohol consumption (glasses per occasion)	175			10654			0.042
1		65	37.1		3339	31.30	
2		69	39.4		5225	49.00	
≥3		41	23.4		2091	19.60	

Table 3. Self-reported data in the two groups.

4.3.4 Paper IV

Of the 14,841 women who had a DXR examination in the STOP cohort, 10,967 returned fully completed questionnaires regarding clinical risk factors. The total observation time was 48,011 person years. Thirty-seven women had previous hip fractures. No-one had a prior major osteoporotic fracture of the same type occurring within 6 months. Fractures after DXR were categorized in three groups: hip, major osteoporotic or any clinical fracture. A total of 605 clinical fractures were identified: whereof 18 hip and 344 major osteoporotic fractures.

DXR T-score showed a highly significant (p<0.01) association with hip, major osteoporotic as well as any clinical fracture. With DXR only, the HR/SD T-score decrease was 2.15 (CI 1.55-3.00) for hip, 1.47 (CI 1.36-1.59) for major osteoporotic and 1.33 (CI 1.26-1.42) for any clinical fracture. When adding age to the model, the HR/SD T-score was somewhat less (1.93, 1.27 and 1.20, respectively for the three categories).

Diabetes was a significant risk factor for hip fractures but not when looking at major nor any clinical fracture. Recent history of fall and smoking were risk factors that showed significant (p<0.05) association with major osteoporotic fractures. Smoking was significant at the 10% level, but not at the 5% level for hip fractures. Recent fall showed a tendency for any clinical fracture as well. Low level consumption of alcohol was inversely associated

