Masterproef
The prediction of BIRADS grades for breast cancer using densitometry on CT thorax

Promotor :
Prof. dr. Marie VANDERSTEEN
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Chelsy Vanbilsen
Scriptie ingediend tot het behalen van de graad van master in de biomedische wetenschappen

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Acknowledgements

Content

List of abbreviations

BIRADS	Breast Imaging – Reporting and Data System
BMI	Body Mass Index
CT	Computed Tomography
HU	Hounsfield Unit
kV	kilovolt
MIRC	Medical Imaging Research Centre
MRI	Magnetic Resonance Imaging
r_s	Spearman's correlation coefficient
RIVM	Rijksinstituut voor volksgezondheid en milieu
US	Ultrasound

1 Summary
1.1 English version

Introduction: Breast density is routinely assessed on mammography using the Breast Imaging-Reporting and Data System (BIRADS) classification, known as an independent risk factor to predict breast cancer risk and used in screening mammography programs. However, this screening program has three major issues. First, only 30% of the patients allowed to participate in the screening program does participate. Second, the screening program starts at the age of 50, but in clinical practice, a lot of breast cancers are seen starting from the age of 40. And third, radiologic imaging such as mammography uses ionizing radiation. This ionizing radiation can cause (breast) cancer. Considering those three problems it is clear that many breast cancers remain undetected until it is too late to obtain curative treatment. Another radiologic examination, Computed Tomography (CT) of the thorax, performed for other clinical reasons than breast cancer screening, includes the breasts as well and is capable of calculating densities in the breasts. We developed a CT-BIRADS classification and hypothesized that this CT-BIRADS classification is correlated with the mammographic BIRADS classification.

Materials & methods: CT thorax and mammograms performed within a period of one year were included of patients aged 40-49 years (n = 35, non-screening group) and 50-69 years (n = 144, screening group). One researcher (CVB) used a semi-automated method to segment the breasts and calculated the CT-BIRADS applying a two-compartment model with a threshold range of -40 until -80 Hounsfield Units (HU) on Syngo.via software. Another researcher (JVDV) scored the BIRADS on the mammograms. The statistical significance of correlation ($P<0.05$) was evaluated using the Spearman's correlation.

Results: In the non-screening group, a Spearman's correlation coefficient of $r_s = 0.864$ ($P<0.05$) was found, suggestive of an excellent positive correlation between the mammographic BIRADS and the CT-BIRADS scores. For the screening group, a Spearman's correlation coefficient of $r_s = 0.572$ ($P<0.05$) was calculated, indicative of a moderate positive correlation between the mammographic BIRADS and CT-BIRADS scores.

Conclusion: CT-BIRADS scores were moderate to highly correlated with the mammographic BIRADS scores. CT-BIRADS classification should be further studied to define its role as a risk factor to predict breast cancer risk. It could be especially useful to suggest the need for dedicated mammography screening in the non-screening patients (40-49 years) undergoing a CT thorax examination for other clinical reasons.

1.2 Nederlandstalige versie

Introductie: Borstdensiteit wordt routinematig onderzocht aan de hand van een mammografie waarop de 'Breast Imaging-Reporting and Data System' (BIRADS) classificatie toegepast wordt. Deze BIRADS classificatie wordt aanzien als een onafhankelijke risicofactor om het risico op borstkanker te bepalen en wordt algemeen gebruikt in mammografische screeningsprogramma's. Toch zijn er drie vorname nadelen met betrekking tot dit screeningsprogramma. Als eerste, neemt slechts 30% van de patiënten die mogen deelnemen aan het screeningsprogramma ook effectief deel. Ten tweede, het screeningsprogramma start vanaf de leeftijd van 50 jaar, maar in de klinische praktijk worden al een grote hoeveelheid borstkankers gezien vanaf 40 jarige leeftijd. Het derde nadeel van het screeningsprogramma is dat radiologische beeldvorming, zoals mammografie, ioniserende straling gebruikt. Deze ioniserende straling kan een oorzaak zijn van (borst)kanker. Wanneer men deze drie nadelen van het screeningsprogramma in rekening neemt, is het duidelijk dat veel borstkankers te laat ontdekt worden om nog een behandeling toe te dienen met een genezing tot gevolg. Een andere vorm van radiologische beeldvorming, Computed Tomography (CT) van de thorax, die voorgeschreven wordt omwille van andere klinische redenen dan borstkankerscreening, visualiseert ook de borsten. Gebruikmakend van deze beeldvormingstechniek is het ook mogelijk om de borstdensiteit te bepalen. In onze studie ontwikkelden we een CT-BIRADS classificatie en stelden de hypothese dat de CT-BIRADS classificatie is gecorreleerd met de mammografische BIRADS classificatie.

Materiaal & methoden: Patiënten tussen de 40 en 49 jaar (n = 35, non-screeningsgroep) en tussen de 50 en 69 jaar (n = 144, screeningsgroep) die een CT thorax én een mammografie ondergingen in een tijdsperiode van één jaar werden geïncludeerd. Eén onderzoeker (CVB) gebruikte een semiautomatische methode om de borsten te segmenteren en berekende de CT-BIRADS classificatie door een twee-compartimentenmodel toe te passen met een drempelwaarde tussen -40 en -80 Hounsfield Units (HU) met behulp van Syngo.via software. Een andere onderzoeker (JVDV) scoorde onafhankelijk de BIRADS op de mammografische beelden. De statistische significantie van de correlatie werd geëvalueerd met behulp van de Spearman correlatie ($P<0,05$).

Resultaten: In de non-screeningsgroep werd een Spearman correlatie coëfficiënt gevonden van 0.864 ($P<0,05$). Deze waarde suggereert een excellente positieve correlatie tussen de mammografische BIRADS en de CT-BIRADS scores. Voor de screeningsgroep werd een Spearman correlatie berekend van 0.572 ($P<0.05$). Deze waarde duidt op een gemiddeld positieve correlatie tussen de mammografische BIRADS en de CT-BIRADS scores.

Conclusie: De CT-BIRADS scores zijn gemiddeld tot zeer sterk gecorreleerd met de mammografische BIRADS scores. De CT-BIRADS classificatie zou verder onderzocht moeten worden om zijn rol te bepalen als een risicofactor om het borstkankerrisico te voorspellen. Het zou specifiek bruikbaar zijn om de nood te suggereren aan een mammografische screening in de non-screening patiënten (40 – 49 jaar) die een CT thorax onderzoek ondergaan hebben omwille van andere klinische redenen.

2 Introduction

Breast cancer, a breast disease in which glandular cells of the breast keep dividing and form a tumor, is a disease with a high incidence worldwide. This research will focus on the situation in Belgium. In 2013, an age-standardized breast cancer incidence of 10,695 per 100,000 (10.7%) women was seen [6]. This high incidence makes of Belgium the country with the highest breast cancer rate in the world, followed by Denmark and France [7, 27]. The mortality incidence ratio of breast cancer in Belgium is 24.7%. This means that almost one out of four patients diagnosed with breast cancer will die due to this disease [1]. Breast cancer is the most frequent tumor in women (35.3%) and it is the leading cause of cancer death in Belgian women (20.2%) [7, 16, 27].

