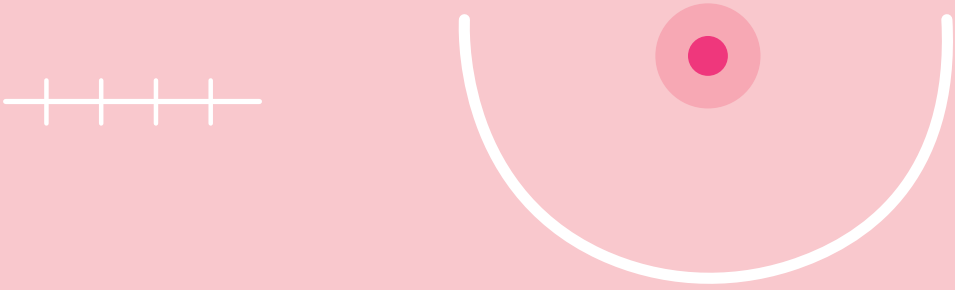

Flemish breast cancer screening programme: is stratification of women according to breast density indicated?

GHENT UNIVERSITY

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FLEMISH BREAST CANCER SCREENING PROGRAMME:

Is stratification of women according to breast density indicated?

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11.06.2019

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FACULTY OF MEDICINE AND HEALTH SCIENCES

There comes a point in your life
when you need to stop reading
other people's books and
write your own.

- Albert Einstein

THANK YOU

Een doctoraat schrijf je niet onder je eentje… Integendeel, het wordt geschreven, vervolmaakt, gevormd en gekneed door vele personen. Deze zorgden er stuk voor stuk voor dat dit 6-jarig durende traject een feest was. Eentje waar ik nog vaak met een grote glimlach aan zal terugdenken. Mijn dankwoord zal waarschijnlijk niet genoeg kunnen beschrijven hoe dankbaar ik wel ben voor alle personen die in dit doctoraatstraject op mijn pad zijn gekomen. Daarom hou ik het bij een korte, maar krachtige…

BEDANKT…

… Pieter, Cédric en Mattias, voor al het stralingsplezier en de lachbuien in het computerlokaal…
… Lynn, Klaartje, Diedelinde en Assunta, om mijn aller aller aller aller aller-beste vriendinnen te zijn…
… Dave, Patrick en Filip, voor de fantastische tijd in Italië…
… Heidi, Annelies, Els, Els, Ellen, Hilde, voor de zalige momenten in het water, op de fiets, tijdens het lopen, op stage, wedstrijd, training en zo veel meer…
… Katrien, om de enige te zijn die mij 'gralijk' uitlacht als ik 'mink' loop en waardoor het met jou altijd lachen is…
… Sofie, Julie en Isabelle, om de Italiëtrip onvergetelijk te maken…
… Dimi en Levi, om "dendervolk", "tooooeeeee", de meest harde lachbui ever en zo veel meer…
… Charlot, om er 3 jaar voor te zorgen dat onze bureau een tweede thuis werd voor mij…
… Bieke, om er de andere 3 jaar voor te zorgen om van onze bureau een tweede thuis te maken…
… Nati, to fill the office with joy and laughter…
… Isabelle, om zo een fantastische collega… euhm nee, vriendin! te zijn…
… Anke, om mij fit te houden…
… Axel, om mijn triatloncompagnon te zijn…
… juryleden, om dit werk naar een hoger niveau te tillen…
… Caro, voor de bazinga's, druisland, tweelingzus, en al de rest…

… promotoren, om mij de voorbije 6 jaar bij te staan met kennis, informatie en goede raad…
… Nancy, voor de vele verhalen en om mijn naam niet te vergeten…
… An DH, voor alle kennis, expertise, weetjes, creaties en de magnifieke zeemeerminstaart…
… Julie, voor de koffie, jouw gemultitask, fietstochtjes, skivakantie en zo veel meer…
… Mama en Papa, om de beste mama en papa te zijn van de wereld…
… Myriam, voor de gezellige babbels…
… Sofie, om zonder omweg te zeggen waar het op staat…
… Charlot, om mij vaak te doen terugdenken aan die mooie gierende momenten…
… Gebouw N7, medische fysica en fysische controle, voor de beste sfeer en mijn beste eerste werk te zijn. What happens in the saloon, stays in the saloon…
… Lothar, om mij al te laten lachen met de mop die nog moet komen…
… Virginie, om er altijd te zijn voor mij…
… Kim, om de middagpauzes op te fleuren…
… An DC, voor mij bijna alles te leren wat ik weet en mij letterlijk 'op te vangen' op donderdagavond…
… Liesbeth, voor alle goede raad, positiviteit en onuitputtelijk kennis…
… Klaartje en Stijn, Finn en Lia, om er te zijn! En om mij op zondagavond nieuw leven in te blazen…
… Karel en Klaartje, Mathias en Silke, Hannah en Marthe, Niels en Evy, om mij altijd welkom te laten voelen…
… Sarah, om altijd de helpende hand te bieden waar nodig met een onuitputtelijke glimlach…
… Tim, om steeds bij te springen waar nodig zonder zuchtje…
… Régine, mij moeiteloos in te leiden in de wereld van het assistentschap…
… Chamberlain, to be the happy, optimistic colleague with the weirdest biorhythm…
… Liesbeth Van Hauwermeiren, om de vakgroepraden op te fleuren en de vele babbels…
… Koen, om een promotor te zijn die mij liet doen, maar insprong waar nodig…
… Klaus, om 3 jaar lang jouw sidekick te mogen zijn als assistent. Ik kon altijd op jou rekenen. Bedankt voor je expertise, jouw helpende hand, jouw antwoorden op mijn

vragen, jouw whatsapps, mopjes, hashtags en zo veel meer. Bedankt om mijn promotor te zijn!

… Prof Thierens, (Bert) om mij 6 jaar geleden onder jouw vleugels te nemen. Dankzij jou ben ik elke dag met plezier naar het werk gekomen. Je bent een vat vol kennis en ervaring. Bedankt voor de babbels, de saloons, de lachsessies. Bedankt om mij bij te staan bij mijn onderzoek, vragen, bedenkingen, problemen. Bedankt voor de fantastische herinneringen. Maar vooral: bedankt om mijn promotor te zijn!

… Jelle, om er altijd voor mij te zijn en om alles 1000 keer leuker te maken. Je bent echt mijn beste lief. Kortom, bedankt voor álles, áltijd en overal!

CONTENTS

3 GENERAL DISCUSSION

SUMMARY

Breast cancer is the most common cancer in women in Flanders. Mammography screening reduces breast cancer mortality because of the early findings of masses and microcalcifications. Therefore, a breast cancer screening programme was started in Flanders in 2001. This is a decentralized screening programme inviting all women in Flanders aged between 50 and 69 years old for a completely reimbursed two-view mammogram every 2 years. There is a lot of information available concerning the Flemish Breast Cancer Screening Programme, however there is limited knowledge about the specific role of breast density.

Therefore, the overall aim of the thesis was to contribute to the understanding of the breast density in the Flemish Breast Cancer Screening programme. To achieve this aim, three major studies were conducted. First, the screening programme was mapped out by investigation of the different imaging techniques and the effect of the digitalisation on the screening parameters and breast density. In a second part, we investigated whether direct radiography (DR) performs better than computed radiography (CR) and screen-film mammography (SFM), specifically in dense breasts. In a third study, we compared tumour characteristics and molecular subtypes of interval cancers versus screen detected cancers to assess the association of tumour aggressiveness with breast density classes.

Regarding the digitalisation, the mean glandular dose (MGD) is dependent of the mammographic device: transition from SFM to CR resulted in a significant increase in patient- and phantom dose. For the transition from SFM to DR, the change in MGD depends on the PMMA phantom thickness: While a significant increase in MGD is found for the 20 mm PMMA phantom, a significant decrease in dose was recorded for the 45 and 70 mm phantom. In the patient dose study, a dose decrease of 26% was found. The screening parameters were not affected by the transition to digital devices. However, a positive change of these parameters over time indicated an improvement of the entire screening programme.

Investigation of interval cancers and screen detected cancers in the different imaging modalities showed that one third of all breast cancers in the screening programme are interval cancers. However, a higher cancer detection rate in DR in comparison with SFM and CR was found. Examination of interval cancers according breast density, which is a risk factor for breast cancer, showed a strong increase of

the interval cancer rate with breast density class. The percentage cancers detected in the screening programme over the total number of cancers registered decreases from 84% for the lowest density class to 46% for the highest class. This result is visible in every image modality. However, in the highest density class, a decrease of the cancer detection rate occurs for SFM and CR, while this reduction does not occur for DR. In DR, the cancer detection rate rises above the interval cancer rate.

Investigation of tumour characteristics confirms a significant difference in screen detected and interval cancers where the least favourable occur in the interval cancers: larger tumour size, more nodal invasion, more expression of oestrogen (ER) and progesterone receptor (PR) negativity and more grade 3 tumours. Breast density also has a substantial effect on the tumour characteristics. Large tumour size and more nodal invasion are more frequently found in higher density breasts while ER- and PR-negative phenotypes and higher grade tumours are less represented in higher breast densities. A significant more presence of triple negative tumours is also found in low density breasts. This concludes that interval cancers in the highest breast density class have a better prognostic tumour biomarker profile compared to low density breasts.

Our findings demonstrate that breast density is an important parameter in breast cancer however, breast density is not the only risk factor of breast cancer. Stratification of the screening trajectory of participating women according to the breast density is just a part of the whole story. This PhD-thesis can be the foundation for further research towards an optimal 'tailor-made' breast cancer screening programme.

SAMEN VATTING

Borstkanker is de meest voorkomende vorm van kanker bij vrouwen in Vlaanderen. Een screeningsmammografie kan afwijkingen en microcalcificaties in de borst vroegtijdig opsporen waardoor de mortaliteit daalt. Daarom startte de Vlaamse overheid in 2001 met een Vlaams Bevolkingsonderzoek Borstkanker. Dit onderzoek spoort alle vrouwen van 50 tot en met 69 jaar oud ertoe aan om elke twee jaar een gratis screeningsmammografie te laten nemen.

Er is reeds heel wat informatie omtrent het screeningsprogramma beschikbaar, maar de rol die borstdensiteit hierin speelt is nog onduidelijk. Met deze doctoraatsthesis hebben wij bijgedragen aan de rol van borstdensiteit in het Vlaams bevolkingsonderzoek naar borstkanker. Dit aan de hand van 3 studies.

Eerst hebben wij het screeningsprogramma in kaart gebracht door de verschillende beeldvormingstechnieken te onderzoeken en het effect van de digitalisatie op de performantieparameters en borstdensiteit. In een tweede luik zijn we nagegaan of direct radiography (DR) toestellen accurater presteren in het screeningsprogramma dan scherm-film mammografie (SFM) of computed radiography (CR), specifiek bij vrouwen met dense borsten. In een laatste onderzoek hebben we de tumorkarakteristieken en moleculaire subtypes vergeleken van intervalkankers en screeningsgedetecteerde kankers om na te gaan of er een associatie tussen agressiviteit en borstdensiteit aanwezig is.

De digitalisatie van het screeningsprogramma heeft een impact gehad op de borstdosis welke afhankelijk is van de gebruikte modaliteit. Zo gaat de overschakeling van een conventioneel SF-toestel naar een CR-toestel gepaard met een significante stijging van zowel fantoom- als patiëntdosis. Bij de overschakeling van SFM naar DR is de verandering van de borstdosis afhankelijk van de dikte van het gebruikte PMMA-fantoom. Zo wordt een significante dosisstijging gevonden bij het gebruik van een 20 mm PMMA-fantoom terwijl er een significante dosisdaling wordt gevonden bij het 45 en 70 mm PMMA-fantoom. In de patiëntdosisstudie werd een algemene dosisdaling gevonden van 26% bij overschakeling naar DR. Digitalisatie had geen effect op de performantieparameters. Wel vertoonde deze parameters een positieve verandering in de tijd wat wijst op een verbetering van het screeningsprogramma door de jaren heen.

Het tweede onderzoek toont aan dat 1/3de van alle borstkankers bij vrouwen die deelnemen aan het bevolkingsonderzoek intervalkankers zijn ongeacht de beeldvormingsmodaliteit. Het aantal kankers gedetecteerd in de screening is wel hoger bij DR-toestellen in vergelijking met SFM en CR. Verder werd ook aangetoond dat er een sterke stijging is van het aantal intervalkankers met stijgende borstdensiteit. Zo worden nog 84% van de borstkankers gedetecteerd in het programma bij de laagste densiteitsklasse, terwijl dit aantal zakt naar slecht 46% bij de hoogste densiteitsklasse. Onderverdeling van de intervalkankers met de verschillende borstdensiteiten in combinatie met de verschillende modaliteiten toont opnieuw dezelfde stijging van intervalkankers met de densiteit. Maar, in de hoogste densiteitsklasse wordt een daling van de kankerdetectiegraad gevonden bij SFM en CR, dewelke niet wordt teruggevonden bij DR-toestellen. Bij DR overstijgt de kankerdetectiegraad de intervalkankergraad in de hoogste densiteitsklasse.

Onderzoek naar tumorkarakteristieken bij intervalkankers en screenings gedetecteerde tumoren in de verschillende borstdensiteiten toont significante verschillen waarbij tumoren met de mist gunstige karakteristieken het vaakst voorkomen in intervalkankers. Zo zijn intervalkankers groter, hebben ze meer nodale invasie, vertonen ze vaker negatieve oestrogeen- (ER) en progesteron- receptoren (PR) en zijn deze vaker graad 3. Bijkomend heeft de borstdensiteit ook een groot effect op de tumorkarakteristieken. Zo worden er grotere tumoren en tumoren met nodale invasie vaker teruggevonden bij vrouwen met een hoge borstdensiteit terwijl ER en PR negatieve tumoren en tumoren met een hoge graad net minder wordt teruggevonden bij vrouwen met een hoge borstdensiteit. Dit wijst er op dat intervalkankers bij vrouwen met een hoge borstdensiteit een betere prognostische tumor biomerker profiel hebben in vergelijking bij vrouwen met lage borstdensiteit.