with major osteoporotic fractures. The AUC for hip, major osteoporotic and clinical fractures were 0.79, 0.69 and 0.65 respectively (Figure 10-12).
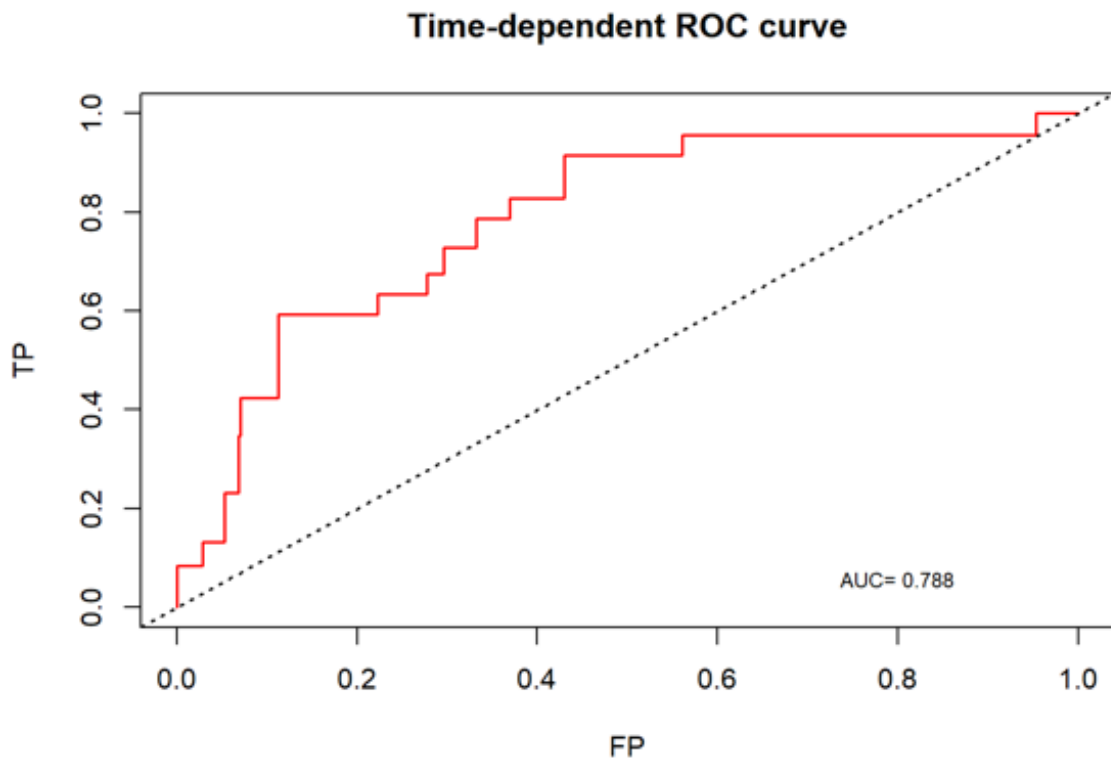
*Figure 10. Age-adjusted ROC curve for hip fracture. **AUC 0.79**. TP = True Positive Rate. FP = False Positive Rate.*
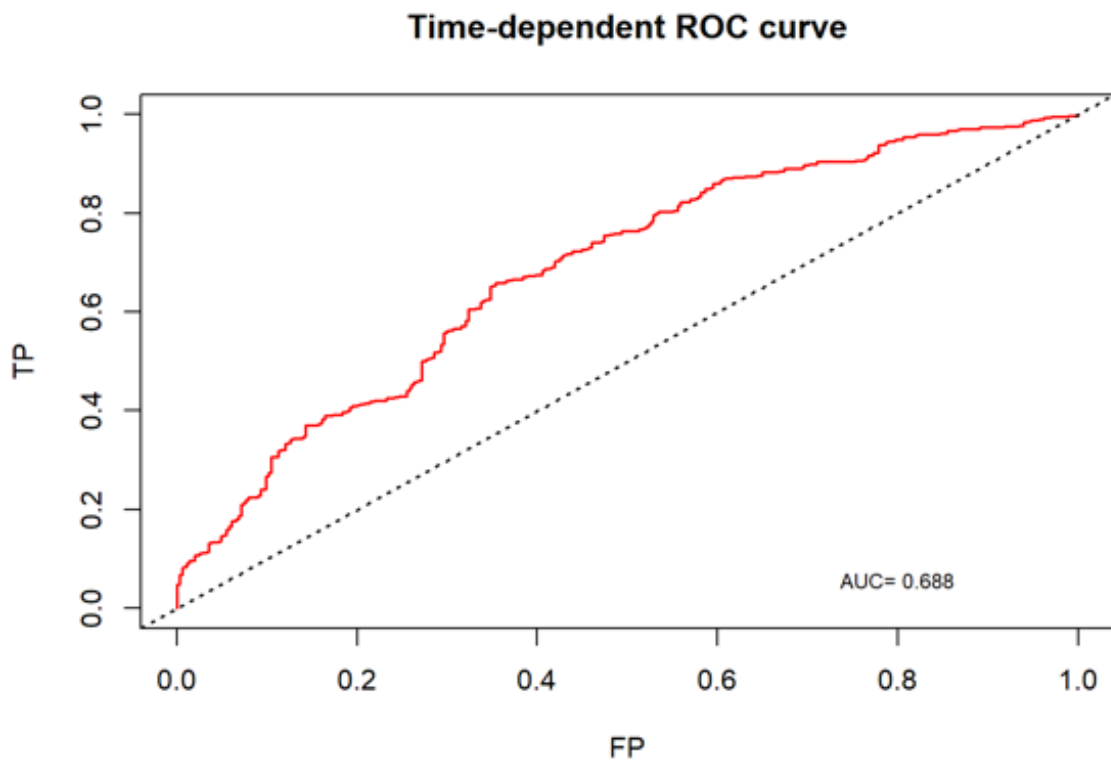