According to the American cancer society, a woman's risk of developing breast cancer can be determined by taking into account different parameters. The seven most important ones are listed here: (1) age, (2) race or ethnicity, (3) family breast cancer history, (4) history of breast biopsies, (5) age at menarche, (6) age at menopause and (7) Breast Imaging-Reporting and Data System (BIRADS) [2]. The first risk factor is the women's age. Most breast cancers are diagnosed in women above the age of 50. At that time, women's hormonal status changes. Before menopause, high levels of the hormone estrogen are present in the blood. This hormone stimulates the growth of breast tissue. After menopause, the estrogen production level falls to a very low level. [25] Next, the amount of breast tissue decreases and the risk of developing breast cancer increases. But note, in clinical practice, a significant amount of breast cancers are seen starting from the age of 40 [10]. In Canada, 18% of all breast cancers are seen in women under the age of 50 [14]. Considering the second risk factor, race or ethnicity, it is clear that in Caucasian women, breast cancer prevalence is higher than in black women [10]. This is probably due to environmental factors that contribute to the development of breast cancer. In Western countries, a lot more industry is present than for example in African countries. The next parameter is the family breast cancer history in first-grade relatives. This means that if a woman's mother or sister has developed breast cancer, her risk of developing breast cancer is also increased. This can be explained by hereditary of breast cancer. Breast cancer can be caused by genetic defects. If this kind of breast cancer is present in first-grade relatives of a woman, her risk to develop cancer is increased significantly. The fourth parameter in the determination of the breast cancer risk is the history of breast biopsies with diagnosis of benign breast disease. In other words, when a woman develops a benign breast disease (i.e. a calcification), the risk of developing breast cancer is also increased [10]. The following risk factor is the woman's age at menarche. If a woman's menstrual cycle starts early (before age of 12), this woman has more menstrual cycles. This causes a longer exposure to estrogen and progesterone, which increases the risk of developing breast cancer [2]. The second last parameter to take into account is the age at menopause. When women go through the menopause after the age of 55, again they have more menstrual cycles. So also these women have an increased breast cancer risk because they are exposed for a longer lifetime to the hormones estrogen and progesterone [2]. The last risk factor is the most important one in this research. This research will focus on the BIRADS breast density, known as an independent risk factor for breast cancer [23].

The BIRADS classification is based on estimation of breast density. This means that breast density is used to predict breast cancer risk. Note that BIRADS breast density is the only risk factor of the list above for which the patient has to undergo a mammography. The other risk factors can be obtained during anamnesis. Considering breast density on mammography, the patient can be divided into one of the four BIRADS groups (classification 2003). These groups are represented in figure 1. Group 1 contains breasts that are almost entirely fatty. The relative amount of dense glandular tissue in these breasts is low, between 0% and 25% of the total breast volume [18]. Unless the area that contains the cancer is not visible in the image field of the mammogram, the mammographic image is highly sensitive in this setting [4]. The second BIRADS group contains breasts with scattered areas of fibro-glandular density. The dense areas of these breasts comprise between 25% and 50% of the total breast volume [18]. In group 3 the breasts are heterogeneously dense and may obscure small masses [4]. The dense areas of the breasts included in this group represent between 50% and 75% of the total breast volume [18]. The group with the highest amount of dense areas is the group that contains extremely dense breasts. These lower the sensitivity of the mammography because small masses can easily be obscured [4]. The breasts are dense in between 75% and 100% of the total breast volume, these patients are classified in the BIRADS 4 category [18].
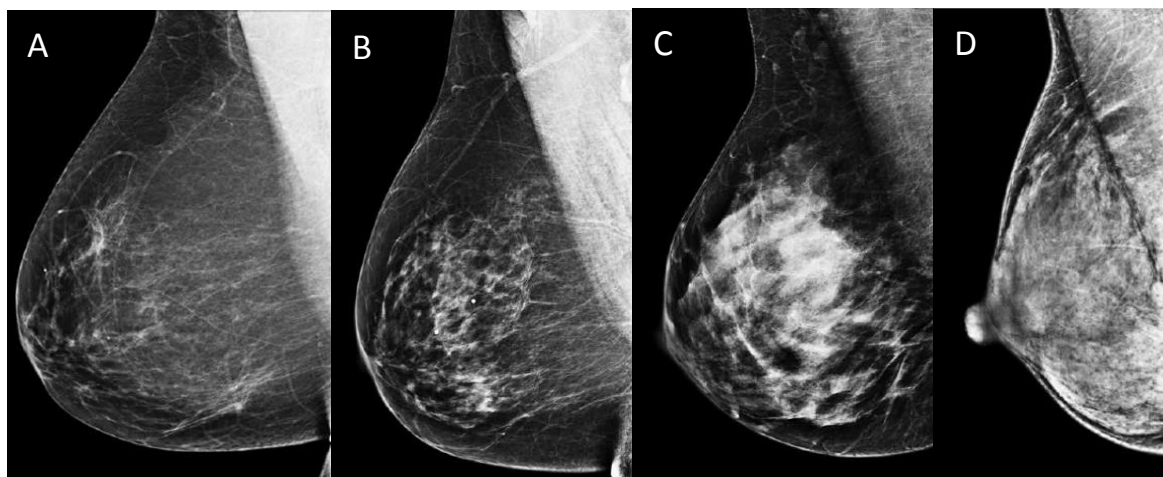

Figure 1 Overview of the four BIRADS groups. A. Relative amount of dense breast areas between 0% − 25%, B. breast density between 25.1% − 50%, C. breast density between 50.1% − 75% and D. breast density between 75.1% − 100%.

As mentioned above, increased breast density causes a decreased mammographic sensitivity: detection of breast cancer is more difficult when the breasts are denser. This is shown in different epidemiological studies [27]. Moreover, Boyd et al. (1995) showed substantial evidence that increased breast density is one of the strongest predictors of breast cancer risk. This research showed as well that in women that belong to the BIRADS 4 group the risk is 2 to 6 times higher than in women belonging to the BIRADS 1 group [9]. Also, Byrne et al. (1995) showed a similar relationship between high breast density and the risk of developing breast cancer. In his research, the calculations were performed independently of age and menopausal status. After adjusting for BMI and family history a 4-5 fold increase in breast cancer risk was seen in women with > 75% of breast density [12]. Even more, in the meta-analysis of McCormack and dos Santos Silva (2006) is stated that breast density was confirmed as the strongest risk factor for breast cancer. This was found independent of the

masking effect when the density is high and not restricted to any particular age bracket [19]. All this contributes to the evidence that BIRADS breast density can be considered as an independent risk factor for breast cancer. This means that when none of the other risk factors are available, but the patient belongs to a high BIRADS group, the risk for that patient to develop breast cancer is increased.

To obtain the BIRADS breast density, the patient has to undergo a mammographic examination. A mammogram is a low-dose x-ray picture of the breast. On these pictures, changes in breast tissue can be detected, together with the density of fibro-glandular tissue in the breast. Mammography can be performed in women following a screening program or in patients with clinical suspicion of breast disease. Screening mammography is performed to look for breast tissue changes in women that do not have any symptoms of breast cancer. No breast problems are present in these patients at clinical examination. The diagnostic mammogram is performed to get more information about changes in the breast(s) (i.e. that can be felt) or women that have breast symptoms or had an abnormal screening mammogram (suspicious lesion) [3, 20]. This research will be focused on the screening mammography. To prevent breast cancer, Belgian women are called upon to undergo a preventive screening mammography every two years, starting from the age of 50 until the age of 69. A disadvantage of this screening program is that ionizing radiation is needed to take a mammogram. A general mammographic examination of the two breasts causes a radiation exposure of 0.4 mSv. This is comparable with the natural exposure to environmental radiation of 7 weeks [3]. The ionizing radiation has a cumulative effect over the years and can cause adverse health effects, including (breast) cancer [20].

In the breast cancer screening program, in 0.41% of the cases, breast cancer is diagnosed [5]. When diagnosed, in four out of five patients (80%) breast cancer can be treated with a curative result. However, for one out of five patients (20%) diagnosed with cancer, the screening program starts too late to obtain a curative treatment [7]. This high number can in part be explained because the breast cancer screening program starts at the age of 50, but in clinical practice, a significant amount of breast cancers are seen starting from the age of 40. This is represented in figure 2. This graph shows that starting from the age of 40 a significant increase in breast cancers is seen. Because the screening program starts at the age of 50, women that develop breast cancer between the age of 40 – 49 years only undergo a mammography when they have breast symptoms, resulting in a high risk that for these patients the diagnosis of breast cancer comes too late to obtain a curative treatment.