Onze bevindingen tonen aan dat borstdensiteit een belangrijke parameter is bij borstkanker. Borstdensiteit is echt niet de enige risicofactor bij borstkanker. Het screeningstraject van deelnemende vrouwen bepalen op borstdensiteit is maar een deel van het verhaal. Dit doctoraatsonderzoek kan gebruikt worden als fundering naar verder onderzoek richting een optimaal 'op-maat-gemaakt' borstkankeropsporingsprogramma.

ACRO NYMS

2D Two-dimensional
3D Three-dimensional

A

a-Se Amorphous Selenium
a-Si Amorphous Silicon
ACR American College of Radiology
AJCC American Joint Committee on Cancer

B

BI-RADS Breast Imaging- Reporting and Data System

C

CDR Cancer Detection Rate
CR Computed Radiography

D

DBT Digital Breast Tomosynthesis
DCIS Ductal Carcinoma in Situ
DDREF Dose and dose rate effectiveness factor
DIR Detection-over-Induction Ratio
DR Direct Radiography

E

ER Estrogen Receptor
ERDs Estrogen-receptor down regulators
EUREF European Reference Organisation for Quality Assured Breast Screening and Diagnostic Services

F

FFDM Full Field Digital mammography
FISH Fluorescence In Situ Hybridization
FSH Follicle Stimulating Hormone

H

HER2 Human Epidermal Growth Factor Receptor 2

I

IARC International Agency for Research on Cancer
IC Interval Cancer

K

kV	kilovoltage

L

LCD	Liquid Crystal Display
LCIS	Lobular Carcinoma in Situ
LH	Luteinizing Hormone
LHRHs	Luteinizing hormone-releasing hormone agents
LumA	Luminal A-like
LumB/HER2-	Luminal B/HER2 negative like
LumB/HER2+	Luminal B/HER2 positive like

M

MGD	Mean Glandular Dose
MRI	Magnetic Resonance Imaging
MyPeBS	My Personal Breast Screening

N

PIP	Powder Imaging Plates
PR	Progesterone Receptor
PMMA	Polymethylmethacrylaat
PMT	Photomultiplier tube
PPV	Positive Predictive Value

R

RBE	Relative biological effectiveness

S

SDC	Screen Detected Cancer
SERMs	Selective estrogen-receptor response modulators
SFM	Screen-film mammography

T

TFT	Thin Film Transistor
TN	Triple Negative
TNM	Tumour, Node & Metastases

Q

QALYs	Quality Adjusted Life Years

PART

Introduction

1 BREAST CANCER

1.1 The normal breast

At birth, the mammary gland is very calm. During puberty, the pituitary secretes follicle stimulating hormone (FSH) and luteinizing hormone (LH). This secretion leads to maturation of ovarian follicles producing estrogen and progesterone resulting in growth and maturation of the breasts and genital organs [1].

The breast is composed of several lobes that drain into a major duct and these converge at the nipple. Each lobe contains lobules composed of glandular tissue, which in lactation, deliver milk to the ducts. The glandular lobes are surrounded with connective tissue, blood and lymph vessels and adipose tissue (see Figure 1.1) [2].

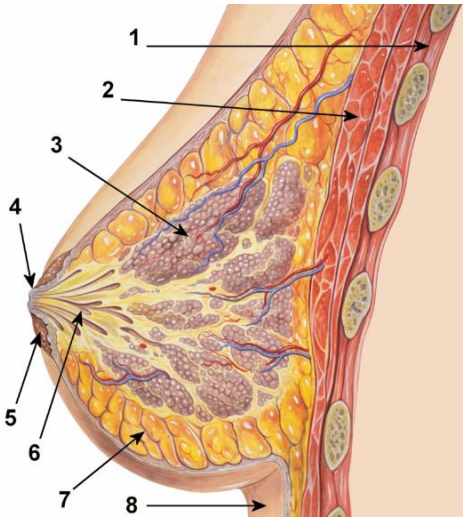

FIGURE 1.1

Side view of the normal breast with 1: Chest wall; 2: Pectoralis muscles; 3: Lobules; 4: Nipple; 5: Areola; 6: Lactiferous ducts; 7: Adipose tissue; 8: Skin

1.2 Breast cancer

Our body exists of billions of cells. The genes, housed in the nucleus of the cell, are responsible for growth regulation. Normally, the cells in our bodies replace themselves through an orderly process of cell growth. Mutations, however, can modify certain genes in a cell. Hereby, the cell gains the ability to continue dividing without control or order, producing more cells that are similar and eventually form a tumour [4]. Cancerous cells also have the property that they can spread into or invade nearby tissues, a process called metastasis.

Approximately 85% of all breast cancers emerge in milk ducts, referred to as ductal carcinomas. The development of breast cancer comprises several steps. First, multiple layers are formed of the epithelium, followed by the presence of atypical nuclei in the epithelial cells. Due to the reformation of the epithelial cells, these cells are now called cancer cells. Further growth of these cells within the duct is appointed as ductal carcinoma in situ (DCIS). Once the cancer cells breach through the basal membrane that delineates the duct, the cancer cells invade the surrounding tissues leading to invasive ductal carcinoma (IDCA) (see Figure 1.2) [5].

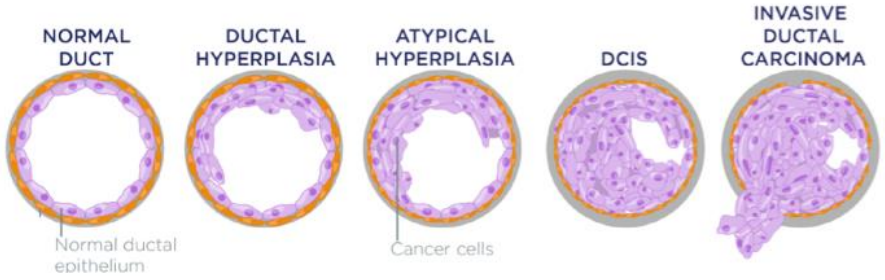

FIGURE 1.2

Different steps in ductal carcinoma tumourigenesis. A normal duct progresses from hyperplasia to ductal carcinoma in situ (DCIS). When the cancer cells breach through the basal membrane, an invasive ductal carcinoma is originated [6].

Once cancer cells become invasive, they have the potential to migrate away from their site of origin. Commonly, they enter the lymphatic system and breast cancer cells may be located in the axillary lymph nodes in the armpit or spread further to a more distant site in the body [2].

A minority of breast cancers arise in the milk-producing lobuli and are called lobular carcinomas. As in ductal carcinomas, lobular carcinomas can be in situ (LCIS) or may become invasive to adjacent structures (ILC). Although lobular carcinomas are more difficult to detect, patients with ILC tend to have a better prognosis when compared to invasive ductal carcinoma [5].

The remaining breast cancers comprise a collection of more rare subtypes like Paget's disease, phyllodes tumour, tubular carcinoma and inflammatory carcinoma [7].

1.3 Tumour characteristics and prognosis

When a suspicious area in the breast is found by palpation or by medical imaging, a breast biopsy is performed. This procedure removes a small sample of breast tissue for anatomopathological analysis. This may eventually lead to diagnosis of breast cancer.

When breast cancer is diagnosed, an evaluation of the tumour with classification is made for several reasons. First, to establish a clear therapeutic schedule according to the tumour stage and hormone receptor status and to objectively evaluate the results of therapy. Second, to estimate prognosis and also for uniformity when medical information is exchanged [8].

1.3.1 TNM-classification and Breast Cancer Stage

Breast cancer is classified according to the TNM-classification proposed by the American Joint Committee on Cancer (AJCC) [9]. This classification is based on tumour size (T), involvement of regional lymph nodes (N) and the presence of distant metastasis (M). Numbers or letters after T, N and M give more details about each characteristic with higher numbers indicating a more advanced cancer. This TNM-classification is compiled by oncologists of all available clinical findings from physical examinations, medical imaging and histopathology of fine needle aspirations (cTNM). Inclusion of pathological information of surgical tumour

resection leads to the pTNM classification. The characteristics of the clinical TNM classes are briefly summarized in Table 1.1 [10, 11].

PRIMARY TUMOUR (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
TIS	Carcinoma in situ
T1	Tumour ≤20 mm in greatest diameter
T2	Tumour > 20 mm but ≤ 50 mm in greatest diameter
T3	Tumour > 50 mm in greatest diameter
T4	Tumour of any size with direct extension tot the chest wall and/or the skin

REGIONAL LYMPH NODES (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident lymph node metastases
N2A	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2B	Metastases only in clinically detected ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3A	Metastases in ipsilateral infraclavicular lymph node(s)
N3B	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3C	Metastases in ipsilateral supraclavicular lymph node(s)

DISTANT METASTASES (M)	
M0	No clinical or radiographic evidence of distant metastases
M1	Distant detectable metastases as determined by classical clinical and radiographic means and/or histologically proven larger than 0.2 mm

Table 1.1

Clinical TNM classification of breast cancer [4].

Based on this TNM-classification, breast cancer patients are divided in different stages ranging from stage 0 (carcinoma in situ) to stage IV (the most advanced stage where the breast cancer has spread beyond the breast and adjacent lymph nodes). This clusters breast cancers with more or less the same prognosis and survival [4] (see Table 1.2).

ANATOMIC STAGE/PROGNOSTIC GROUPS			
STAGE 0	Tis	N0	M0
STAGE IA	T1	N0	M0
STAGE IB	T0	N1mi	M0
	T1	N1mi	M0
STAGE IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
STAGE IIB	T2	N1	M0
	T3	N0	M0
STAGE IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
STAGE IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
STAGE IIIC	Any T	N3	M0
STAGE IV	Any T	Any N	M1

Table 1.2

Staging of breast cancers based on TNM-scores [9].

While the 5-year survival rate in stage III breast cancers is still 72%, it drops to only 22% in stage IV. The presence of distant metastasis, which is typical for stage IV, accounts for this poor prognosis [4].

1.3.2 Breast Cancer Grade and Ki-67

Tumour grade is a score that indicates how abnormal the appearance and growth patterns of tumour cells are compared to normal healthy breast cells. This will rate the aggressive potential of a breast tumour on a scale from one to three. Clinicians use this information to guide treatment options for patients and as an important predictor of overall survival [12].

Grade 1 or low grade (also called well differentiated) cancer cells look only slightly different from normal cells. These cancer cells grow slowly and in well-organized patterns.

Grade 2 or intermediate grade (moderately differentiated) cancer cells do no longer resemble normal cells. They grow and divide faster than normal.

Grade 3 or high grade (poorly differentiated) cancer cells look very different from normal cells. These cells grow quickly in disorganized, irregular patterns and divide fast [4, 10, 13].

Ki-67 is a nuclear protein. It is present in all proliferating cells, and can be used as a cell proliferation marker [14]. Ki-67 is detected by immunohistochemistry (IHC) in the cell nuclei and reported as index, which represent the percentage of labelled cells within the investigated cell population [15]. However, no standard operating procedure or generally accepted cut-off definition for Ki-67 exists [16]. Nevertheless, grade and Ki-67 have a similar behaviour: both are associated with proliferation [17].

1.3.3 Hormone Receptor Status

By using an immunohistochemistry (IHC) assay, a breast cancer sample is investigated for the presence of hormone (estrogen and/or progesterone) receptors on/in the cells [4, 18]. If they are hormone receptor positive, binding of hormones to the matching receptor on the cancer cells can influence the cell's behaviour and also its proliferation.

Knowing the presence of hormone receptors on breast cancer cells is important information for treatment decision. Hormonal therapy can be used in hormone-receptor-positive breast cancer cells to interrupt the influence of hormones on the cells growth and overall functioning. Blocking hormones with medication results in less survival of cancer cells.

Main types of hormonal therapy include Selective estrogen-receptor response modulators (SERMs), Aromatase inhibitors, Estrogen-receptor downregulators (ERDs) and Luteinizing hormone-releasing hormone agents (LHRHs) [19, 20].

1.3.4 HER2 status

HER2 (Human Epidermal Growth Factor Receptor 2) is a gene that plays a role in the development of breast cancer. HER2 genes make HER2 proteins that are receptors on breast cells. They help the breast cells to grow, divide and repair themselves. When the HER2 gene does not work properly, this results in uncontrolled dividing of breast cells [4].

Breast cancers with HER2 protein overexpression tend to grow faster, are more likely to spread and have a higher recurrence rate in comparison with HER2 negative breast cancers.

A biopsy or resection specimen is tested for HER2 with an IHC test or a Fluorescence In Situ Hybridization (FISH) test. Treatments specifically for HER2 positive breast cancers are available. Examples are Herceptin, ado-trastuzumab, neratinib, pertuzumab or lapatinib [21].

1.3.5 Triple-Negative Breast Cancer

When breast cancer cells are tested negative for estrogen receptors (ER-), progesterone receptors (PR-) and HER2 (HER2-), this breast cancer is called triple-negative (TN).

Triple-negative breast cancers tend to be more aggressive than other types of breast cancer. Studies have shown that TN tumours are more likely to spread beyond the

breast and to recur after treatment. They also tend to have a higher grade than other types of breast cancer [22].

The growth of cells in triple negative tumours is not supported by hormones nor by the presence of HER2 receptors. They are typically treated with a combination of surgery, chemotherapy and radiation therapy [20, 23]. Survival of patients with triple-negative breast cancer is less than in other breast cancer patients.