*Figure 11. Age-adjusted ROC curve for major osteoporotic fracture. **AUC 0.69**. TP = True Positive Rate. FP = False Positive Rate.*
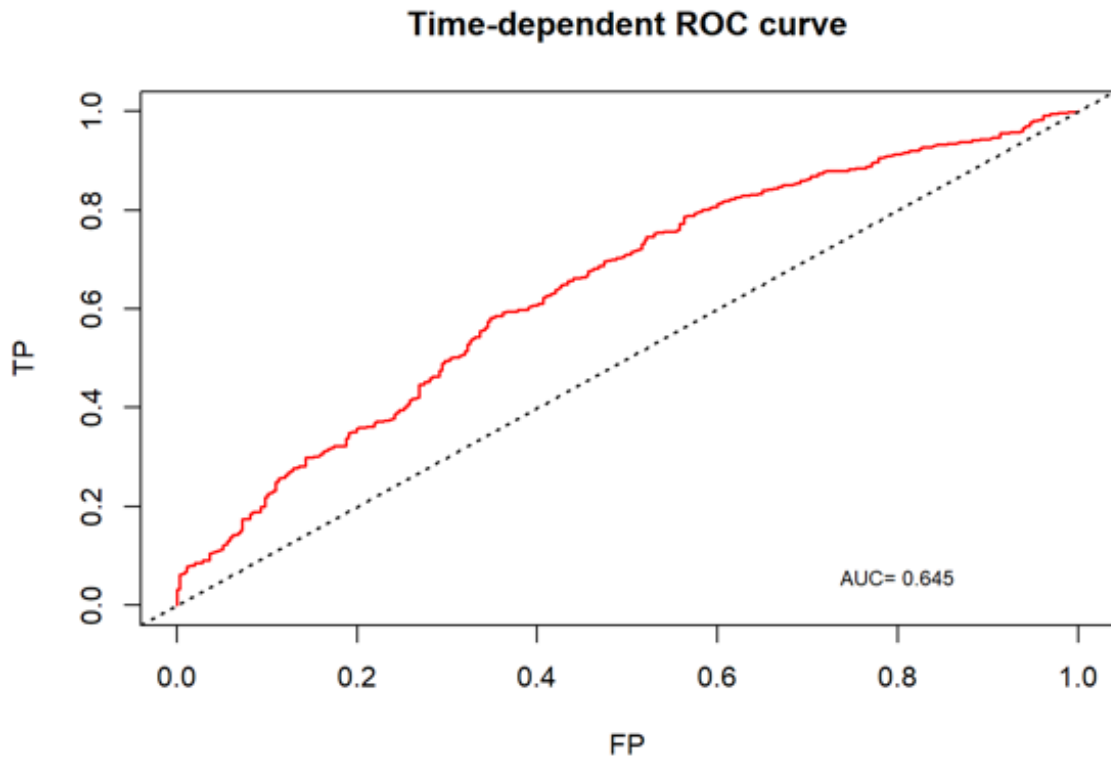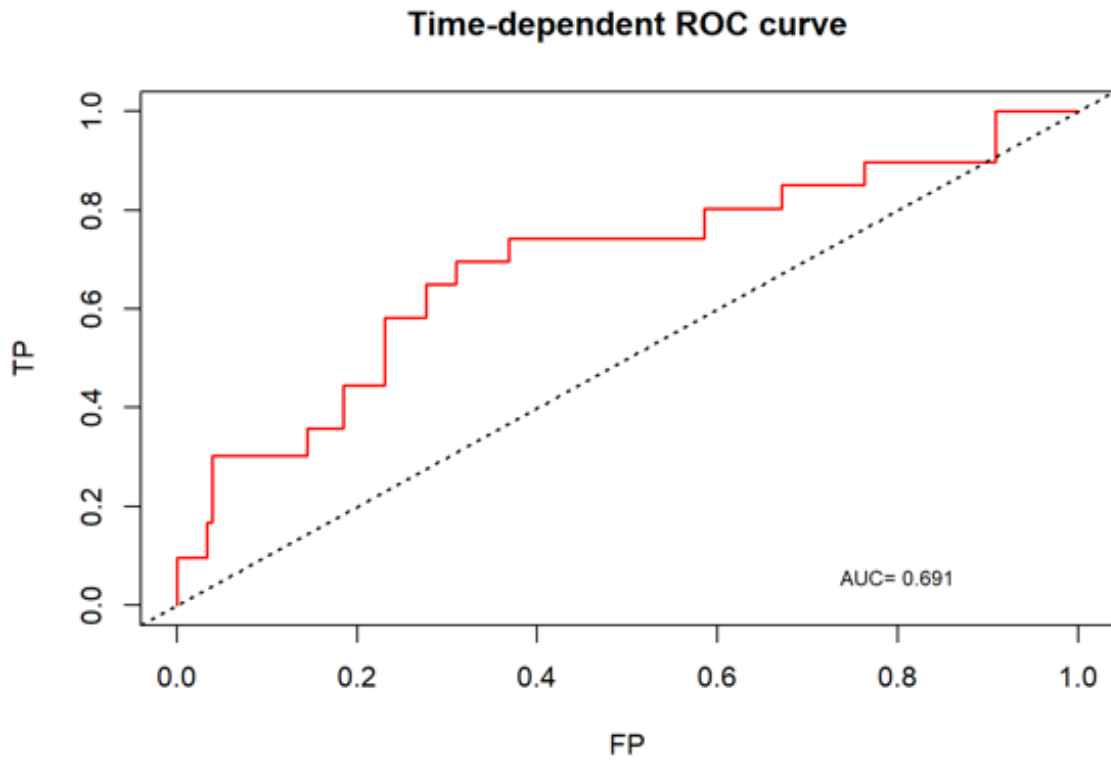