Furthermore, it can be retrieved that for 99.59% of the patients participating the mammographic screening program, the mammograms are taken without any personal benefit [5]. In these patients only negative health effects can arise due to the accumulation of ionizing radiation exposure. Another consideration is that 0.7% of all kinds of cancer in the human body develop due to ionizing radiation exposure. In women aged between 50 and 60, 0.014% of all breast cancers are probably introduced by participation in mammographic screening programs [13].
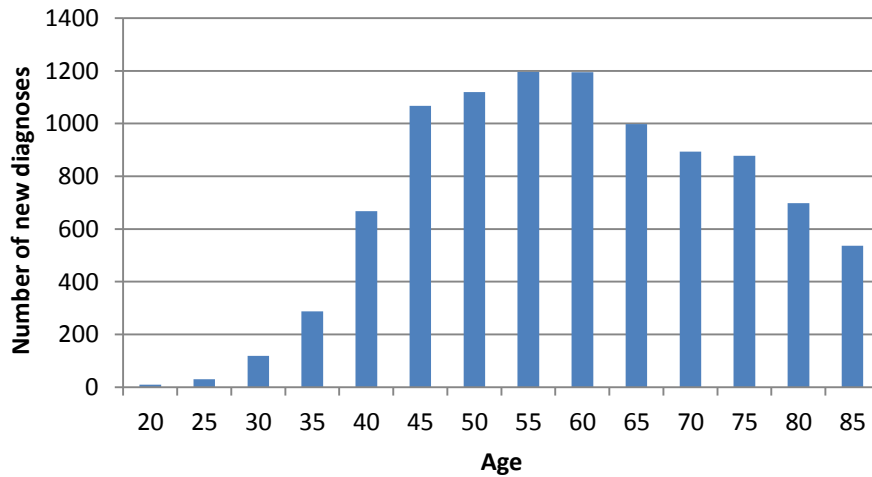
Figure 2 Overview of the number of new diagnoses per age. *Adapted from Belgian cancer registry 2011*

A second disadvantage of the mammographic screening program is that not every woman between 50 and 69 years old participates in the screening program. As represented in figure 3, in 2012 the participation grade was only 32% (red line). This means that only one out of three women that were called upon to undergo the mammographic screening, participated. Another consideration for these results is that in 68% of the female population between 50 and 69 years old, women only undergo a mammogram when they have breast symptoms. But at that moment it can be too late to obtain a curative treatment. The green line in figure 3 represents the participation rate in Flanders. In 2012, almost 50% of the women between 50 and 69 years old participated. This participation rate is almost four times higher than the participation rate in Brussels and Wallonia (blue and orange line). The dashed line in figure 3 is the European target screening rate. This line is laid down on 75%. Considering this, it is clear that the participation rate has to increase by more than 40%. This can be made possible by doing a lot more sensitization in the Belgian population [8].
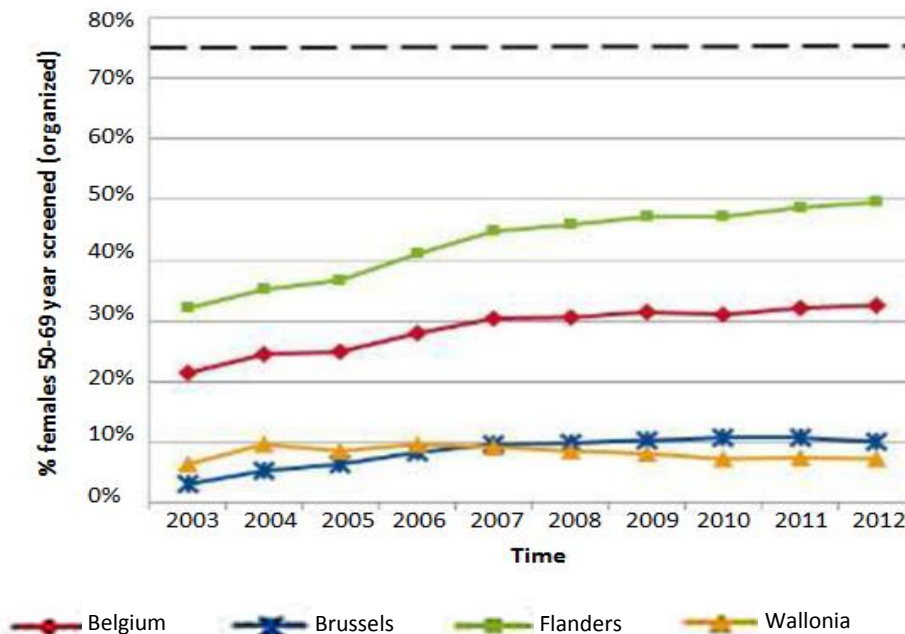

Figure 3 Coverage of breast cancer screening in women 50-69 years old, by region (2003-2012) *Adapted from IMA Atlas 2015*

In short, it is known that the BIRADS breast density is an independent risk factor for breast cancer. This BIRADS breast density is obtained by taking mammograms of the breast. But this has some disadvantages: (1) patients that undergo a mammographic examination are exposed to ionizing radiation. This may cause adverse health effects over the years such as (breast) cancer. (2) A mammographic screening program is set up to achieve early diagnosis of breast cancer, but this screening program has a low participation rate. (3) The mammographic screening program starts at the age of 50, but in clinical practice, many breast cancers are seen starting from the age of 40.

Figure 4 shows that according to the 'Rijksinstituut voor volksgezondheid en milieu' (RIVM) of the Netherlands (2000), more than 6 out of 100 women (6.3%) underwent a CT of the chest before the age of 50. Almost half of these CT thorax examinations (3.3%) are performed in women between 40 and 50 years old (green). In the patient group between 50 and 69 years old, allowed to participate in the screening program, this is 5.9% (orange) [21]. These CT examinations of the chest are often performed to evaluate clinical conditions such as pneumothorax, thorax trauma, lung emboli, etc. [26]. Interestingly, these CT images also include the breasts, demonstrating fibro-glandular tissue with a higher density and fatty tissue with a lower density, much like mammograms. Accordingly, patients could be classified in BIRADS groups using these CT images, which can be called the CT-BIRADS classification.
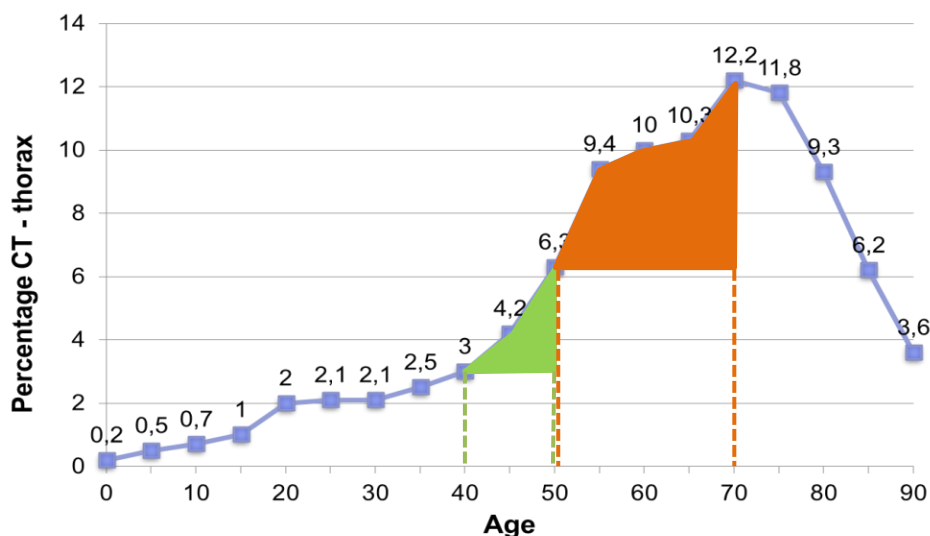
Figure 4 Percentage of women that undergo a CT of the chest at a certain age.
Adapted from Rijksinstituut voor volksgezondheid en milieu (RIVM), 2000.

This study aims to evaluate the correlation between the CT-BIRADS classification and the mammographic BIRADS classification. The key objective of this study is to examine whether semi-automated breast density calculation on CT thorax images is correlated with the visual estimation of the breast density on mammographic images. Hypothesized is that the CT-BIRADS and the mammographic BIRADS are well-correlated. If this hypothesis can be confirmed, women that underwent a CT thorax examination for other clinical reasons could be stratified for breast cancer risk according to CT-BIRADS classification.