1.3.6 Molecular subtypes

Based on hormone and HER2 status as well as proliferation markers or histological grade, breast cancers are divided in molecular subtypes [24]. The molecular subtypes correspond reasonably well to a clinical characterization. This classification was recommended by the St. Gallen Expert Consensus, and it has become the accepted standard in routine clinical patient care [25]. The original classification includes Ki-67 as a proliferation marker. However, if a reliable Ki-67 index is not available, histological grade is used as a measure of proliferation. This was also added later in the classification by the St. Gallen Expert Consensus [26].

MOLECULAR SUBTYPE	ER AND/OR PR	HER2	GRADE	KI-67
Luminal A-like *(LumA)*	+	-	1-2	<14%
Luminal B/HER2 negative-like *(LumB/HER2-)*	+	-	3	≥14%
Luminal B/HER2 positive-like *(LumB/HER2+)*	+	+	Any	Any
HER2-type *(HER2)*	Both -	+	Any	Any
Triple Negative *(TN)*	Both -	-	Any	Any

Table 1.3

Molecular Subtype. Molecular Subtypes is based on hormone and HER2 status as well as proliferations markers or histological grade.

Classification into five molecular subtypes helps to subdivide patients into groups with different prognoses. Overall survival studies showed a 5-year survival above 95% for Luminal A type cancers. On the other hand, patients with TN subtype have a 5-year survival of less than 80% [27].

1.4 Breast Density

Breast density refers to the relative amount of radio-opaque glandular and fibrous tissue compared to the amount of radiolucent fatty elements seen at mammography. Breast density is ranked in classes, according to a system developed by the American College of Radiology (ACR). The 4th edition Breast Imaging-Reporting and Data System (BI-RADS) classification system identifies four levels of breast density with increase in the amount of fibroglandular tissue: BI-RADS I with less than 25% glandular tissue, BI-RADS II with 25–50% glandular tissue, BI-RADS III with 51–75% glandular tissue and BI-RADS IV, a class with extremely dense breasts with more than 75% glandular tissue [28] (see Figure 1.3).

In the 5th edition guidelines, this percentage-based system was removed, and more emphasis was put on the masking effect of dense tissue [29]. This more subjective four-category overall assessment classification consists of BI-RADS A, which are almost entirely fatty breasts, BI-RADS B exhibit scattered areas of fibroglandular density. BI-RADS C are heterogeneously dense breasts and BI-RADS D are extremely dense breasts (see Figure 1.4).

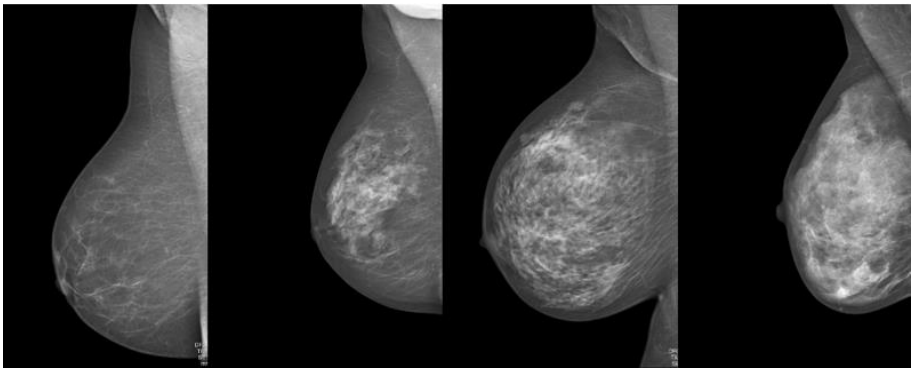

Figure 1.3

BI-RADS 4th edition breast density [30]

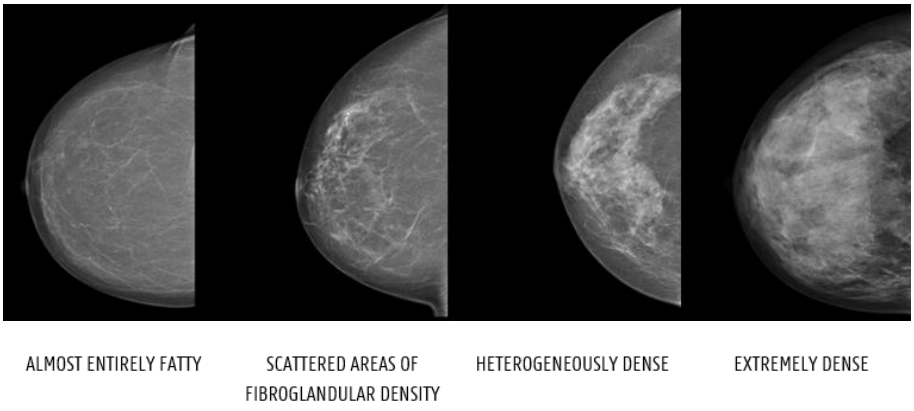

Figure 1.4

BI-RADS 5th edition breast density [30]

Breast density has been shown to be a strong risk factor for breast cancer, with women with a high breast density having a four-six times enhanced risk to develop the disease compared to women with completely fatty breasts [31-36]. High density

breasts are also associated with a decreased sensitivity of cancer detection in mammography screening programmes [37-41]. Consequently, women with dense breasts are more likely to be diagnosed with an interval cancer. These are defined as tumours diagnosed in women who participate in the breast cancer screening programme, after a negative screening result and before the next planned screening mammography (see section 3.4 - Limitations) [37, 42-44]. However, the role of breast density has not yet been completely elucidated [42, 45]. A masking effect related to hiding tumours by fibroglandular tissue as well as a biological effect related to tumour growth has been proposed [45, 46].

Younger, pre- or perimenopausal women are known to have a higher proportion of dense breast tissue [47, 48]. Due to the loss of estrogen and progesterone production after menopause, the glandular tissue shrinks and is replaced by adipose tissue [1].

2 MAMMOGRAPHY

Mammography is an examination where an image is made of the breast by means of X-rays. This technique is widely used for the detection and diagnosis of breast cancer, tumours and cysts of the mammary gland (see Figure 2.1, Figure 2.2) in symptomatic women and for screening in asymptomatic women [2].

The breast is positioned on the detector of the mammographic device and is compressed using a compression plate. This results in less motion blur and less superposition. Moreover, there is less scatter radiation, which results in a better contrast. In addition breast compression keeps the glandular dose as low as possible. Because of this compression, the examination of the breast can be unpleasant or even a bit painful [49]. Two images, one craniocaudal (see Figure 2.1) and one oblique view (see Figure 2.2), are taken of each breast.

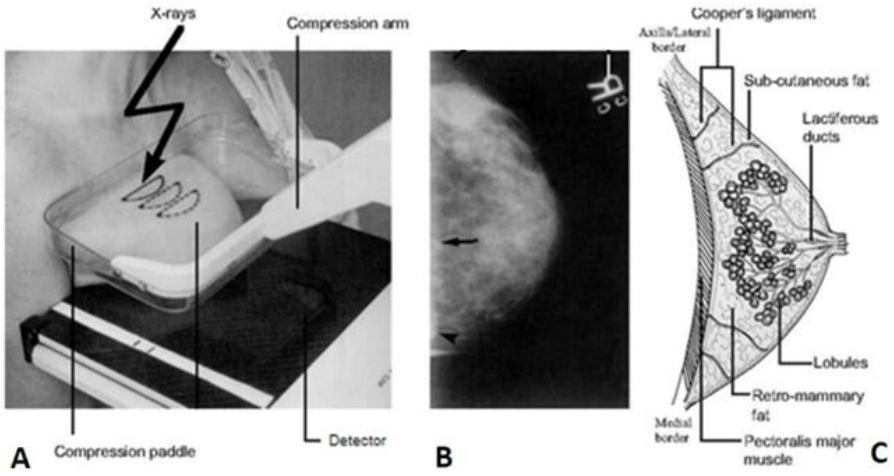

Figure 2.1

Mammographic cranio- caudal examination. Image is made from the breast by using X-rays. A: A compression paddle is used to position the breast on the detector in the craniocaudal direction. B: A typical mammographic image of the breast. C: A drawing of the different breast tissues [50].

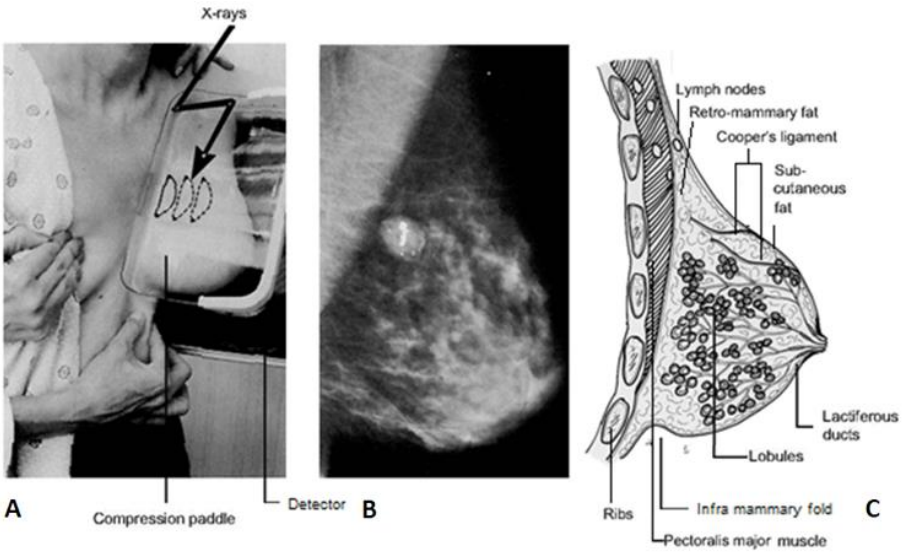

Figure 2.2

Mammographic medio-lateral oblique examination. Image is made from the breast by using X-rays. A: A compression paddle is used to position the breast on the detector in the medio-lateral oblique direction. B: A typical mammographic image of the breast. C: A drawing of the different breast tissues [50].

Mammography is one of the most demanding imaging technologies. It is challenging to produce high image quality images while keeping the dose of the patient as reasonably achievable using low-energetic X-rays [51]. The mean glandular dose (MGD) is typically 3-5 mGy per two-view mammography [52-54]. This is dependent on the used mammographic device, the glandular fraction of the women's breast, the comprised breast thickness and the used anode/filter combinations.

In order to visualize the subtle changes associated with breast cancer, the imaging system must precisely measure the transmitted X-ray intensity through all regions of the breast. Much of the important information in the mammogram is in the fine details, associated with calcified particles and small fibres that radiate from a tumour (see Figure 2.3). Therefore, the spatial resolution of the imaging system must be very high [2].

A mammographic examination is typically performed with a tube voltage between 24 and 33 kV and with a detector system with high resolution in combination with

specific anode/filter combinations allowing appropriate X-ray spectral adjustments [55]. The use of these different anode/filter combinations as a function of breast thickness lead to a reduction of breast dose without loss of diagnostic information and a better contrast [51].

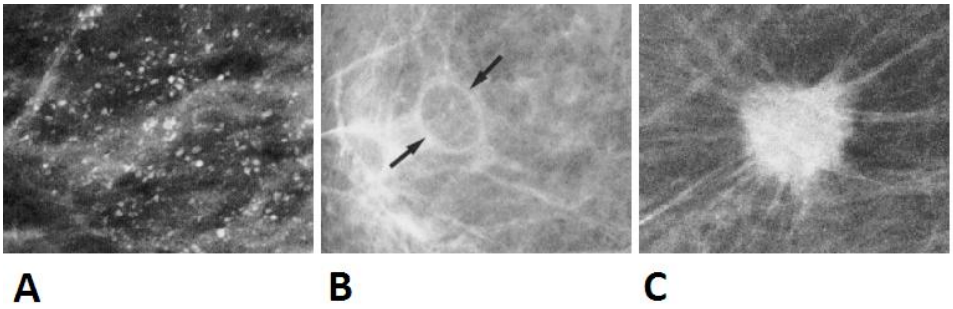

Figure 2.3

Three different types of lesions that can be found in mammography. A: Microcalcifications. B: Circumscribed Lesions. C: Spiculated Lesions [56].

2.1 Detectors

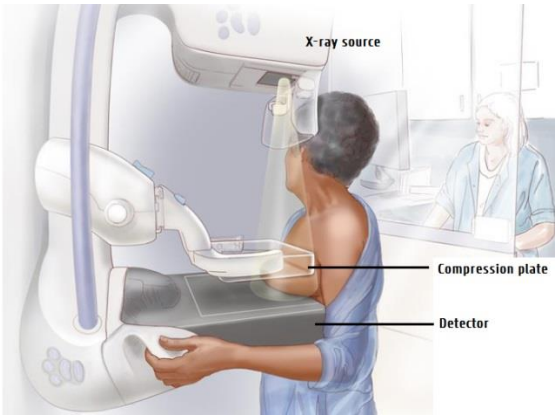

Figure 2.4

Mammographic examination of the breast. X-rays emitted from the X-ray source go through the breast to end in the detector [57].

When taking a mammographic examination, X-rays emitted by the X-ray source pass through the breast to end in the detector (see Figure 2.4). Due to different attenuation coefficients between glandular and adipose tissue of the breast, the X-ray beam at the detector level is heterogeneous. These attenuation differences form the basis of breast imaging in mammography (see Figure 2.5).

The image is formed in the detector. In mammography, different detection systems exist: conventional and digital detectors. In the detector, the absorbed X-ray energy is converted to an analogue or digital image.