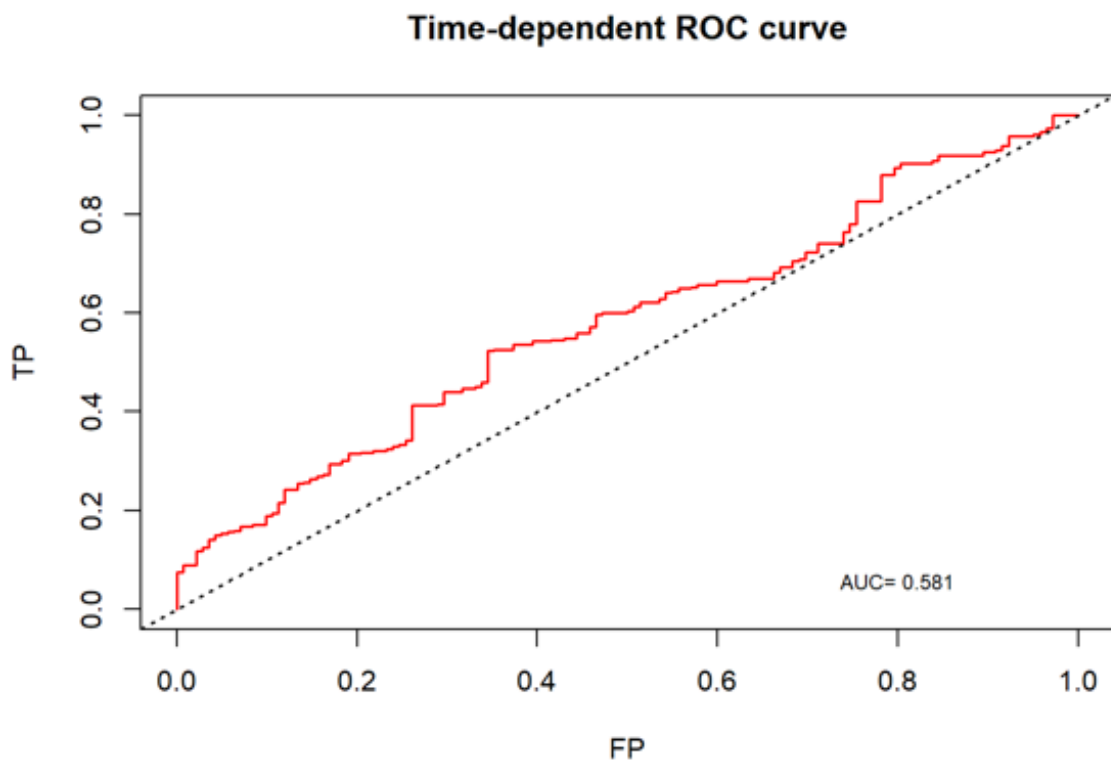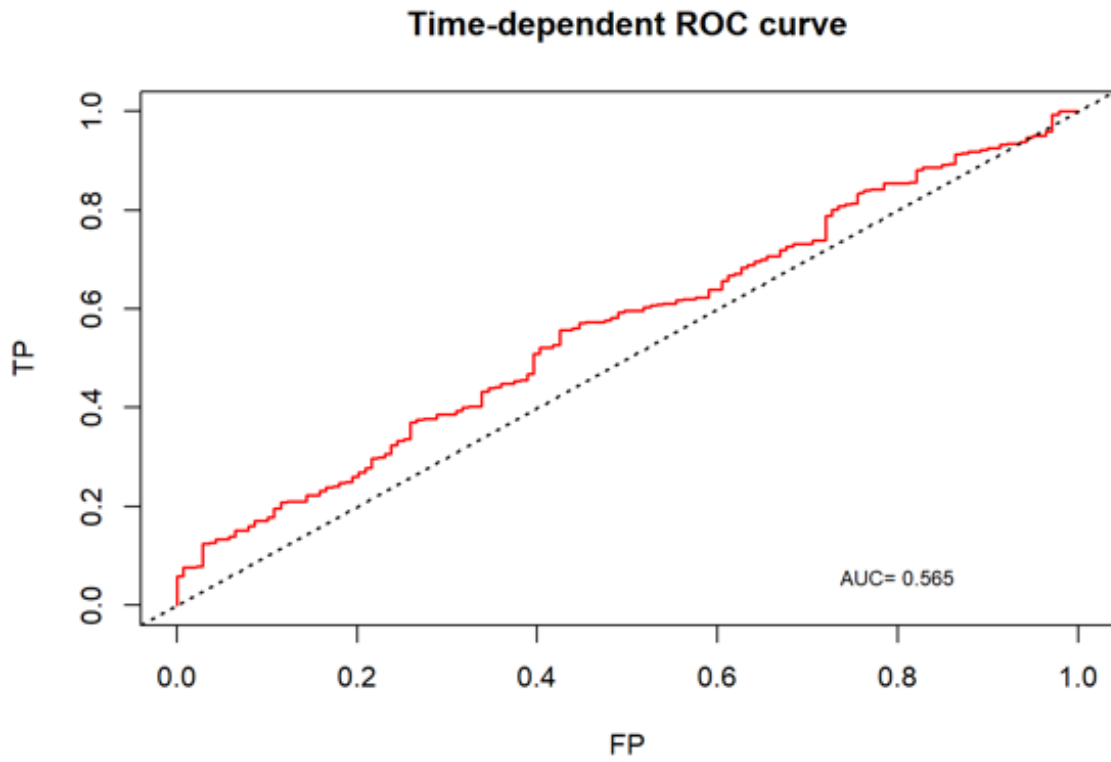
*Figure 12. Age-adjusted ROC curve for any fracture. **AUC 0.65.** TP = True Positive Rate. FP = False Positive Rate.*