3 Materials and methods

3.1 Patient selection

Before starting, the committee of medical ethics of Ziekenhuis Oost-Limburg (Genk, Belgium) and the committee of medical ethics of Hasselt University (Diepenbeek, Belgium) gave the approval to perform this retrospective study. The patient selection started from a large database containing all women, starting from the age of 40 that underwent a mammographic examination and/or a CT of the chest between January 2014 and October 2016 at Ziekenhuis Oost-Limburg. Using this database, the patients aged between 40 and 69, that were asymptomatic and had underwent both a CT of the chest and a mammographic examination within 12 months were selected. After checking if all breast tissue was included in the field of view of the CT examinations, a study population of 179 patients (358 breasts) was found.

Only asymptomatic patients were included, so excluding patients that ever had breast cancer, lung cancer, single or double mastectomy, other breast surgery or had some other treatments that could have had an effect on breast density. Also patients with breast prostheses were excluded. Next, breast density was scored independently on mammography (BIRADS) and on CT thorax images (CT-BIRADS). Because breast density changes with age, only a time span of 12 months was allowed between both radiologic examinations.

The study population was divided into two age groups. The first group contained all patients aged between 50 and 69 years old, the screening group. This age group contained 144 patients. The mean age of this age group was 60 years. These patients were allowed to participate in the mammographic screening program. The second age group included all patients aged between 40 and 49 years old, the non-screening group. This age group was selected because in this age group breast cancers are seen in clinical practice but they could not participate in the mammographic screening program. This age group contained 35 patients. The mean age in this group was 45 years.

3.2 Image acquisition

In Ziekenhuis Oost-Limburg, the CT images of the chest were obtained using SOMATOM Definition, SOMATOM Definition AS and SOMATOM Emotion 6, devices of Siemens (Erlangen, Germany). CT imaging protocols differed between patients, the kilovolt (kV) values used ranged from 80 – 130 kV. Both CT examinations with or without intravenous contrast administration were included. The mammographic images were obtained using MAMMOMAT Inspiration of Siemens (Erlangen, Germany). All images were saved using the IMPAX 6.5.1.1077 'Enterprise Unlimited' software (AGFA – Gevaert N.V., Mortsel, Belgium).

3.3 Image analysis

All 179 CT images of the chest were analyzed using Syngo.via VB10B (2015) (Siemens, Erlangen, Germany). This is a semi-automated software: regions of interest were delineated manually and the density of this region was calculated automatically. The first step in using Syngo.via was uploading the image out of the IMPAX software. In order to edit the images, the multi-modality oncology workflow was applied. After opening the image, a generic segmentation was drawn in one of the breasts. This was done by drawing a longitudinal line through one breast from left to right from skin to skin on the transverse plane. After this, the software constructed a delineation of the breast. This delineation was modified manually until the whole breast was segmented in 3D. Modifying the breast segmentation, different borders were taken into account into the different anatomic planes. The first delineation (green) was performed in the transverse plane, indicated at figure 5. In this plane, the anterior border was the skin and the posterior border was the muscle of the thoracic wall. The medial border was defined at 1 cm of the lateral border of the sternum (indicated in orange). The lateral border was chosen at the skin point having the sharpest angle (indicated in yellow). The next anatomical plane that was used to delineate the breast was the sagittal plane (figure 6). On this view, again the anterior border was the skin and the posterior border was the muscle of the thoracic wall (green delineation on figure 6A). Additionally, on this plane the superior and inferior border of the breast were delineated. The superior border of the breast was set at the superior border of the manubrium of the sternum (yellow line on figure 6B). The inferior border of the breast was set at the inferior border of the corpus of the sternum (blue line on figure 6B). Note that if the patient has large breasts, the skin makes an angle lower than the inferior border of the corpus of the sternum. In these patients, a manual adjustment was performed and the skin angle was chosen as inferior border of the breast. Looking at the coronal plane (figure 7), the skin and muscle of the thoracic wall were used as borders again. The delineation on this anatomic plane ensured that the entire breast was included, however excluding the nipple. When the whole breast was segmented, the breast density was calculated.
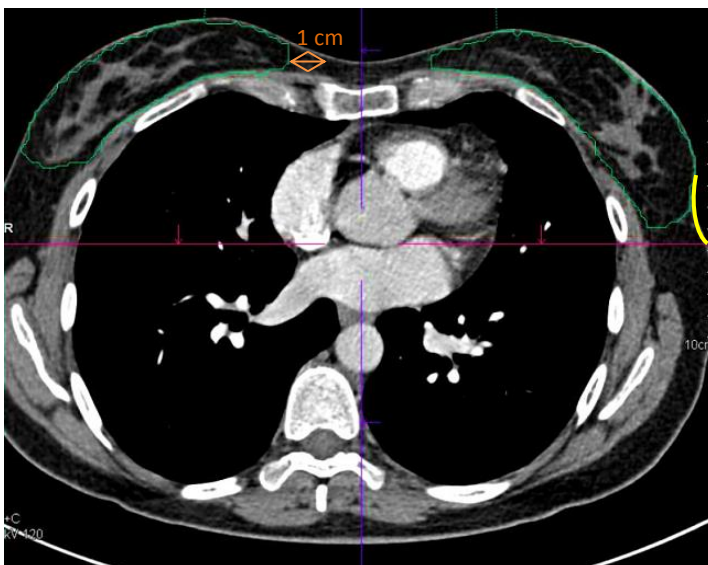

Figure 5 Breast segmentation in the transverse plane. The anterior border was the skin, the posterior border was the muscle of the thoracic wall. The medial border was taken at 1 cm of the lateral border of the sternum (orange). The lateral border was the at the skin point having the sharpest angle (yellow).

Figure 6 Breast segmentation in the sagittal plane. A: On this anatomical plane, the anterior border was the skin of the breast. The posterior border was the muscle of the thoracic wall. B: The superior border of the breast was set at the superior border of the manubrium of the sternum (yellow line), the inferior border at the inferior border of the corpus of the sternum (blue line).
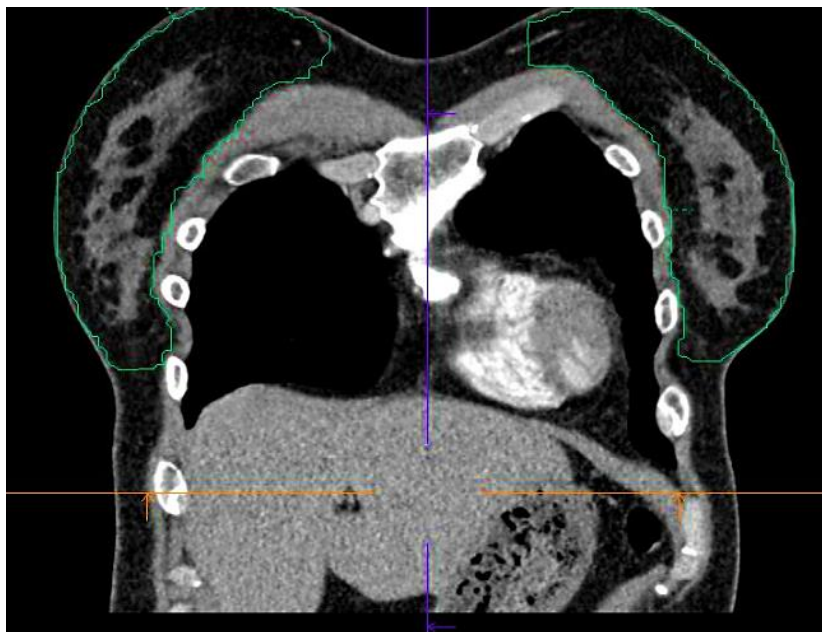

Figure 7 Breast segmentation in the coronal plane. The borders used on this anatomical plane were anterior the skin and posterior the muscle of the thoracic wall.

This calculation was performed considering the breast as a two-compartment model. Note that for every patient a separate calculation was performed for each breast. To calculate the breast density a specific Hounsfield Unit (HU) was set as threshold. This threshold represented the transition from fat tissue to fibro-glandular tissue. All pixels with a density lower than this HU were considered as fat tissue, the pixels with an equal or higher density were reported as fibro-glandular tissue. Considering this percentage the breast densities were divided into four different grades, the CT-BIRADS grades: grade 1 corresponds to fatty breasts with a fibro-glandular density in 0-25% of the total breast volume; grade 2 contains breasts with a fibro-glandular density between 25 and 50% of the total breast volume; grade 3 are breasts with a fibro-glandular density between 50-75% of the total breast volume and grade 4 corresponds to breasts with a fibro-glandular density between 75 and 100% of the total breast volume. The thresholds used in this study were -40, -50, -60, -70 and -80 HU.