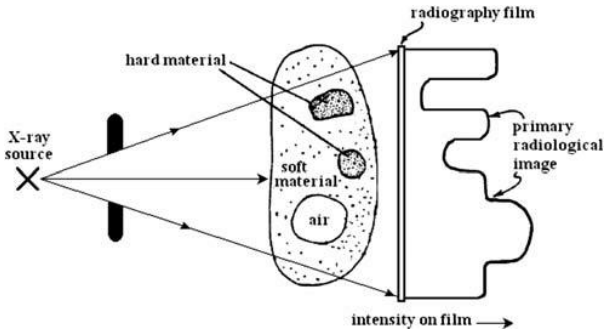

Figure 2.5

Attenuation of X-rays in matter. Different tissues with their attenuation coefficients are shown. This results in different intensities on the detector (here film) [58].

2.1.1 Conventional mammography

Conventional mammography use a screen-film combination (SF).

A film is a transparent material coated with an emulsion. A film emulsion consists of silver halide granules in a layer of gelatine. These granules are organised in a crystal structure. Exposure of the film to light or X-rays ionises the silver in the crystal structure leading to a latent image [59].

Screens consist of a scintillation material, typically phosphors are used in medical imaging. This material absorbs the incident X-rays and emits ultraviolet or visible light. The light-sensitive (emulsion) layer on the film then captures this light. A screen in combination with film is used in order to keep radiation dose of patients

as low as possible as film is more sensitive to light than for the X-rays themselves [59] (see Figure 2.6).

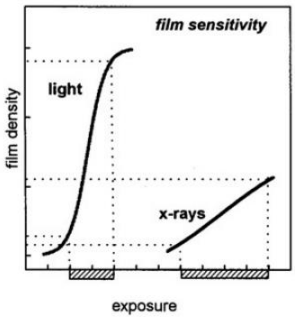

Figure 2.6

Film sensitivity. A film is more sensitive to light than to X-rays. For this reason, a mammography film is always combined with a screen to change the X-rays into light [60].

For optimal resolution, film with a single light-sensitive side in conjunction with a screen, positioned below the film, is typically used in mammography

The screen-film system is housed in a light-tight cassette made of radio-transparent material that can be placed in the bucky of a mammographic imaging system. The cassette also contains a foam that pushes the film against the screen as a tight screen-film contact is required for good image quality (see picture Figure 2.7) [61].

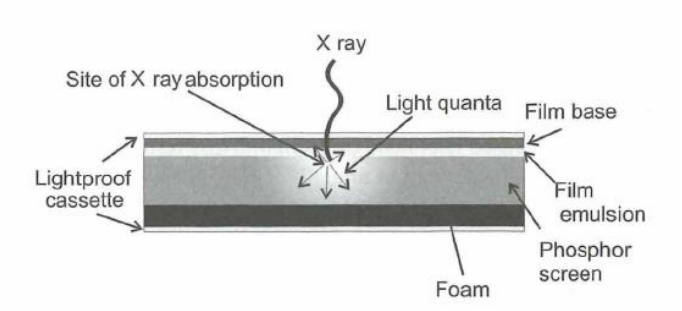

Figure 2.7

Screen-film in mammography. Configuration for a mammographic screen film image receptor: A single emulsion radiographic film is held in close contact with a fluorescent screen in a lightproof cassette [59].

To develop the film after exposure, it is removed from the cassette (in a dark room) and fed into the input chute of a film processor. The film is then guided by a system of rollers along the processor through a developer tank, into a fixer tank, and then in a wash tank. After washing, the film continues its path through the dryer, where temperature-regulated air is blown across the film surface allowing the film to dry (see Figure 2.8) [62]. By the developing, fixation and washing procedures, the latent image is converted to a permanent visible image by a chemical process.

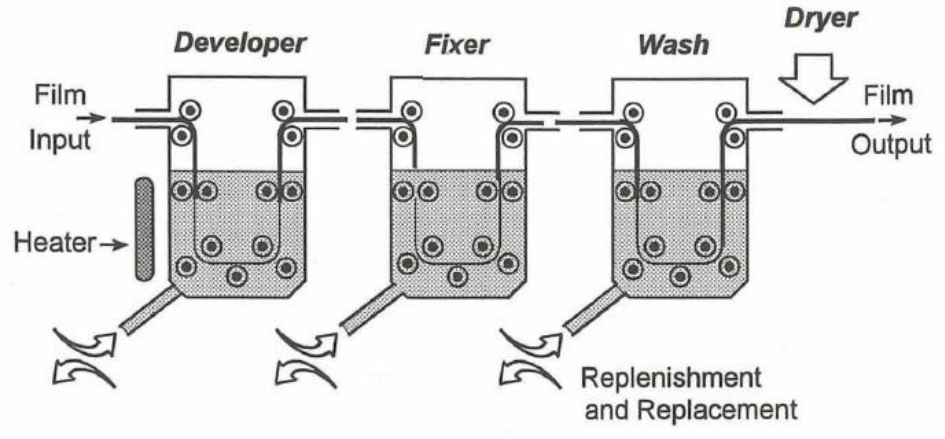

Figure 2.8

A Film processor. The basic components of a film processor showing separate tanks holding developer, fixer and washing water. Developer and fixer are replenished continuously.

2.1.1.1 Pros and Cons

Although this detector has a good contrast and high resolution, it has also some disadvantages. The chemical reactions that are used to develop a mammographic film, are highly dependent on both temperature and chemical concentrations, which can lead to a variable image quality. Pumps in the processor circulate the liquid in each tank to ensure adequate thermal and chemical mixing. As sheets of film are run through the processor, the chemical reactions deplete the concentrations of the chemicals in the tanks. The processor replenish chemicals by pumping fresh liquids from storage tanks. This is not a maintenance- and environmentally friendly detector system [62].

Another limitation is that a screen-film combination has a limited dynamic range. If the dose of the recording is not optimal, there is a risk of over- or underexposure of the images (see Figure 2.9) [62].

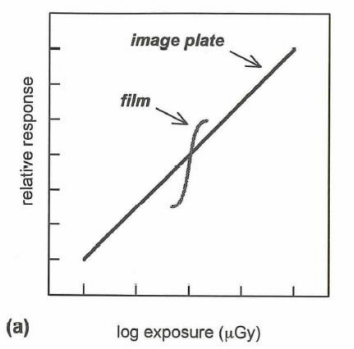

Figure 2.9

Dynamic Range. Dynamic Range of film compared with a digital detector.

Finally, this detector does not allow the characteristics of the image to be changed or processed after recording and development. Film must act both as an image acquisition detector as well as a storage and display device. This makes distribution and archiving of the radiographic images more difficult [55].

2.1.2 Digital mammography

Soon after conventional detection systems, digital detection systems were developed and gained an increasing popularity due to many advantages over SF. In digital mammography, development of films is eliminated and data storage and retrieval is easier. Digital images are displayed on a high resolution monitor which makes it possible to influence the dynamic image, such as zooming and adjustment of contrast and brightness is possible. This is in contrast with the conventional light boxes, which are used in screen-film mammography. Digital mammography comprises two imaging modalities.

2.1.2.1 Computed Radiography

In computed radiography (CR), the imaging plate (a flexible screen made of a photostimulable phosphor) is positioned in a light tight cassette. These cassettes are, like conventional SFM cassettes, placed in the bucky system of the mammographic device [62].

The photostimulable phosphors do not emit light immediately after absorption of X-rays in contrast to phosphors used in screens in conventional SF. Most X-ray energy remains trapped on the phosphor plate (see Figure 2.10): after exposure of a phosphor plate with X-rays, the electrons of the phosphor crystals are transferred from the valence band to the conduction band and are captured. The proportion of captured electrons is proportional to the absorbed X-ray energy. In this way a latent image is formed.

After exposure, the cassette is placed in a CR mammography reader. Here, the phosphor plate is removed from the cassette and is scanned with laser light. By adding this extra energy, the captured electrons fall back from the conduction band to the ground state whereby visible light is emitted. The intensity of this emitted light is proportional to the absorbed X-rays [62].

An image is build up by collecting the emitted light and converting it via a photomultiplier tube (PMT) into a strong electrical signal. These signals are stored as pixel values on a pixel matrix. The digital image is displayed on a monitor.

After scanning the plate with a laser, it is flooded with light. This causes all the electrons to fall back into ground state and any residual image is erased. The phosphor plate is placed back into the cassette in the readout unit and is ready for reuse [62].

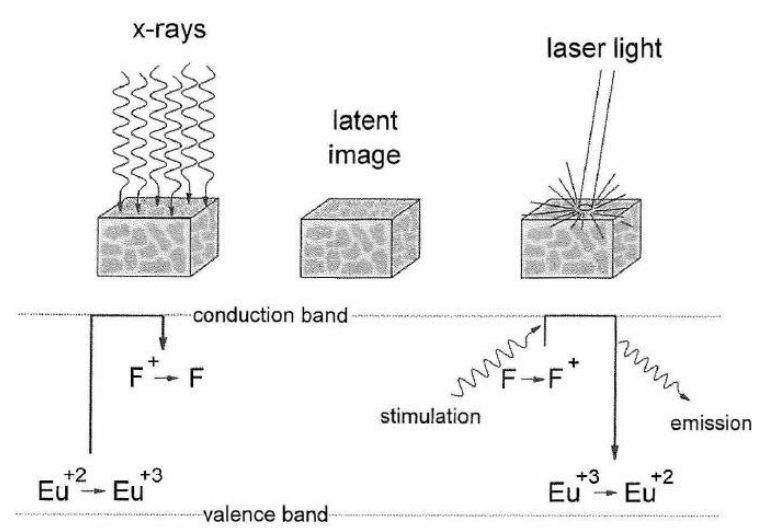

Figure 2.10

Exposure and readout of a photostimulable phosphor [62].

There are two types of CR plates: the powder imaging plates (PIP) and the needle imaging plates (NIP). The active layer of the powder imaging plate consists of phosphor crystals, held together by a binding polymer (see Figure 2.11).

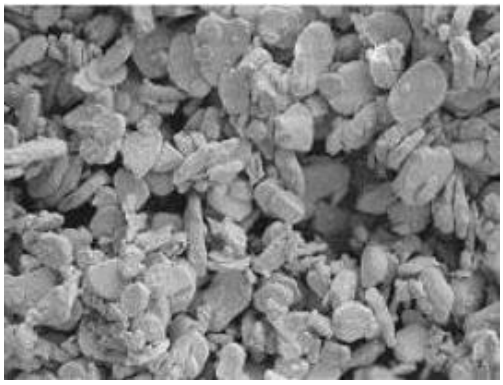

Figure 2.11

Scanning Electron Microscope image of a powder plate [63].

Needle imaging plates consist of phosphor crystals who are evaporated in a needle shape. These needles act as light guides through the phosphor layer and thus reduce the lateral light distribution [55, 64]. This results in a better resolution of the image. Moreover, due to the absence of binding material, more phosphor is present, which results in a more efficient conversion of X-rays into light (see Figure 2.12).

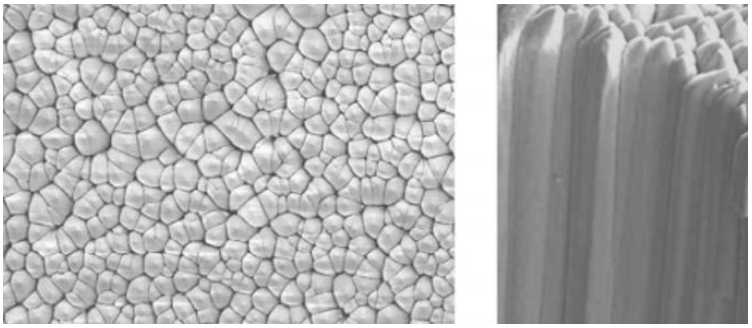

Figure 2.12

Top and side scanning electron microscope images of a needle crystalline phosphor plate [63].

2.1.2.2 Direct Radiography

In Direct Radiography (DR), also known as full field digital mammography (FFDM), the digital detector is completely integrated in the mammographic device. After exposure of the breast to X-rays, the image is produced immediately on the monitor of the radiologist [65, 66].

Several different types of DR detectors are used for digital mammography.

A first type are flat panel detectors. These can be divided into indirect and direct flat panels. In case of indirect flat panels, the upper layer of the detector consists of a scintillator, e.g. CsI, and a photodiode. The absorbed X-ray energy is converted first into visible light through the scintillation crystal. This light is then converted into an electric charge via a photodiode, this is light-sensitive material e.g. amorphous silicon (a-Si) [67, 68]. This charge is read via a thin film transistor array or also called a TFT-array. The term indirect refers to the two-step process in which X-rays first have to be converted into light, followed by the conversion in electric charge.

Direct flat panel detectors consist of a sensitive photoconductor that is usually made of amorphous selenium (a-Se). When X-rays interact with the selenium, they are directly converted into electron-hole pairs. An applied electric field sweeps the charges towards electrodes which are connected with a TFT array. No intermediate production of visible light is necessary, which results in better spatial resolution [67, 68] (see Figure 2.13).

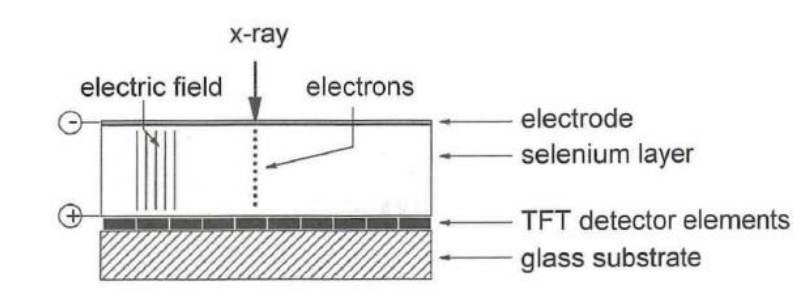

Figure 2.13

Direct Flat Panel Detector. A layer of amorphous selenium photoconductor coupled to a thin-film transistor (TFT) array. The X-ray interaction in the selenium layer releases electrons, which are used to form the signal. An electric field applied across the selenium layer minimizes the lateral spread of the electrons, preserving spatial resolution [62].