Due to young age of the cohort, another analysis was restricted to women >55 years, thus including 6,309 women with DXR whereof 4,704 women had returned fully completed questionnaires. Among this older subset there were 15 hip fractures, 220 major osteoporotic fractures and 345 clinical fractures. The corresponding AUC:s were 0.69 (hip), 0.58 (major osteoporotic) and 0.57 (clinical fracture), respectively (Figure 13-15). This effect is probably mainly mathematical. Younger individuals have higher BMD and very low risk of fracture. Risk assessment including those will therefore result in a very high specificity, biasing ROC. The predictive value of DXR in this study was less compared to central DXA [89]. Strengths of this study include prospective design with a normal population sample

and good follow-up. The main weakness is the short follow-up period with regard to the low fracture risk in the study population, resulting in few incident fractures.

Time-dependent ROC curve

AUC= 0.691

Figure 13. Age-adjusted ROC curve for hip fracture in women >55 years. **AUC 0.69.** *TP = True Positive Rate. FP = False Positive Rate.*

Time-dependent ROC curve

AUC= 0.581

Figure 14. Age-adjusted ROC curve for major osteoporotic fracture in women >55 years. **AUC 0.58.** *TP = True Positive Rate. FP = False Positive Rate.*

*Figure 15. Age-adjusted ROC curve for any clinical fracture in women >55 years. **AUC 0.57.** TP = True Positive Rate.*
FP = False Positive Rate.

5 GENERAL DISCUSSION

Osteoporosis is a silent disease [90] that will affect a large portion of both the female and male population, though it is more prevalent among women [18]. DXA is considered the gold standard for diagnosis of osteoporosis and has by far been studied the most and been the basis for many risk-assessment and pharmaceutical studies [8, 91]. Currently, no studies have monitored treatment effects with DXR-BMD. This is a major obstacle for DXR when it comes to be considered a diagnostic method on which clinicians can rely on to initiate or follow osteoporosis treatment. Further studies in this field are thus warranted.

Though DXA-BMD is the gold standard in osteoporosis work-up [28] most individuals who suffer fragility fractures are more likely to have normal bone mass or with osteopenia (T-score between -1 and -2.5) according to DXA rather than osteoporosis (T-score ≤ -2.5) [92-95]. Other factors than DXA-BMD are therefore likely to account for fracture risk [21]. Since fractures are what accounts for the excess mortality, morbidity as well has health care cost related to osteoporosis [18]. Fractures, rather than DXA, should be considered the most relevant study endpoint.

While some have looked at fractures [84, 96-98], other studies of newer bone mass assessment techniques have mostly been focused on DXA association [52, 99-101]. This is probably because a clear association would facilitate diagnosis and management based on non-DXA methods. Since most individuals with fractures do not have osteoporosis [92-94] comparing a new method with DXA might mean making a comparison with a suboptimal method. However, due to the nature of osteoporosis and fracture risk, large cohorts and long follow-up times are often needed. This makes it a costly and lengthy process to assess new methods with fracture as endpoint. As a result, fracture risk and prevention studies have often looked at older (>60-85 years) populations with higher fracture risk than the STOP cohort [77, 102-104].