One radiologist (JVDV) reviewed all mammographic images to obtain the mammographic BIRADS grades. This review was performed without knowledge of the CT images of the chest nor the semi-automatically obtained CT-BIRADS grades. The mammographic BIRADS grades were also estimated per breast per patient. Corresponding examples of the CT-BIRADS grades and mammographic BIRADS grades are represented in figure 8 – 11 On figure 8 BIRADS grade 1 is discussed. On the upper part of the figure (A), the CT image is shown. The lower part of the figure represents the mammographic images of respectively the right and left breast (B and C). On the CT image, the fibro-glandular tissue is shown in red. The breast density shown on these images is given in percentage. On the mammographic images the fibro-glandular tissue is shown in white. Figure 9, 10 and 11 BIRADS grades 2, 3 and 4 are discussed respectively.

Figure 8 A 45-year old woman with CT-BIRADS grade 1 and mammographic BIRADS grade 1.

A: Axial CT thorax image. The calculated CT breast density of the left breast is 3.90% and of the right breast is 3.80%, resulting in CT-BIRADS grade 1 on both sides.

B and C: Mammographic images of right and left breast respectively. The breast density is interpreted as grade 1 in both breasts.
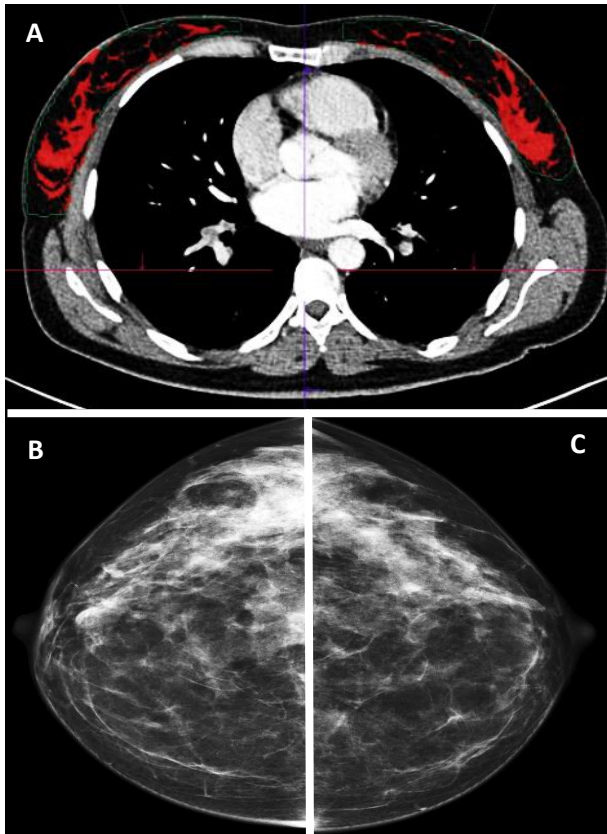
Figure 9 A 43-year old woman with CT-BIRADS grade 2 and mammographic BIRADS grade 2.

A: Axial CT thorax image. The calculated CT breast density of the left breast is 35.20% and of the right breast is 31.80%, resulting in CT-BIRADS grade 2 on both sides.

B and C: Mammographic images of right and left breast respectively. The breast density is interpreted as grade 2 in both breasts.
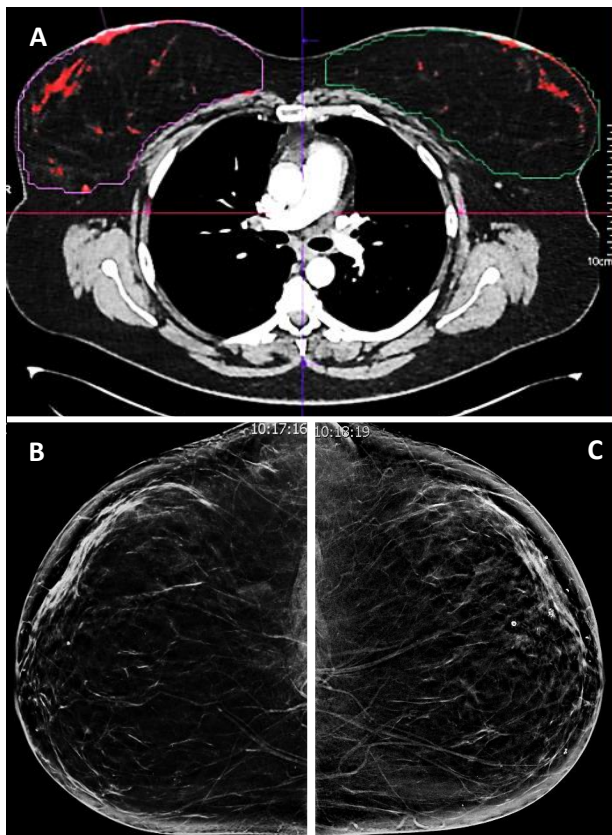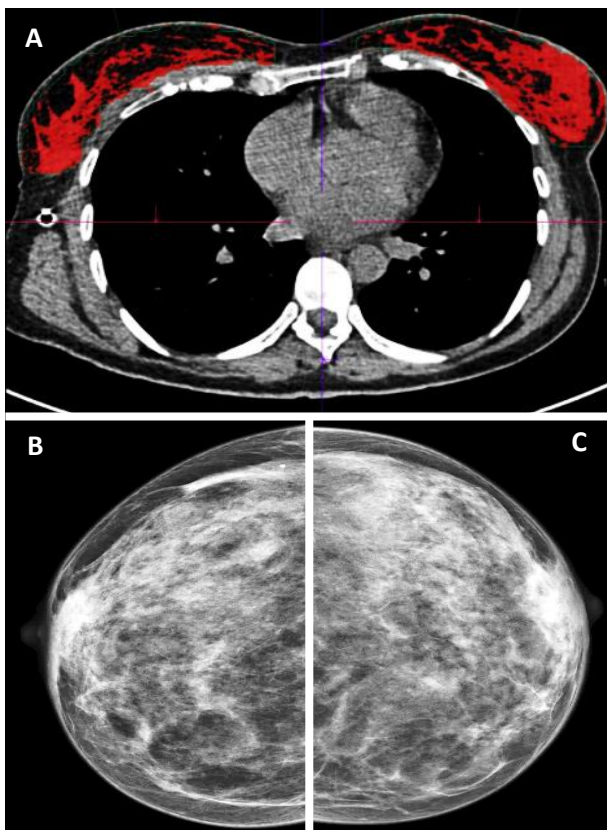

Figure 10 A 40-year old woman with CT-BIRADS grade 3 and mammographic BIRADS grade 3.

A: Axial CT thorax image. The calculated CT breast density of the left breast is 50.60% and of the right breast is 57.00%, resulting in CT-BIRADS grade 3 on both sides.

B and C: Mammographic images of right and left breast respectively. The breast density is interpreted as grade 3 in both breasts.
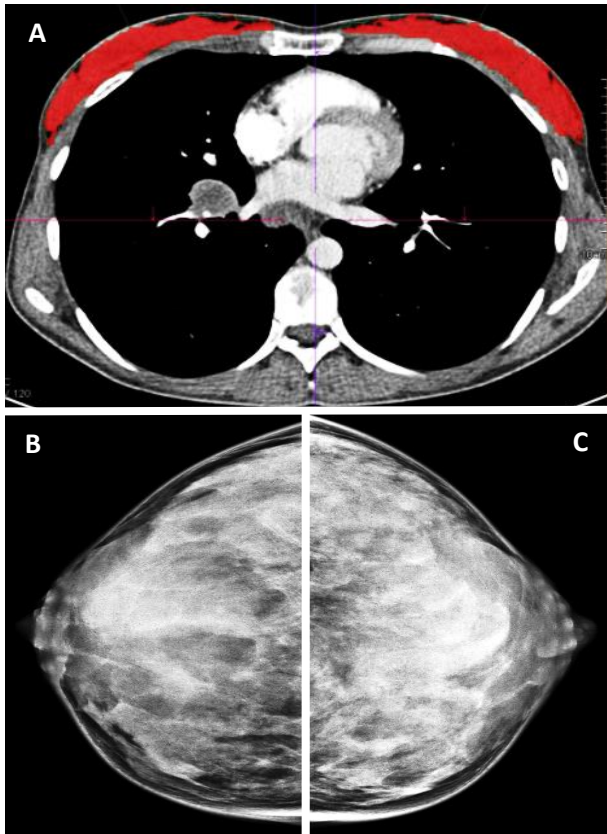
Figure 11 A 40-year old woman with CT-BIRADS grade 4 and mammographic BIRADS grade 4.