To keep the noise in digital images as low as possible, a second type of DR detector system has been developed: a-Se/Optical Switch. This consists of a double layer of amorphous selenium. The X-rays in the first layer are converted into electron-hole pairs as in direct flat panels. The lower selenium layer acts as an optically controlled switch that transfers the stored charge to a set of readout lines. This avoids the need for TFT arrays which reduces the geometric efficiency of the detector. This combination of direct conversion and the optical switch allows to achieve high resolution images with low noise [67, 68].

A third type of DR detector system is a scanning multislit system with a photon counting detector. The X-rays are collimated into a narrow beam that moves across the surface and the detector follows the beam. The detector consists of a matrix of silicon chips that absorb the X-rays. The electron-hole pairs produced from each

interacting X-ray are collected in an electric field and shaped into a pulse, which is counted one by one [68].

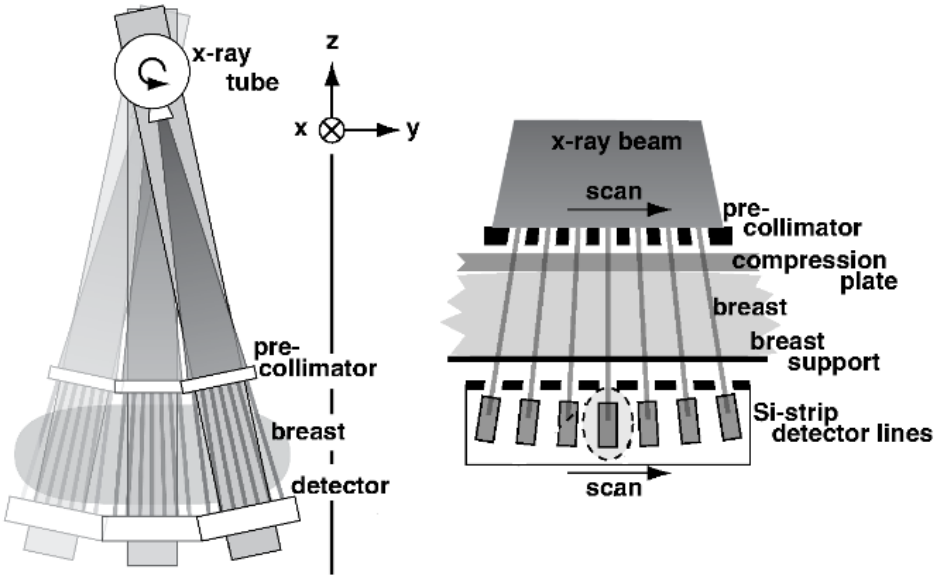

Figure 2.14

A scanning multislit system with a photon counting detector [69].

2.1.2.3 Pros and cons

Imaging the breast is difficult as it consists of tissues of contrasting densities: glandular tissue interspersed with fat. However, digital detectors have a number of advantages over the conventional screen-film detector. For example, when comparing digital mammography to conventional SFM, the overall diagnostic accuracy in detecting breast cancers was similar [70, 71]. However, digital mammography detectors are superior to SFM in younger women and women with dense breasts. This is due to the large dynamic range of digital detectors [68] (see Figure 2.9). This dynamic range has the possibility of optimizing contrast and brightness in areas of dense parenchyma [64, 72]. Another advantage of digital mammography is the ability to manipulate the digital information after exposure. With SFM, an over- or under-exposed image will lose its diagnostic quality and a retake will be necessary. Digital mammography has the ability to zoom, magnify and

manipulate contrast. The overall image also delineates soft tissue better, especially the subcutaneous skin which is an area that was not well seen on SFM [73].

It is also stated that converting a SFM into a DR-system improves the throughput of mammography cases due to a more efficient workflow [74]. The major reason is the abolishment of film processing time. However, the time to interpret soft-copy digital mammography images has been found to be longer compared to hard-copy images. This is mainly due to the time taken to manipulate the image using the available tools on the workstation.

By using digital detectors, the processes of image acquisition, image display, image storage and retrieval of images are disconnected. This allows each domain to be automated and individually optimized [55]. Optimization of each part of this imaging chain results in a high quality technique. Digital mammography also eliminates lost or misplaced films and digital images can be viewed by several different people at the same time. Digital mammography also has the potential to implement advanced applications such as contrast-enhanced mammography and computer-aided diagnosis.

A specific advantage of CR systems are the use of removable cassettes. After digitization, this is cost saving in comparison with DR systems because the cassettes can be inserted in the bucky tray of a standard SFM mammographic device. However, it still requires that phosphor plates are manually transported to the reader for processing [64]. Purchasing a DR device will be more expensive, but no manual transactions need to be performed to view the final breast image on the monitor. Another advantage of DR compared to CR is that DR devices require a lower dose for generating acceptable image quality [68]. Where digitalization to CR is accompanied with a dose increase, a decrease of dose is found after digitalization to DR [75, 76].

2.1.3 Image display

In conventional screen-film mammography, the films were analysed on conventional lightboxes. In digital mammography, images are displayed on high

quality Liquid Crystal Display (LCD) devices with high resolution. In mammography, five megapixel screens are recommended [66].

2.2 Breast tomosynthesis

Two-dimensional (2D) mammography is a reliable technique for breast cancer screening and diagnosis but a minor percentage of breast cancers are still missed. Studies have shown that these percentages range from 1% to 35% [77, 78]. In mammography, the three-dimensional (3D) breast structure is projected on a single 2D image. Due to this projection radiography, different structures can be superpositioned, leading to a limited visibility of lesions or normal structures appearing as lesions. This masking effect can be reduced or avoided by using a pseudo-3D breast imaging technique: Digital Breast Tomosynthesis (DBT) [79].

In DBT, a number of low dose projection images are obtained over a typical angular range of 10°-50° around the breast. The X-ray tube may be moved in a continuous or discrete way (see Figure 2.15). As with mammography, the total acquisition time must be minimized to avoid patient motion. This technique reconstructs planar cross-sectional images of the breast that reduces the superposition of tissue with the aim of improving cancer detection [80].

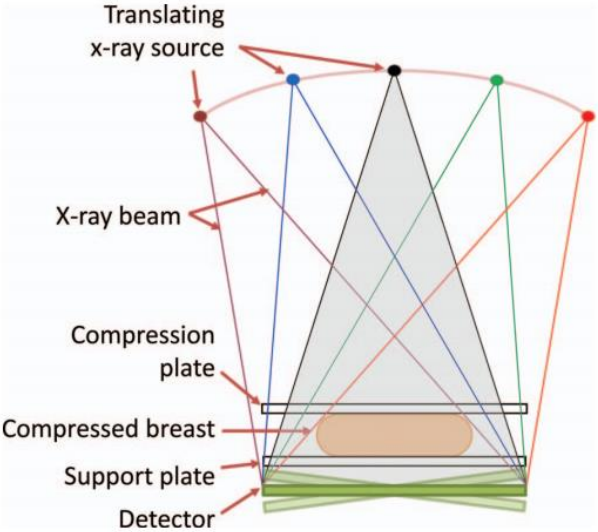

Figure 2.15

Schematic presentation of a digital breast tomosynthesis (DBT). During a DBT acquisition, a number of projection images is acquired of the compressed breast while the X-ray source rotates and the detector remains either static or rotates, depending on the system design [80].

In general, studies have demonstrated the potential for DBT to decrease the false positive recall rate and increase cancer detection rates. However, conflicting results have been published. Studies have reported improved lesion visibility of soft-tissue masses and architectural distortions, but the sensitivity for detection of microcalcifications is mixed. Cancer detection rate is increased especially for invasive cancers and not for ductal carcinomas in situ [81]. In most studies, DBT was added to DR, which doubles the radiation dose a woman would receive in routine breast screening. There is an opportunity to use synthetic 2D images in combination with DBT that results only in a slight increase in dose. Once synthetic 2D images have been shown as an acceptable alternative, the marginal increase in radiation dose becomes much less of an issue [81].

Before new imaging modalities, such as DBT, can be integrated into screening programmes, scientifically sound evidence is required which state that the use of DBT improves lesion detectability. Justifying the use of this new technology in a screening programme is complex and involves a wide range of aspects, including

economic analyses [82]. In recent years, a variety of clinical studies [83-86] and technical evaluations, based on both measurements and simulations, [80, 87, 88] have been established for DBT and have provided evidence of the potential of DBT in screening. However, further investigations dealing with periodically quality assurance and large patient studies still need to be performed. Therefore, the Flemish government has not yet approved tomosynthesis in the Flemish Breast Cancer Screening Programme. Diagnostic breast examinations on the other hand, are performed regularly with tomosynthesis in Flanders.

3 Population screening for breast cancer

3.1 Flemish Breast Cancer Screening Programme

In Flanders, breast cancer is by far the most common cancer in women [89]. The lifetime risk is approximately one in eight. Moreover, European registry data show that Belgium has the highest breast cancer incidence in Europe [90]. Studies suggest that mammography screening reduces breast cancer mortality with 20-30% [91, 92] because of the early findings of masses and microcalcifications and increases the chance of complete recovery and less aggressive treatment [72, 93, 94].

A Breast Cancer Screening Programme was started in Flanders in 2001 [7]. In this Programme, women aged between 50 and 69 years are invited every 2 years to undergo a free mammography screening examination. In mammographic units recognised by the Flemish government, two images, a craniocaudal and an oblique view, are taken of each breast. Two independent radiologists interpret these images. The first reading takes place at the mammographic unit where the mammograms are taken. Afterwards the images are sent to the Centre for Cancer Detection where a second reading is performed without any knowledge of the outcome of the first reader. In case of discordance in interpretation between the two readers, the Centre for Cancer Detection organises a third reading. All relevant data associated with each participating woman is stored into the centralised database, 'Heracles', of the Flemish Breast Cancer Screening Programme [7].

The participation of women at the Flemish Breast Cancer Screening Programme is stable the last years at a level of 65% however, the target value of 75% is not reached. This means that one third of the target population does not participate. The reason for this is uncertain. Currently, a large-scale investigation and survey is implemented to examine the lower participation grade. Due to a mixed culture in Flanders, the language barrier is suggested to play a role in this as do the recurrent critical sounds in the media. Raising awareness of the target population together with uniform, spreading qualitative and clear information is also an ongoing aim of the screening programme. 86% of the women who went to the previous screening examination also participate the next round, which states that the participants are

loyal. The main reason of eventually dropping out of the screening programme is related to false-positive results [95].

At the start of the Flemish Breast Cancer Screening Programme, all mammographic units used screen-film mammography (SFM) as imaging technique. When the European Guidelines were expanded in 2006 with a new chapter dedicated to digital mammography systems, more units gradually made the transition to digital mammography [66]. By the end of 2011, the proportion of mammographic units that used digital mammography in Flanders had reached 78%. Currently, only digital mammography is used in the Flemish Breast Cancer Screening Programme.

All mammographic devices used in the screening programme comply with the European Guidelines which describe the recommendations for physical-technical quality assurance in breast cancer screening and diagnostics [66]. This includes a typetest procedure for each new model of mammographic device before introduction in the Flemish Breast Cancer Screening programme, confirming it can meet the criteria of the Flemish Working Group based on the European Guidelines. After purchase of a mammographic device that passed the typetest by a mammographic unit, it also needs to pass an acceptation test after installation. Afterwards, a periodic supervision occurs of each mammographic device and monitor every 6 months. This quality procedure assures a good image quality and a low dose in a screening programme where asymptomatic women participate. Additionally, a daily test is also acquired by the mammographic unit and verified by the medical physicist to detect sudden malfunctions.

In order to maintain a high quality programme, the Flemish Breast Cancer Screening Programme is subjected to a yearly evaluation. In this report, performance parameters as sensitivity (66.5%) and specificity (98%) are included. In addition, the cancer detection grade (5.6‰) is indicated. These performance parameters are appropriate parameters to evaluate the screening programme. They are also compared with the European Guidelines and adjustments are made if necessary. These performance parameters also give an indication of the quality of the programme throughout the years and after implementing new techniques such as digital imaging in comparison to conventional screen-film imaging [95].

3.2 Requirements population based screening programme

The aim of a breast cancer screening programme is to prevent death from breast cancer by early detection, when the cancer is minimally invasive and before metastasis has occurred [96, 97]. Not all cancers will be detected in the screening programme. For example, fast growing cancers will quickly lead to symptoms and eventually death. These tumours are too advanced when eventually detected in a screening programme or they appear between screening rounds (interval cancers) (see Figure 3.1.) Very slow growing tumours on the other hand will be detected in the screening programme. However, these are defined as tumours that never causes problems because the patient will die of some other cause before the cancer is large enough to produce symptoms. In fact, it is not necessary to detect these very-slow growing cancers. This effect is called "overdiagnosis" and is one of the limitations of a screening programme (see Figure 3.1) [98].

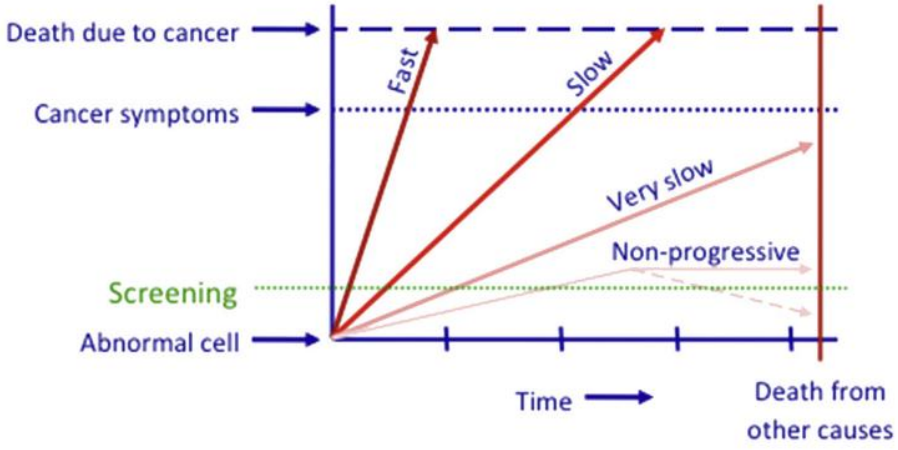

Figure 3.1

Heterogeneity of cancer progression: Fast growing cancers quickly leads to symptoms and death. Slow growing cancers leads to symptoms and death but after many years. Very slow growing cancers are cancers that never causes problems because the patient will die of some other cause before the cancer is large enough to produce symptoms [98].