In this thesis we present investigations of DXR in two large cohorts (one retrospective and one prospective) where clinical fracture was the main outcome measured. The retrospectively sampled cohort (Paper I) included individuals of both sexes that for any reason had obtained a hand or wrist radiograph (depicting metacarpals II-IV) in any of three major hospitals in Stockholm. Though data was collected retrospectively, a prospective chain of events (examination and following fracture) was analyzed. Paper I showed that DXR-derived BMD was highly predictive of hip fractures with high sensitivity and specificity in that study population. Due to the study participant selection (hand or wrist radiographs obtained for any indication), the cohort in Paper I most likely had an inherent high risk of fracture since most patients probably obtained their radiograph due to trauma of some sort. However, from a clinical perspective the method might still be a useful tool for opportunistic detection of individuals with high fracture risk. Similar opportunistic approaches such as fracture-liaison services have already been adopted in many different regions to identify individuals with high fracture risk at an early stage with the ambition to address modifiable risk factors and initiate potential treatments [85-87]. Furthermore, opportunistic screening through analysis of thoracic or abdominal CT scans done for other purposes has also been studied and suggested [45, 81, 82, 84, 105].

The STOP cohort was prospectively sampled with participants from the Swedish population-based mammography-screening program and thus only included women (Paper II). In Sweden women aged 40-74 are invited for mammography screening biannually. In contrast to the retrospectively sampled cohort (Paper I), the STOP cohort is young and

considered to have a low fracture risk in general. In a descriptive analysis of the STOP cohort we found it to be representative of the general population in the same county (Paper II). DXR T-score was also shown to be associated with several known risk factors for osteoporosis.

BMD is known to decrease with age [106]. However, osteoporosis is defined and diagnosed based on BMD measurements when compared with a sex-matched young, healthy reference population (T-score). The rationale for this has been that a fracture threshold (as opposed to relative) BMD is considered more clinically relevant [107]. Another way of looking at pathological BMD processes is to compare BMD with age-matched cohorts (Z-score). Previous studies have indicated that this might be a way of identifying individuals with secondary osteoporosis, i.e. osteoporosis due to other causes. Therefore, women from the STOP cohort with the 2% lowest DXR-Z-score were invited to further examination with pre-specified blood tests, DXA and clinical consultation at an osteoporosis department at a university hospital (Paper III). In this subset, a high prevalence of DXA-verified osteoporosis (33%), potential causes of secondary osteoporosis as well as clinical risk factors for osteoporosis were detected, leading to a change in clinical management.

DXR's fracture prediction was prospectively assessed by matching the STOP cohort with Swedish national patient registries (Paper IV). Despite the young study population, relatively few fractures and short follow-up time, DXR T-score was significantly associated with hip, major and any clinical fractures. This indicates that DXR-derived BMD could be of clinical value in fracture risk assessment also in normal (Paper IV) and not only high risk (Paper I) populations.

Based on our results, we conclude that DXR might play a role in screening programs, e.g. as a selection tool for further investigation with DXA or as a part of fracture liaison-services in individuals who do not have fractures but who have been investigated for a suspected hand or wrist fracture. Regarding hypothetical population-based screening, e.g. in conjunction with mammography, beginning at age 40 seems too early. Our results from paper IV indicate this, as do various national recommendations and discussions regarding population-based screening [69, 70, 76, 78-80]. Further studies with longer follow-up should aim to assess how DXR can be best put to clinical use.

6 CONCLUDING REMARKS AND FUTURE DIRECTIONS

The objective of this thesis was to evaluate whether DXR analysis can predict fracture risk and identify individuals with high risk of secondary osteoporosis using standard clinical hand or wrist radiographs.

DXR-BMD is highly predictive of hip fractures in both women and men when using retrospectively collected hand and wrist radiographs from hospital settings (Paper I).

Known clinical factors for osteoporosis are associated with DXR-BMD. Furthermore, DXR can be integrated in a mammography screening workflow with high participation rate (Paper II).

There is a high prevalence of secondary osteoporosis in subjects with low DXR Z-score (Paper III).

DXR-BMD is significantly associated with, and predicts, risk of hip, major osteoporotic and all clinical fractures in a large, female, population-based cohort. (Paper IV).

Before suggesting potential implementation in clinical practice, health economic analyses and considerations are needed. Studies assessing treatment effects with DXR are also of interest for potential future uses of the technology. However, questions such as who will be responsible for the follow-up and management of detected individuals at risk should be discussed before considering clinical use of DXR

We hope that the STOP cohort can be used for further studies on how DXR performs over time and look at refining fracture prediction models (with regard to e.g. clinical risk factors, age groups, repeat examination intervals etc) for potential, population-based, use of the method.

7 ACKNOWLEDGEMENTS

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