A: Axial CT thorax image. The calculated CT breast density of the left breast is 90.80% and of the right breast is 93.00%, resulting in CT-BIRADS grade 4 on both sides.

B and C: Mammographic images of right and left breast respectively. The breast density is interpreted as grade 4 in both breasts.

3.4 Statistical analysis

The agreement between breast density based on mammography and based on CT images of the chest was compared using the Spearman's correlation coefficient (r_s). The interpretation of the Spearman's correlation coefficient values was performed using a prior classification system. This system is the following: r_s between 0 and 0.19, very weak agreement; r_s between 0.20 and 0.39, weak agreement; r_s between 0.40 and 0.59, moderate agreement; r_s between 0.60 and 0.79, strong agreement and r_s between 0.80 and 1.00, excellent agreement. The statistical analyses were conducted by using software (SigmaStat, version 3.5 (2005), SysStat Software, USA). The statistical analyses were performed using a significance level of 0.05.

In order to be able to correlate our results with the literature, the percentage of agreement between the mammographic BIRADS and the CT-BIRADS was also calculated.

4 Results

Overall, the frequency of the breast density category 1 (0-25%) was the most frequent in each study group. On figure 12A, the distribution of the breast density categories is given for the non-screening group (40-49 year, n = 70). This graph shows that almost 50% of the patients of this study group belonged to the breast density category BIRADS 1. On figure 12B, the breast density data of the screening group (50-69 year, n = 288) is presented. Here, still, a higher amount of patients belonged to the lowest breast density category. More than 70% of the patients were in the BIRADS 1 category. Even more, in this study group, no patients were found belonging to the BIRADS 4 breast density category. Figure 12C gives the breast density distribution over the total study population (40-69 year, n = 358). In this group, more than 65% of the patients was classified in the BIRADS 1 category.
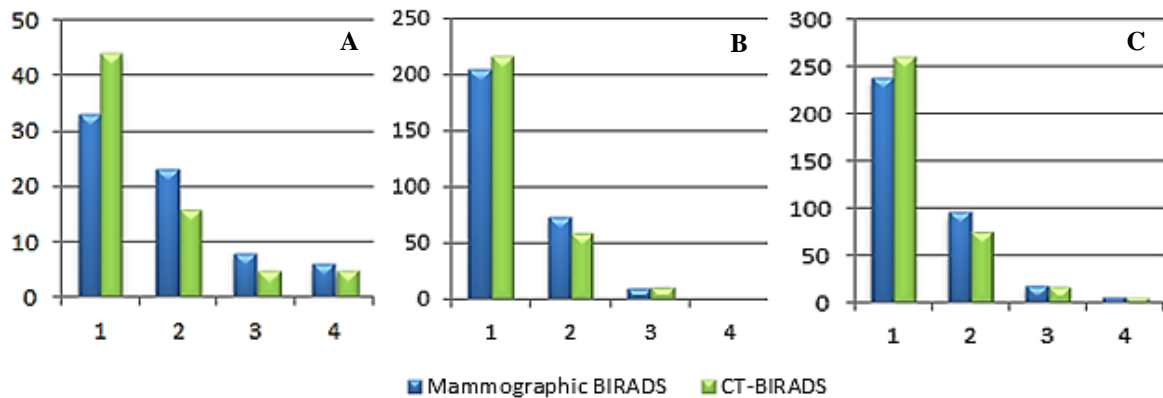
Figure 12 Overview of breast density in the different study groups. On the X-axis the mammographic BIRADS and CT-BIRADS categories are represented. The Y-axis gives the number of patients. All data represented is calculated at a threshold of -40 HU. A: Overview of the breast densities in the non-screening group (n = 70). B: The breast densities found in the screening group (n = 288). C: The breast density distribution in the total study population is presented (n = 358).

After semi-automatic segmentation of the breasts and calculation of breast density on the CT thorax images, the correlation between the mammographic BIRADS breast density and the breast density calculated on the CT images (CT-BIRADS) was analyzed using the Spearman's correlation coefficient (r_s). This coefficient was calculated for every HU threshold in the non-screening study group and in the screening study group. Also for the total study population, the r_s was calculated. Even more, for every study group, the statistical analysis was performed for all left breasts separately, for all right breasts separately and for all breasts, left and right, together. The results of these calculations are presented in Table 1.

Table 1 Spearman's correlation coefficient for breast density categories applied on mammography and on CT thorax using different Hounsfield Units (HU) as threshold on CT. The underlined results were the best results for each category. All statistical analyses were performed using 0.05 as the significance level. For -40 HU, the percentage of agreement was calculated for left breast, the right breast and both breasts together.

	- 40 HU	- 50 HU	- 60 HU	- 70 HU	- 80 HU	% (- 40 HU)	P-value
40 – 49 years (n = 35)							
Left and right breast	0.862	0.861	0.864	0.860	0.854	68.5%	<0.05
Left breast	0.844	0.847	0.845	0.853	0.834		<0.05
Right breast	0.876	0.879	0.879	0.868	0.873		<0.05
50 – 69 years (n = 144)							
Left and right breast	0.572	0.559	0.541	0.517	0.481	90.9%	<0.05
Left breast	0.574	0.560	0.542	0.518	0.482		<0.05
Right breast	0.569	0.558	0.543	0.516	0.479		<0.05
All data (40 – 69 years, n = 179)							
Left and right breast	0.644	0.632	0.617	0.597	0.568	86.6%	<0.05
Left breast	0.641	0.628	0.614	0.593	0.561		<0.05
Right breast	0.647	0.636	0.624	0.601	0.573		<0.05

Considering the data of the whole study population (40 – 69 years) in Table 1, all correlation coefficients were between 0.50 and 0.70. Overall, this means that a moderate to strong positive correlation was found. The best results (underlined) were found at a threshold of -40 HU. In general, it can be suggested that -40 HU was the best threshold to work with in this study population. At this optimal threshold, the mammographic BIRADS and the CT-BIRADS classification were strongly correlated (P < 0.05).

In the non-screening group, the results were all situated between 0.80 and 0.90, meaning that an excellent correlation was found in this study group. The best results were found at other thresholds, but to get uniformity into the results, also here the results at -40 HU were used to discuss. At this threshold for the left breast a Spearman correlation coefficient $r_s = 0.844$ was found, for the right breast $r_s = 0.876$. Considering this, it can be suggested that for the non-screening group an excellent correlation was found between the mammographic BIRADS and the CT-BIRADS classification (P < 0.05).

In the screening group, the best threshold value was again -40 HU. All results were between 0.40 and 0.59, suggesting a moderate positive correlation between mammographic BIRADS and CT-BIRADS classification (P < 0.05).

Additionally, the percentage of agreement was calculated at the -40 HU threshold (Table 1). This percentage was calculated to be able to compare the results of another study to our results. The best result was found in the screening group. Here, a 90.9% agreement was found between the mammographic BIRADS and the CT-BIRADS classification.

5 Discussion

The BIRADS classification for breast density (relative amount of glandular tissue) is known as an independent risk factor for breast cancer and is therefore applied to screening mammograms. CT of the thorax, performed for other clinical reasons, includes the breasts as well and allows for differentiation between dense and fatty tissue in the breasts. We developed a CT-BIRADS classification and hypothesized that it is well-correlated with the mammographic BIRADS classification. The correlation was tested in a non-screening group (women aged between 40 – 49 years old), a screening group (women aged between 50 – 69 years old) and in the whole study population.