Therefore, a population based breast cancer screening programme focuses on women, in a particular age category and without any complaints, to detect asymptomatic breast cancers.

An ideal screening programme must meet a number of important conditions: it must be able to find premature abnormalities (high sensitivity), with a low amount of false positives (high specificity) and the investigation needs to be simple and inexpensive [99].

Mammography in women aged between 50 and 69 years meets these requirements at an acceptable level (see Figure 3.2-A and section 3.3: Age limits).

Other imaging techniques can also envision breast tissue on a non-invasive manner. However, these imaging techniques below are less suited to be in a screening programme with its own different reasons.

3.2.1 Ultrasound

Some studies claim that mammography screening alone is inadequate and it would be better to supplement it with ultrasound. This holds specifically for women with dense breasts, which are more likely to develop breast cancer and where the mammographic sensitivity is lower [31-33, 100].

However, adding ultrasound in a population screening programme has important disadvantages. First, small cancers and benign abnormalities are barely distinguishable from each other in ultrasound. This results in an increase of the proportion of false-positives involving a considerable increase of (unnecessary) biopsies [99]. Ultrasound is a very different imaging technique from mammography. This is illustrated in Figure 3.2-B where a mammographic image and an ultrasound image of the same breast tumour are depicted.

Secondary, a screening examination needs to be simple. To perform an additional screening ultrasound, even only in high dense breasts, would result in a significant increase of workload and thus extra costs for the government. Also, the quality of ultrasound is highly operator dependent. In addition, due to the absence of a

structural transfer of images to the centre of cancer detection, an interpretation by a second radiologist is impossible [99].

Although using ultrasound in a population based screening programme may not be ideal, it can be a screening tool in women with high risk, women with breast implants or women with extremely dense breasts [101]. However, the use of MRI in this group even show better results.

3.2.2 MRI

Using Magnetic Resonance Imaging (MRI) for imaging the breasts has superior sensitivity to ultrasound and mammography in the detection of breast cancer (see Figure 3.2-C). However, it is often criticized for a decreased specificity, which results in twice more unnecessary follow-up examinations and three times more unnecessary biopsies [102-104]. Furthermore, the availability of MRI-devices are limited and the cost of the investigation is very high. This makes that MRI is not recommended as a screening method at population level.

Breast cancer screening with MRI is only employed in women with a high risk, e.g. women with a mutation of BRCA-1 or BRCA-2 gene [102-104].

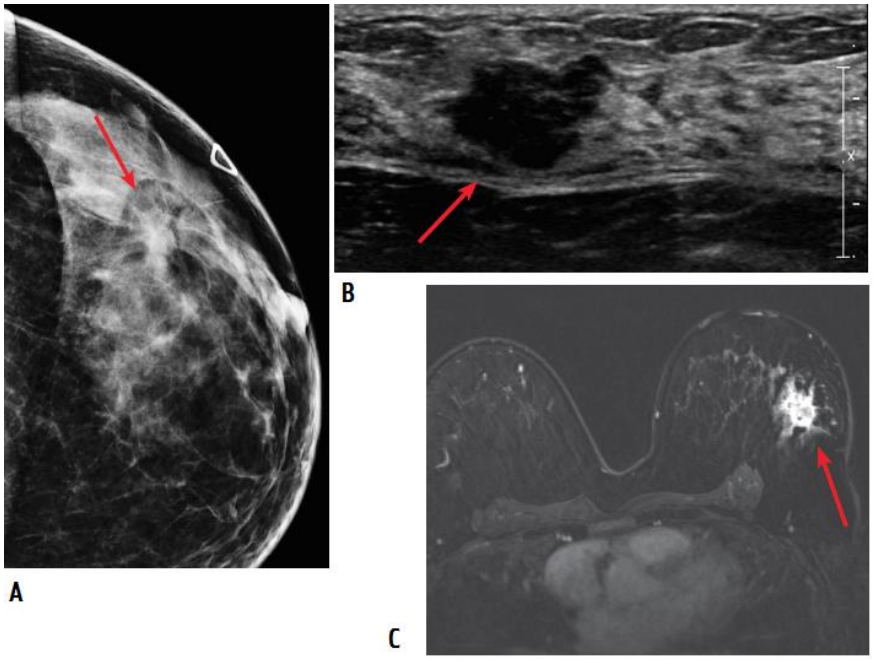

Figure 3.2

Different imaging techniques of a breast cancer. A: Mammogram of speculated mass with scattered microcalcifications. B: Same lesion on ultrasound. C: Same lesion on MRI [105].

3.3 Age limits

The Flemish breast cancer screening programme only invites women from 50 to 69 years old. The Flemish government follows the European Guidelines [66] referring to the International Agency for Research on Cancer (IARC) expert working group [106]. This IARC working group has reached consensus on the recommendation that screening, offered as a public health policy, should be directed to woman 50-69 years old with a two-yearly mammography.

In Flanders, 70% of all breast cancers are found in women older than 50 [107] (see Figure 3.3). For women in this age category, mammography is considered the best way to detect breast cancer before the woman has symptoms or before changes are present that may indicate a breast cancer.

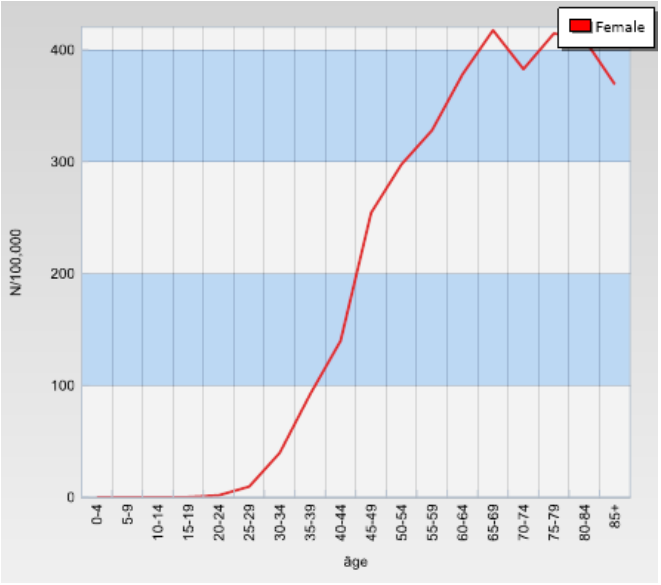

Figure 3.3

Age-specific incidence of breast cancer [89].

For younger women, screening mammography is less suitable for early detection of breast cancer [108]. Younger woman often have more glandular tissue. This requires a larger dose to achieve the same effect on the detector. This makes it also more difficult to assess the X-ray images by the radiologist. In addition, the breast tissue is even more sensitive to radiation and therefore also for radiation-induced breast cancers induced by the mammography X-rays [109].

In women older than 70, the benefits of screening do not necessarily outweigh the disadvantages. Screening in this population would yield a small profit in years of life, but there is a risk that their global quality of life would be affected by overdiagnosis and false-positives [110].

3.4 Limitations

The sensitivity of the Flemish Breast Cancer Screening programme ranges from 65.0% to 68.3% in the period from 2010 till now [95]. It measures the proportion of

women with breast cancer that are correctly identified as having the disease. This is highly dependent on breast density and ranges from 36% in dense breasts to 90% in women with adipose breast parenchyma [42, 47]. This means that in Flanders, approximately 1/3 of all cancers in the screened population are interval cancers (IC). These are defined as tumours diagnosed in women who participate in the breast cancer screening programme, after a negative screening result and before the next planned screening mammography. Interval cancers are considered more aggressive and larger than screen detected cancers (SDC) and have a worse prognosis [111-113]. Interval cancers may occur for different reasons. First, the cancer may not be detectable at screening examination and grow quickly. This is, according to the European guidelines an occult or true interval cancer. Second, an abnormality may be clearly visible during screening and the cancer may be missed. This is a false negative result. Last, there is a possible subtle abnormality on the screening image. These are defined as minimal sign cancers [66]. In the Flemish Breast Cancer Screening programme, this categorization has not yet been performed on a large scale. However, other mammography screening programmes reported a range between 13 and 35% of breast cancers in the screening population to be false-negative cancers (missed). The vast majority of interval cancers were not missed at screening and comprises both true interval cancers (about 50%) as minimal signs (about 20%) [114].

Specificity of a screening programme measures the proportion of women with an actual negative screening result that are correctly identified as such. The higher the specificity of a programme, the less presence of false positives. In Flanders, the specificity of the programme ranges from 97.3% to 98% in the period from 2010 till now [95]. This means that 2.0 to 2.7% of the women participating in the Flemish breast cancer screening programme were called back for further work-up after a divergent mammography but eventually there was no breast cancer diagnosis. This leads to unnecessary fear, discomfort and even pain [115].

There is also a concern about the use of ionizing radiation and associated glandular dose. Radiobiological studies showed that low energetic X-rays, typically used in mammography, are more effective in inducing biological damage than high

energetic X-rays [109]. This damage can evolve into a breast cancer: this is a radiation-induced breast cancer [115]. In addition, glandular tissue is also highly sensitive to radiation. This cannot be neglected in view of the large population size and the recurrent character in this asymptomatic screening programme. Because of this, the doses of mammography need to be as low as possible [93].

To gain a better understanding of the induced breast cancers due to screening, a detection-over-induction rate (DIR) can be calculated. This is the ratio of the amount of detected breast cancers in the screening programme on the amount of radiation-induced breast cancers and gives a good indication of the benefit-risk ratio of a screening programme [109, 116]. The cancer detection rate on one hand, which is a screening parameter, is calculated using data of the screening programme. The amount of radiation-induced breast cancers on the other hand, is extrapolated by the linear-no-threshold model. The screening age and mean glandular dose are implemented as variables to assess the induction rate. Correcting for extrapolation of high dose rate to low dose rate was performed with a dose and dose rate effectiveness factor (DDREF) of 2, adopted from the International Commission on Radiological Protection [117, 118]. As research state that mammography x-rays have a relative biological effectiveness (RBE) of 4, this was also implemented in the calculations [109].

When a DIR is bigger than 100, screening is trivial. This suggests that the risks are small in proportion with the years of life saved as a result of the screening programme and screening remains justified. However, when the result is smaller than 10, which is the critical threshold from screening programmes, screening is irresponsible [119]. In Flanders, the analysis of the DIR resulted in 48 for SFM, 36 for CR and 67 for DR [75].

4 AIM OF THE RESEARCH

The overall aim of this PhD thesis was to contribute to the understanding of how breast density has an impact on the Flemish Breast Cancer Screening Programme. More specifically, we wanted to investigate the behaviour of breast density in different mammography imaging techniques, which imaging technique has the preferred efficiency in dense breasts and whether the tumour characteristics are different in various breast density groups. The main goal was to investigate whether breast density could be used as a parameter for stratification in a tailor-made screening programme.

A FIRST AIM of this thesis was to map out the Flemish Breast Cancer Screening Programme by investigating the different image modalities and impact of this digitalization on performance parameters, breast density and breast dose. The results of this research is the foundation of further investigation of the screening programme.

Data from 975,673 mammographic examinations were collected from units that digitized from SFM to CR (41 units) or to DR (72 units) in the period 2005-2011. Performance parameters were calculated before and after digitalisation including cancer detection rate (CDR) and false-positives results as well as the proportion of third readings and positive predictive value (PPV). Additional parameters collected in the study are a number of characteristics of detected abnormalities: percentage of ductal carcinomas in situ, percentage invasive cancers smaller than 1 cm and the number of invasive cancers that are lymph node negative. Also breast density was collected. Mean glandular dose (MGD) was calculated for all units before and after digitalisation, using PMMA-phantoms with various thicknesses. In addition, a patient dosimetry study was performed where the median MGD was determined of at least 50 successive patients before and after digitalisation.

A SECOND AIM of this thesis was to investigate whether DR performs better than SFM and CR, specifically in dense breasts. As there is ample evidence that breast density is recognized as a risk factor of breast cancer and the sensitivity is decreased in high density breasts. To this end, data from 351,532 women, who participated in the Flemish Breast Cancer Screening programme in 2009 and 2010, were collected. The proportion of screen detected cancers (SDC) and interval cancers (IC) were studied within the different BI-RADS density classes for the various image modalities.

A THIRD AIM of this PhD-thesis is to compare tumour characteristics and molecular subtypes of IC versus SDC and to assess the association of tumour aggressiveness with breast density classes. As breast density influences both risk and detection of breast cancer as well as the likelihood of developing certain pathological subtypes [120, 121], studying tumour characteristics of screen detected and interval cancers as a function of breast density is of great interest. Therefore, by combining data of the Flemish Breast Cancer Screening Programme and the Belgian Cancer Registry, tumour characteristics of 983 women with a screening detected or interval cancer are collected. These women are spread in the four breast density groups. Additionally a molecular subtype analysis was performed.

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PART

Outline of the research

Article 1: Impact of the digitalization of mammography on performance parameters and breast dose in the Flemish Breast Cancer Screening Programme

Article 2: Screen-detected versus interval cancers: Effect of imaging modality and breast density in the Flemish Breast Cancer Screening Programme

Article 3: Tumour characteristics of screen-detected and interval cancers in the Flemish Breast Cancer Screening Programme: A mammographic breast density study

Original Research

II

OUTLINE OF THE RESEARCH

Article 1

Impact of the digitalisation of mammography on performance parameters and breast dose in the Flemish Breast Cancer Screening Programme

Timmermans L, De Hauwere A, Bacher K, Bosmans H, Lemmens K, Bleyen L, Van Limbergen E, Martens P, Van Steen A, Mortier G, Van Herck K, Thierens H.
European Radiology 2014; 24:1808-1819

To evaluate the impact of digitalization, mean glandular dose and performance parameters were investigated before and after the digitalization of mammographic units who participated in the Flemish Breast Cancer Screening Programme. Data is collected from 41 units who made the transition from SFM to CR and from 72 units who made the transition from SFM to DR. No significant change in CDR, DCIS or small breast cancers were found. Digitalisation did result in an increased PPV and a decreased recall rate. Changing from conventional SFMto digital CR resulted in a glandular dose increase of 30%. However, a 30% dose reduction was found when the mammographic unit digitalized to DR.

Article 2

Screen-detected versus interval cancers: Effect of imaging modality and breast density in the Flemish Breast Cancer Screening Programme

Timmermans L, Bleyen L, Bacher K, Van Herck K, Lemmens K, Van Ongeval C, Van Steen A, Martens P, De Brabander I, Goossens M, Thierens H.
European Radiology 2017; 27:3810-3819

To investigate if DR perform better in dense breasts, screen detected and interval cancers, classified in different breast densities and different imaging modalities,

were observed. An overall interval cancer rate of 33 % was found in the different imaging modalities. However, categorizing in different breast densities shows that the interval cancer rate increases gradually with breast density. In high density classes, the interval cancer rate even exceeds the screen detection rate in SFMand CR, but not in DR.

Article 3

Tumour Characteristics of screen-detected and interval cancers in the Flemish Breast Cancer Screening Programme: A mammographic breast density study

Timmermans L, De Brabander I, Van Damme N, Bleyen L, Martens P, Van Herck K, Depyere H, Thierens H*, Bacher K*.

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Submitted to: Plos One

To examine if breast density has an impact on tumour characteristics, the characteristics were analysed in different breast density classes of 983 woman with a screen detected or an interval breast cancer applying a logistic regression model. Screen detected cancers exhibit favourable characteristics in tumour size, nodal invasion, ER and PR negativity and grade 3 tumour, which are significant in comparison with interval cancers. This significant difference was also found in molecular subtype analysis. Analysis of the tumour characteristics and molecular subtypes in the different breast density classes showed larger tumours and more nodal invasion in IC. On the contrary, investigation of aggressive grade 3 tumours, ER/PR negative phenotypes and TN breast cancers resulted in a presence of more aggressive features in the low breast density classes. High density breast have a better prognostic tumour biomarker profile compared to low density breasts.

ARTICLE 1

Impact of the digitalization of mammography on performance parameters and breast dose in the Flemish Breast Cancer Screening programme

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European Radiology 2014; 24:1808-1819

Abstract

Objectives: To investigate the impact of digitalization on performance parameters and breast dose of the Flemish Breast Cancer Screening Programme. Both computed (CR) and direct radiography (DR) are compared to screen-film mammography (SFM).

Methods: Data from 975,673 mammographic examinations were collected in 41 and 72 units, who changed from SFM to CR or DR respectively in the period 2005-2011. Performance indicators were obtained by consulting the Screening Programme database. Phantom and patient dosimetry data were acquired from the physical technical quality assurance of the programme.

Results: Digitalization induced no significant change in cancer detection rate (CDR), percentage DCIS and percentage breast cancers smaller than 1cm. A decrease in false positive results and third readings was observed, which was a time related observation. After digitalization, positive predictive value (PPV) increased and recall rates decreased. Compared to SFM an increase of 30% in mean glandular dose (MGD) was found for CR while a similar change in the opposite direction was found for DR.

Conclusions: No major differences in performance parameters after digitalization were found. Transition of SFM to CR resulted in a higher MGD and associated lower detection-over-induction ratio (DIR) while the change to DR induced an improvement of DIR.

Introduction

In Flanders, breast cancer is the most common cancer in women. The lifetime risk is approximately 1 in 9. Moreover, European registry data show that Belgium has the highest breast cancer incidence in Europe [1]. Previous studies suggest that mammography screening reduces breast cancer mortality because of the early findings of masses and microcalcifications [2,3]. A Breast Cancer Screening Programme was started in Flanders in 2001 [4]. This screening programme complies with the European Guidelines that describe the recommendations for quality assurance in breast cancer screening and diagnostics [5].

In the Flemish Breast Cancer Screening programme women aged between 50 and 69 years, are invited every two years to undergo a free screening mammography. In mammographic units recognized by the Flemish government, two images, a craniocaudal and an oblique view, are taken of each breast. These images are interpreted by two independent radiologists: The first reading takes place at the mammographic unit where the mammograms are taken. Afterwards the images are send to the Centre for Cancer Detection where the second reading is performed within 3 days without any knowledge of the outcome of the first reader. In case of a discordance in interpretation of the two readers, the Centre for Cancer Detection organizes a third reading, again without knowing the previous two results. This Centre also enters all data associated with each woman into the centralized database 'Heracles' of the Flemish Breast Cancer Screening programme [4].

At the beginning of the screening, all mammographic units participating in the programme used screen-film mammography (SFM) as imaging technique. In 2006 the European Guidelines were expanded with a new chapter dedicated to digital mammography systems [5]. Since 2007, gradually more units made the transition to digital mammography. By the end of 2011, the proportion of mammographic units that used digital mammography in Flanders had reached 78%.

Digital mammography comprises several technologies. On one hand there is 'computed radiography' (CR) which uses removable cassettes containing a phosphor screen. After image taking and the read-out, the phosphor plate can be reset and reused [6]. Two different types of phosphor plates are used in screening mammography: powder and needle imaging plates [7,8]. On the other hand, in 'direct digital radiography' (DR) there are no cassettes required because the detector is fully integrated in the mammographic device. After interaction of the detector with X-rays, it immediately processes the absorbed

signals and produces the image for viewing. Different types of detectors are available in DR. Indirect detector flat panel systems contain a scintillator coupled to a photodiode material. Direct detector flat panels contains a photoconductor [9]. Finally the low dose full field digital mammography (FFDM) equipment of Philips makes use of photon counting [6]. Before introduction in the Flemish Breast Cancer Screening programme, each digital mammography device has to pass a typetesting procedure showing that the device is able to meet the criteria of the European Guidelines [10].

The aim of present study was to investigate the impact of the digitalization in mammographic units of the Flemish Breast Cancer Screening Programme. The performance parameters, which were extracted from the Heracles database, and the mean glandular dose (MGD), which include both patient and phantom dosimetry data, were compared pre- and post-digitalization. Using the acquired cancer detection rate (CDR) and MGD, the impact of digitalization on the Detection-Over-Induction Ratio (DIR) of the Flemish breast cancer screening programme was assessed separately for transition of SFM to CR and SFM to DR. This parameter gives a good indication of the benefit-risk ratio of the screening programme.

Materials and Methods

Population

The study implies a comparative design where the digital period, for both CR as DR, is compared with the earlier conventional screen-film period. This way, the period before digitalization refers to the same mammographic units and radiologists as after digitalization. Data has been collected retrospectively from patients participating the screening programme in mammographic units that changed from SFM to CR (n=41) or to DR (n=72) between January 1st 2005 and December 31st 2011. These mammographic units are followed up by the Leuven and Ghent University (respectively LUCMFR and QCC-Gent) with respect to physical technical quality assurance. A total of 975,673 mammographic examinations of women were included in the study which corresponds to 78% of all mammographic examinations in the Flemish Screening Programme during that period. This amount of examinations refers to 441,685 women, since women have participated in the programme multiple times. All participating women gave permission to use their screening data for scientific studies by signing the informed consent. An ethical committee has approved the Breast Cancer Screening Programme and data collection studies within the framework of this programme.

To exclude time over the years of this study as confounding factor, data from 27 mammographic units, who had not been digitalized by the end of 2011, were used for control. As the beginning of 2009 is the average date of digitalization for the mammographic units in the study, this time point was chosen for categorization in the control study. The period of seven years is split up in two parts. The data of the first part of that period, 2005-2008, can be considered as a control for the data prior to digitalization, the second part, 2009-2011, as a control after digitalization. Additionally, some units had to cope with technological defects of their digital device. When replacement of a digital system was necessary, both digital devices were compared with the same conventional device.

Performance Parameters

Using the Heracles database, all performance parameters were calculated for the mammographic units before and after digitalization. An analysis was performed separately for the units with transition from SFM to CR and SFM to DR. Furthermore, all performance parameters were extracted separately from the Heracles database for the initial and subsequent screening rounds.

First important variables are cancer detection rate (CDR) and the percentage false positive results (%FP). The CDR is the number of detected and confirmed breast cancers on the total number of mammographic examinations in the screening programme. The %FP is the proportion of women participating in the screening programme who are recalled for an additional follow-up (FU) exam, but for whom no breast cancer or any other malicious lesion was found. The FU examinations include ultrasound, MRI, mammography and also more invasive interventions like fine needle aspiration cytology and biopsy. If the patient needs an additional FU exam, as a result of the screening programme, she can refuse to store her data concerning this additional exam on the database of the screening programme, Heracles. This is the main reason for unknown follow-up of patients. The percentage of recalls with unknown follow-up in the Heracles database before and after digitalization goes from 21% to 13% for CR and from 19% to 13% for DR. Therefore a correction is made to the calculated parameters above to take into account the missing results of the follow-up exam in Heracles. This correction is based on the extrapolation of the outcome of the FU exams of the patients registered in Heracles to all women with a recall exam.

$$\mathrm{CDR} = \frac{\text{Known FU and Cancer} * \left(\frac{\text{Number of Recall}}{\text{Known FU}}\right)}{\text{Total number of mammographic examinations}}$$

$$\%FP = \frac{Known\ FU\ No\ Cancer * \left(\frac{Number\ of\ Recall}{Known\ FU}\right)}{Total\ number\ of\ mammographic\ examinations}$$

Next parameters calculated in present study are the percentage of mammographic examinations in the screening necessitating a third reading and the positive predictive value (PPV), which is the percentage of women with a positive screening result having a cancer according to the follow-up exam. For the PPV a range is derived defined by the assumption that the unknown follow-up cases are all cancer cases (PPV max) or all negatives (PPV min).

The BI-RADS (Breast Imaging-Reporting and Data System) classification is a first parameter reflecting the radiological image evaluation and interpretation considered for the study. Mammograms are categorized by radiologists according to their interpretation [11,12]. This classification consists of 5 classes whereas classes I (negative) and II (benign) contain women with a negative screening result for cancer. Classes III (probably benign), IV (suspicious abnormality) and V (highly suspicious lesion) are women who are recalled for additional investigation. A second important parameter in radiological imaging is the breast density score [12]. This ranges from I to IV with the percentage of fibrous and glandular tissue of the breast less than 25 %, 25-50%, 51-75 % and more than 75 % respectively. In the Flemish Breast Cancer Screening Programme, the density score is a radiological image parameter unrelated to the BI-RADS classification.Last parameters included in present study are a number of detected characteristics: the percentage ductal carcinoma in situ (DCIS), the percentage invasive cancers that are smaller than 1cm, and the number of invasive cancers that are lymph node negative. This latter means that no cancer cells are spread from the tumour to the lymph nodes. All these type characteristics have a good prognoses and are hereby reliable parameters in the screening programme.

Dosimetry

Dosimetry data from the participating mammographic units were obtained from the records of the physical technical quality assurance. Mean glandular dose (MGD) was calculated according to the method of Dance et al [13] and with use of the database from the UK National Co-Ordinating Centre for the Physics of Mammography available online [14], using the Air Kerma and several conversion factors to correct for glandularity of the breast and X-ray spectra. On one hand the MGD was calculated for all units before and after digitalization using the PMMA-phantom measurements of the periodic quality assurance tests. These dose measurements are performed for phantom thicknesses between 20mm and 70mm corresponding to compressed breast thicknesses from 21 till 90mm. On the other hand, for all units a patient dosimetry study was performed before and after digitalization: the median MGD was

determined from the MGD's of at least 50 successive patients (200 views) per unit. The median MGD, and not the mean, was chosen to correct for the outliers that are present in these populations. In units that use DR mammography, the necessary information needed for MGD calculation can be extracted from the DICOM-header of the images. In units equipped with CR and also for SFM, the exposure parameters required for patient dose calculation are manually registered for at least 50 successive patients. However, some units were already digitalized when the national patient dose inventory began in 2009. Dosimetry of 50 patients prior to digitalization in these units was not available. Therefore the available phantom dosimetry was used to deduce the missing patient dosimetry: all the available median patient MGD of DR, CR and SFM of each mammographic unit were plotted versus the MGD corresponding with the 45 mm PMMA-phantom of the same unit and modality which results in a satisfactory linear fit (R2 = 0,59). This linear fit was used to derive the median patient MGD from the 45 mm PMMA-phantom dose measurement in the mammographic units for which SFM patient dosimetry was not available.

Detection- over- Induction Ratio (DIR)

The DIR is calculated by means of the determined CDR, deduced from the Heracles database, and the estimated breast cancer induction rate. The induction rate is derived from the linear-no-threshold risk model with probability of a radiation induced breast cancer depending on women's age, using the measured median patient MGD for SFM, CR and DR [15,16]. As recent papers indicate a relative biological effectiveness (RBE) around 4 for mammography X-rays compared to conventional X-rays, this RBE was adopted in the calculations [17]. To correct for the risk extrapolation from high dose high dose rate to low dose low dose rate, a dose and dose rate effectiveness factor (DDREF) of 2 was adopted from the International Commission on Radiological Protection [18,19].