In the total study population, a Spearman's correlation coefficient r_s of 0.644 (P<0.05) was found at -40 HU when all left and right breasts were included. This represents a strong positive correlation between the mammographic and CT-based BIRADS classification. Considering left and right breast separately ($r_{s,left}$ = 0.641, $r_{s,right}$ = 0.647, P<0.05), a strongly positive correlation was found as well.

In the screening group, a Spearman's correlation coefficient of r_s = 0.572 was calculated at a threshold of -40 HU for left and right breast together. This represented a moderate positive correlation between the mammographic and CT-based BIRADS classification. The same correlation was found for left and right breast separately ($r_{s,left}$ = 0.574, $r_{s,right}$ = 0.569, P<0.05). This study group comprised patients that were allowed to participate in the mammographic breast cancer screening program.

In the non-screening group, a Spearman's correlation coefficient of r_s = 0.862 was found for both breasts together at a threshold of -40 HU, meaning that an excellent positive correlation between the mammographic BIRADS and the CT-BIRADS classification was demonstrated. For the left and right breast, the correlation coefficients were respectively 0.844 and 0.876 (P<0.05), also representing an excellent positive correlation. Based on the results of all three study groups, the CT-BIRADS classification could be considered equivalent to the mammographic BIRADS classification. In other words, the results confirmed the hypothesis that the CT-BIRADS classification is correlated with the mammographic BIRADS classification.

Additionally to this confirmation of the hypothesis, the three major issues contributing to the mammographic breast cancer screening program could be solved partly when the CT-BIRADS classification will be implemented. The first issue was that the mammographic breast cancer screening program has a low participation rate. Only one out of three women do participate [8]. This is the reason why many breast cancers in the screening group are detected too late to obtain a curative treatment. But when the breast cancer risk can be determined using CT thorax images, made for other clinical reasons, this issue can be minimized. In numbers: In total, Belgium contained 11 099 554 inhabitants in 2013. Of these, 1 381 504 were women aged between 50 and 69 (= screening population). It is known that only one out

of three women do participate in the screening program, so 921 002 women do not participate. Additionally, 5.9% of the women aged between 50 and 69 undergo a CT thorax examination. This agrees with 54 339 women undergoing a CT thorax and not participating in the mammographic screening program. It is known that at screening mammography, 0.41% women are diagnosed with breast cancer [5]. Therefore, 223 women of the screening population, but not participating in the mammographic screening program (0.41% of 54 339) are expected to have breast cancer and potentially could be identified using CT-BIRADS classification in Belgium each year.

The second issue about the mammographic breast cancer screening program was that it only starts from the age of 50. But in clinical practice, a significant amount of breast cancers are seen starting from the age of 40. For these patients, often detection comes too late to obtain a curative treatment. When breast cancer risk can be obtained earlier in life using CT thorax images, a certain number of women (categorized as CT-BIRADS 3 or 4) could be advised to have a screening mammography. This may result in earlier detection of breast cancer in the non-screening group and may increase patients chances to obtain a curative therapy. This can be expressed in numbers: In 2013, Belgium contained 789 748 women aged between 40 and 49 years. In general, 3.3% of the women aged between 40 and 49 underwent a CT thorax examination. This agrees with 26 061 women. Women aged between 50 and 69 years have a risk of 0.41% to be diagnosed with breast cancer. If one may extrapolate this number to the 40 – 49 years old women, 107 (0.41% of 26 061) breast cancers are expected to occur in women belonging to the non-screening population each year in Belgium. Together with the screening group, 330 breast cancers (223 + 107) could potentially be detected additionally per year in the female Belgian population using the CT-BIRADS classification.

The third issue about the mammographic breast cancer screening program is that radiologic imaging such as mammography and CT uses ionizing radiation to visualize the body. This ionizing radiation is harmful to the body and can cause (breast) cancer. In medicine, a general rule is: 'avoid medical imaging that utilizes ionizing radiation as much as reasonably possible'. When CT thorax images can provide the BIRADS category, patients with a high BIRADS category can be advised to participate in the mammographic screening program. Patients belonging to BIRADS category 1 could be advised not necessarily to participate in the screening program.

The application of the CT-BIRADS classification contributes completely to the strategy applied for early diagnosis. Strategies for early diagnosis are optimized by the knowledge of breast density derived from mammograms, so if the chance exists that this breast density can be derived from CT thorax images, this should be applied in clinical practice. Even more, when the breast cancer risk can be determined using mammograms and CT thorax examinations, the risk determination can be performed for more women. This may lead to a decrease in the breast cancer mortality. If it is possible to put the CT-BIRADS data directly into the medical files of the patient, it will be completely free information without additional effort for radiologists. Additionally, a newer paradigm in radiology is risk factor analysis that can be derived from CT images, but these risk factors are not specifically requested on the

ordering of examination [17]. CT images are already opportunistically used for automatically scoring coronary arterial calcification [22] and bone density assessments [11]. The results of this study suggest that breast density determination can be an added risk factor that can be incorporated into CT thorax image analysis. When a patient has a high breast density, the patient has a high breast cancer risk as well. The referring physician may refer the patient to a screening mammography, but also to an additional imaging examination such as ultrasound (US) or magnetic resonance imaging (MRI).

In the literature, two studies compared semi-automated CT breast density calculations with subjective mammographic assessments. The first was the study of G.J. Bansal *et al.* (2014). In that study 77 breast cancer patients were included, aged between 23 and 91 years. The study calculated no correlation coefficient. They used two researchers that read mammograms and compared this with the semi-automated CT measurements. For reader 1, they found an agreement of 68.8%, for reader 2 84.4%. This study did not mention which threshold they used [15]. In our study, we found an agreement of 86.6%. The second study, of W.K. Moon *et al.* (2014) compared semi-automatic CT density measurements with subjective mammographic estimations in 69 patients. These patients were aged between 37 and 66. They all underwent a low-dose CT and a mammography. They found a very strong correlation and used only non-contrast images and the kV values ranged from 120-140 [28]. In our study, a high positive correlation was found, but we used CT images both with or without intravenous contrast administration.

Just because our study included patients with or without intravenous contrast administration, the results between the non-screening group and the screening group could differ so much. After all, contrast administration increases the density of tissue containing blood vessels. The fibro-glandular tissue contains more blood vessels than fat tissue, so possible intravenous contrast administration can cause a higher fibro-glandular density on CT. For example, when the non-screening group contained more patients with intravenous contrast administration than the screening group, the results can be influenced. We performed the statistical analyses again for only patients with intravenous contrast administration. A Spearman's correlation coefficient $r_s = 0.836$ (P<0.05) was found for the non-screening group ($n_{+C} = 58$) at a threshold of -40 HU, representing an excellent positive correlation. This result agrees with the result obtained in the whole non-screening group. For the screening group ($n_{+C} = 232$), a Spearman's correlation coefficient r_s of 0.568 (P<0.05) was found at a threshold of -40 HU when only the patients with intravenous contrast administration were included. This result agrees with a moderate positive correlation, the same as the result of the non-screening group taken all breasts, left and right, together. Considering this, we can conclude that contrast administration did not have a significant influence on the results of our study.

Another limitation of our study is that a broad range of kilovolt (kV) values was included: 80-130 kV. This kV value has an influence on fat density, when the kV value increases, the fat density decreases. Because all possible kV values were included in this study, this could have an effect on the results of both study groups. But when looking at the average kV values in both groups, in the non-screening group an average kV value of 115.71 kV was found, in the

screening group, the average kV value was 116.03 kV. In both groups, the median kV value was 120 kV (= standard). Because of the kV values were comparable in both groups, also this factor will probably not be the reason for the different results in both groups.

Another suggestion to explain the reason for the different result between both, the non-screening and the screening group, could be that breast density decreases with increasing age. Some anatomical structures could be visible on CT or mammography in the 40-49 years old patients, but not in the patients between 50 and 69 years old because breast density lowers. When in one of both imaging techniques these structures are visible and in the other one this is not the case, the correlation will be lower. But probably, this is not expected to be the reason for the different results. Considering the non-screening group, this study population only contains 35 patients. The screening group contained 144 patients, almost four times more. It can be suggested that this significant difference in population size will be the cause of the different results in both groups. Even more, it is clear that in the non-screening group, patients are equally divided within the four BIRADS categories on mammography and on CT. But when looking at the screening group, almost 90% of the study population has a mammographic and CT breast density classified as BIRADS 1 or 2. In this group, no patients are classified in the BIRADS 4 breast density category. This shift to lower BIRADS categories can also be a realistic observation because of the decrease in breast density with increasing age, but this unequal distribution of breast density can contribute to the different results in both groups.

In our study for every study group, the results were calculated at different thresholds, ranging from -40 HU to -80 HU. The best results in the screening group and in the total population are found at -40 HU. For the non-screening group, no single optimal threshold was found, but the results that were used were these at -40 HU to have uniformity in the results. Further, the statistical analyses were performed for the left and right breast separately but also for the left and right breast together. In that case data of left and right breast were considered as independent data. But because the breast density of both breasts is almost more or less the same in every woman and because in one patient both breasts contain the same genetics, left and right breast theoretically cannot be considered as independent.

The development of the breast segmentation on CT thorax images was the most difficult part of this study because breasts have a significant range of radiologic appearances. To undergo a CT thorax examination, the patient lays on his back, mostly with the arms upwards. Sometimes the breast(s) fall(s) aside, but sometimes not. Also, a variable range of breast sizes is present. Because of the wide range of radiologic appearances of the breast, it is difficult to find parameters to segment breasts automatically and can be applied to all patients. Also, image noise is a problem in calculating breast density because image noise is represented as light pixels on the image. In obese patients and patients with the arms on the chest, image noise is more prominent.

This study was performed using the BIRADS classification of 2003. The newer version, BIRADS 2015, takes clustering of fibro-glandular tissue into account. When the fibro-glandular tissue is clustered, the risk of developing breast cancer is increased. If this clustering can be determined on CT images is not known yet. Further studies are necessary to unravel if the newest version of the BIRADS classification can also be applied on CT thorax images.

After validating the results of this study on a large population, two additional aspects are necessary to implement the CT-BIRADS classification as a general tool in medicine. First of all, the CT-BIRADS classification needs to be calculated automatically. We already started a cooperation with the Medical Imaging Research Centre (MIRC) at the catholic university of Leuven to develop an automated tool to segment the breasts on CT thorax images. During this project, a tool was developed that could segment the breasts. This tool was able to eliminate automatically all tissue except the breast tissue on CT thorax images. Comparing to the manual segmentation of the breast an acceptable delineation of the borders of the breast tissue was found. Although the tool seemed time-consuming, it is a big step forward in the automatization of breast segmentation [24]. In the future, further improvement of this tool is needed. The second aspect that has to be implemented is that the CT-BIRADS classification has to be reported in the patient's medical files. Doing so, every doctor knows the risk of developing breast cancer of the patient and specific patients can be recommended to start breast cancer screening at an earlier age.

The mammographic BIRADS classification nowadays is limited by the use of the four BIRADS categories (BIRADS 1 – 4). The computer-generated CT-BIRADS classification is calculated in percentages. This percentage allows determining the extent of the density variability more specifically. However, using these four categories is the current practice for reporting breast density. Further, it is clear that breast density estimated using mammograms is rather subjective. The percentage-based manner of breast density determination using the CT thorax images is objective because it is computer-calculated. Future research to highlight the usefulness of the computer-generated percentage values is needed. In general, the CT-BIRADS classification should be further studied to define its role as a risk factor to predict breast cancer risk and the additional value of the percentages of breast density has to be further investigated as well.

In conclusion, we found that the CT-BIRADS scores were moderate to excellently correlated with the mammographic BIRADS scores. The CT-BIRADS classification could be especially useful to suggest the need for dedicated mammography screening in the non-screening patients (40 – 49 years) undergoing a CT thorax examination for other clinical reasons. This can contribute to the strategy of early diagnosis of breast cancer and may reduce breast cancer mortality.

6 Bibliography

1. Agentschap zorg en gezondheid. (2011). Retrieved from Agentschap zorg en gezondheid: www.zorg-en-gezondheid.be

2. American cancer society. (2016, June 1). *Breast cancer risk and prevention*. Retrieved from American cancer society: https://www.cancer.org/

3. American Cancer Society. (2016, August 18). *Mammogram Basics*. Retrieved from American Cancer Society: www.cancer.org

4. American College of Radiology. (2013). Mammography. In *ACR BI-RADS ATLAS* (pp. 121-140).

5. Beemsterboer PM, W. (1998). Radiation risk of mammography-related to benefit in screening programs: a favorable balance? *Journal of medical screening*, 81-87.

6. Belgian Cancer Registry . (2014). *Borstkanker*. Retrieved from Belgian Cancer Registry : http://www.kankerregister.org

7. Belgian cancer registry. (2008). *Cancer incidence in Belgium.* Brussel: Stichting kankerregister.

8. Belgian Health Care Knowlegde Centre. (2016). *Performance of the Belgian health system - report 2015*. Brussels: KCE Reports.

9. Boyd NF, B. J. (1995). Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study . *J Natl Cancer Inst*, 87:670-675.

10. Breast cancer surveillane consortium. (2016, January 31). *Breast cancer surveillance consortium risk calculator*. Retrieved from http://tools.bscs-scc.org/BC5yearRisk/

11. Budoff MJ, H. Y. (2010). Measurement of thoracic bone mineral density with quantitative CT. *Radiology*, 434-440.

12. Byrne C, S. C. (1995). Mammographic features and breast cancer risk: Effects with time, age and menopause status. *J Natl Cancer Inst*, 87(21):1622-1629.

13. Canadian breast cancer foundation, Institute of cancer research. (2014). *Breast cancer in young women.* Retrieved from Canadian breast cancer foundation: http://www.cbcf.org

14. Centrum voor kankeropsporing vzw. (2016). *Kan ik borstkanker krijgen door de straling van een mammografie?* Retrieved from Bevolkingsonderzoek borstkanker: www.bevolkingsonderzoek.be

15. G.J. Bansal, S. (2014). How does semi-automated computer-derived CT measure of breast density compare with subjective assessments to assess mean glandular breast density, in patients with breast cancer? *Br J Radiol*.

16. Henau K., F. J. (2011). *Cancer incidence in Belgium in 2008.* Belgian cancer registry .

17. Lee CI, F. H. (2010). What we can and cannot see coming. *Radiology*, 313-314.

18. M. Salvatore, L. M. (2014). Breast density: Comparison of chest CT with mammography. *Radiology*, 67-73.

19. McCormack VA, d. S. (2006). Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*, 15(6): 1159-1169.

20. National Cancer Institute. (2016, December 7). *Mammograms*. Retrieved from National Cancer Institute: www.cancer.gov

21. Rijksinstituut voor volksgezonheid en milieu. (2000). Retrieved from Rijksinstituut voor volksgezonheid en milieu: www.rivm.nl

22. Shemesh J, H. C. (2010). Ordinal scoring of coronary artery calcifications on low-dose CT scans of the chest is predictive of death from cardiovascular disease. *Radiology*, 541-548.

23. Susann E. Schetter, D. (2014). Breast density as an independent risk factor for cancer. *J Am Osteopath Radiol*, 10-19.

24. Tea Kostic, Agustina La Greca (2017). *Automated breast segmentation in CT images.* Leuven: KU Leuven - Faculty of engineering in science.

25. The North American Menopause Society. (2010). *Changes in Hormone Levels*. Retrieved from The North American Menopause Society: www.menopause.org

26. U.S. Department of Heath & Human Services. (2012, February 29). *What is a chest CT scan?* Retrieved from National heart, lung and blood institute: www.nhlbi.nih.gov/health/health-topics/topics/cct

27. Van Gils CH, O. J. (1998). Effect of mammographic breast density on breast cancer screening performance: a study in Nijmegen, The Netherlands. *J Epidemol Community Health*, 52(4): 267 - 271.

28. W.K. Moon, C. L. (2014). Quantitative analysis for breast density estimation in low-dose chest CT scans. *J Med Syst*.

29. World cancer research fund international. (2015, January 2015). *Breast cancer statistics*. Retrieved from World cancer research fund international: www.wcrf.org

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The prediction of BIRADS grades for breast cancer using densitometry on CT thorax

Richting: **master in de biomedische wetenschappen-milieu en gezondheid**
Jaar: **2017**

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