Statistical Analysis

Statistical calculations were performed using SPSS Statistics 21. For the analysis of the performance parameters, a Chi-square test for the comparison of two proportions, expressed as a percentage, was used. For dosimetry, a nonparametric paired test, in particular the Wilcoxon signed rank test was applied. Since every mammographic unit has one mean patient glandular dose before and after digitalization, a paired test was chosen to compare SFM versus digital systems. This also applies to phantom dosimetry carried out on different thicknesses. In order to test significance, for all tests, a confidence interval of 95% was used. Power testing was calculated with GPower

Results

Performance Parameters

Performance parameters of the mammography screening programme in Flanders before and after digitalization are summarized in Table 1.

Digitalization did not have any impact on CDR and this as well for the transition SFM to CR as for the transition SFM to DR as graphically depicted in Figure 1. Also in the non-digitalized group of mammographic units the CDR remained constant over time. The %FP decreased significantly when transition was made from conventional screen film to digital mammography. However, in the SFM group, without digitalization, also a decrease in %FP was observed showing that the strong decrease is not only linked to the transition to digital mammography but is a time related effect. Completely the same behaviour was observed for the % third readings: a significant decline was present after digitalization as well in the first round as in the subsequent rounds. A similar decrease with time was also found in the SFM control group although not significant in the first round. Statistical power of more than 0.99 was achieved in statistical significant different performance parameters above.

Minimal and maximal values of PPV increase after digital transition and also with time in the SFM group. This is clearly more pronounced in subsequent rounds, where the increase is statistical significant and where a statistical power of more than 0.99 was achieved, compared to the first round. The percentage breast cancers smaller than 1 cm, the percentage DCIS and percentage invasive cancers with negative lymph node tumours were also recorded as these are one of the criteria of the European Guidelines. These parameters did not change significantly after transition to digital mammography, nor in the control group.

In Table 2, the data regarding the recall rates before and after digitalization are summarized. A subdivision of these recall rates in BI-RADS III, IV and V, which lead to an additional examination, are also given. A decrease after digitalization of the recall rates are found. Also here a statistical power of more than 0.99 was achieved. This decrease is almost completely related to a reduction of BI-RADS class III (probably benign). This positive effect for the screening cannot be exclusively attributed to the digitalization as the same tendency is also present in the mammographic units that continued using SFM.

In Figure 2, a distribution of the breast density scores of the total screening population (all rounds) before and after digitalization is presented. This figure shows clearly that when a digital switch to DR is made, density of the breasts is estimated to be less dense: low density

PERCENTAGES (%)	First Screening Round								
	SFM	CR	P*	SFM	DR	P*	SFM 2005-2008	SFM 2009-2011	P*
CDR	0.74 (± 0.04) n = 37327	0.67 (± 0.06) n = 21204	0.36	0.81 (± 0.03) n = 99 178	0.71 (± 0.04) n = 43 103	0.05	0.69 (± 0.05) n = 30264	0.66 (± 0.06) n = 19 061	0.74
False-Positives	6.77 (± 0.13) n = 37327	5.14 (± 0.15) n = 21204	0.00	5.47 (± 0.07) n = 99 178	4.76 (± 0.10) n = 43 103	0.00	5.76 (± 0.13) n = 30264	5.34 (± 0.16) n = 19 061	0.05
Third Readings	9.27 (± 0.15) n = 37327	7.75 (± 0.18) n = 21204	0.00	8.13 (± 0.09) n = 99 178	7.50 (± 0.13) n = 43 103	0.00	8.11 (± 0.16) n = 30264	7.74 (± 0.19) n = 19 061	0.15
PPV min	7.60 (± 0.50) n = 2804	9.73 (± 0.84) n = 1233	0.03	10.06 (± 0.38) n = 6224	10.99 (± 0.64) n = 2357	0.23	8.15 (± 0.62) n = 1951	8.75 (± 0.84) n = 1143	0.61
PPV max	9.90 (± 0.64) n = 2152	11.55 (±0.99) n = 1039	0.18	12.85 (± 0.48) n = 4873	12.93 (± 0.75) n = 2003	0.96	10.64 (± 0.80) n = 1494	11.00 (± 1.04) n = 909	0.84
DCIS	21.13 (±2.80) n = 45	19.17 (±3.59) n = 23	0.90	19.97 (1.60) n = 125	26.64 (2.75) n = 69	0.20	22.01 (±3.29) n = 35	25.00 (±4.33) n = 25	0.97
Invasive Cancer < 1 cm	27.98 (± 3.46) n = 168	23.71 (± 4.32) n = 97	0.90	23.75 (± 1.90) n = 501	27.89 (± 3.25) n = 190	0.20	25.00 (± 3.89) n = 124	25.33 (± 5.02) n = 75	0.97
Invasive Cancers with lymph node negative tumors	68.04 (± 3.60) n = 168	80.00 (± 4.06) n = 97	0.05	66.50 (± 2.11) n = 501	65.94 (± 3.44) n = 190	0.96	66.10 (± 4.25) n = 124	67.12 (± 5.42) n = 75	0.99

PERCENTAGES (%)	Subsequent Screening Rounds								
	SFM	CR	P*	SFM	DR	P*	SFM 2005-2008	SFM 2009-2011	P*
CDR	0.53 (± 0.03) n = 82491	0.56 (± 0.03) n = 74043	0.45	0.56 (± 0.01) n = 271 796	0.59 (± 0.02) n = 167 848	0.21	0.50 (± 0.03) n = 64 581	0.56 (± 0.03) n = 64 777	0.16
False-Positives	3.32 (± 0.06) n = 82491	2.14 (± 0.05) n = 74043	0.02	2.47 (± 0.03) n = 271 796	1.97 (± 0.03) n = 167 848	0.00	2.72 (± 0.06) n = 64 581	1.88 (± 0.05) n = 64 777	0.00
Third Readings	5.45 (± 0.08) n = 82491	3.91 (± 0.07) n = 74043	0.00	4.07 (± 0.04) n = 271 796	3.83 (± 0.05) n = 167 848	0.00	4.49 (± 0.08) n = 64 581	3.39 (± 0.07) n = 64 777	0.00
PPV min	11.16 (± 0.56) n = 3172	18.20 (± 0.86) n = 1995	0.00	15.26 (± 0.40) n = 8215	20.12 (± 0.61) n = 4300	0.00	12.41 (± 0.72) n = 2079	18.63 (± 0.98) n = 1578	0.00
PPV max	13.76 (± 0.68) n = 2573	20.63 (± 0.96) n = 1760	0.00	18.42 (± 0.47) n = 6806	22.93 (± 0.68) n = 3772	0.00	15.65 (± 0.89) n = 1649	22.97 (± 1.18) n = 1280	0.00
DCIS	19.21 (±2.09) n = 68	12.67 (±1.75) n = 46	0.51	19.62 (1.12) n = 246	18.50 (1.32) n = 160	0.89	18.60 (±2.42) n = 48	20.07 (±2.34) n = 59	0.96
Invasive Cancer < 1 cm	33.22 (± 2.79) n = 286	29.34 (± 2.56) n = 317	0.35	31.55 (± 1.46) n = 1008	29.79 (± 1.72) n = 705	0.47	26.67 (± 3.05) n = 210	26.38 (± 2.87) n = 235	0.97
Invasive Cancers with lymph node negative tumors	76.22 (± 2.52) n = 286	76.97 (± 2.36) n = 317	0.91	73.70 (± 1.39) n = 1008	72.53 (± 1.68) n = 705	0.63	77.25 (± 2.89) n = 210	71.01 (± 2.96) n = 235	0.17

* Chi-Square test

Table 1

Overview of the performance parameters of the Flemish Breast Screening Programme for the transition screen-film mammography (SFM) to computed radiography (CR) and SFM to direct radiography (DR). To take into account the time as confounding factor, variable parameters are also given for mammographic units that are not digitalized for the time frames 2005-2008 and 2009-2011. Uncertainties indicated are the standard errors of proportion. N= number of mammographic screening examinations used to calculate the percentages.

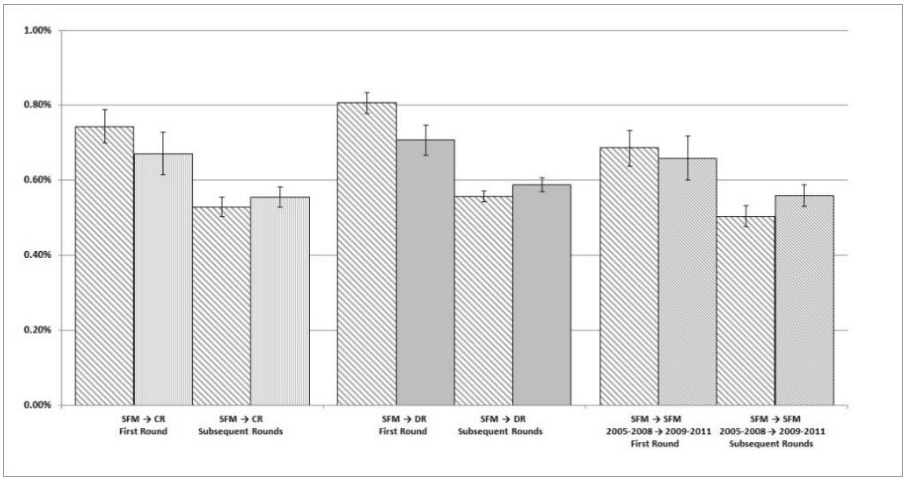

Figure 1

Comparison of cancer detection rate (CDR) in the first and subsequent rounds before and after digitalization for CR and DR systems. To investigate time as confounding factor, CDR values for the time frames 2005-2008 and 2009-3011 for not digitalized mammographic units are also given. The indicated error bars are the standard errors of proportion.

class I is almost doubled and high density class IV almost halved. The phenomenon of lower density estimation after digitalization is also present for the transition SFM to CR but less pronounced. As the control population shows only a slight tendency with time in the same direction, digitalization, especially for DR, is responsible to a large extent for the effect of lower density estimation.

Dosimetry

The impact of the transition from SFM to CR and DR on glandular dose based on the PMMA phantom measurements (20mm, 45mm, 70mm) of the physical technical quality assurance is depicted graphically in Figure 3 for the individual mammographic units. The data regarding the change in patient MGD related to digitalization deduced from the dose measurements of a population of at least 50 women are presented in Figure 4. MGD values of the phantom and patient measurements averaged over the mammographic units pre- and post-digitalization for CR and DR are given in Table 3.

For the transition from SFM to CR , a significant increase in phantom MGD is observed for nearly all mammographic units and this for PMMA thicknesses of 20mm, 45mm and 70mm, which results in an average increase of 35-48 % and this with a statistical power of more than 0.99 (Figure 3, Table 3). For the transition from SFM to DR the change in MGD depends on PMMA phantom thickness. While a

significant increase (38%) in MGD is found for the 20mm PMMA phantom measurements (Fig 3a), a significant decrease in dose was recorded for the 45mm and 70mm PMMA phantom measurements (26 and 36 % respectively) (Figure 3b, 3c; Table 3). Also here a statistical power of more than 0.99 was achieved.

The patient dose study provides similar results as the phantom dose study with the 45 mm PMMA phantom as this thickness of PMMA has a comparable attenuation of a compressed breast of 53 mm. This was the average compressed breast thickness of women participating in the screening. With a few exceptions, there was a systematic increase in patient dose for mammographic units changing from SFM to CR and a systematic dose decrease for units when digitalization involved DR systems (Figure 4). According to the patient dose measurements, the change of the median patient dose was +29% and -26% for transition from SFM to CR and DR respectively with a statistical power of more than 0.99 (Table 3).

Detection- over- Induction Ratio (DIR)

The estimation of the DIR resulted in 48 for SFM. After digitalization, the DIR is 36 for CR and 64 for DR. This means that the DIR decreases with 25% when the digital transition is made to a CR system and increases with 34 % when a switch is made from SFM towards a DR system, while in the control SFM group, the DIR remained unchanged.

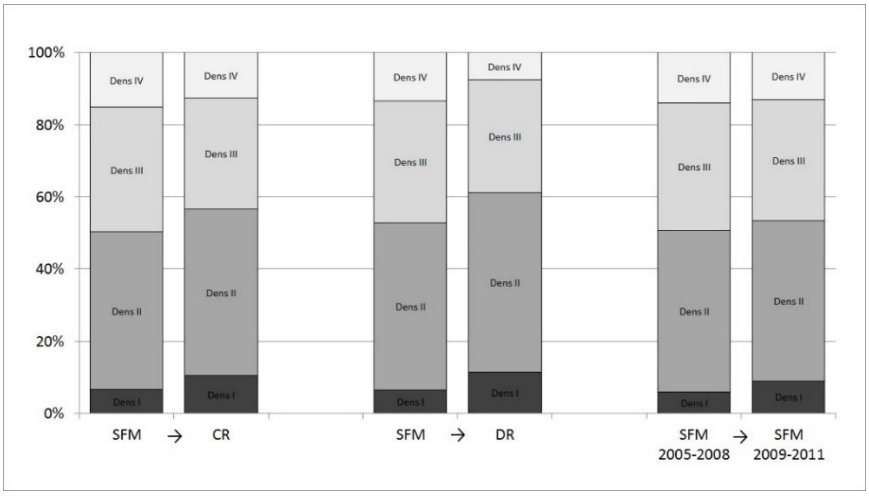

Figure 2

Comparison of breast density classification distribution of the screening population in all rounds before and after digitalization. Data for the non-digitalized mammographic units as a function of time are also given.

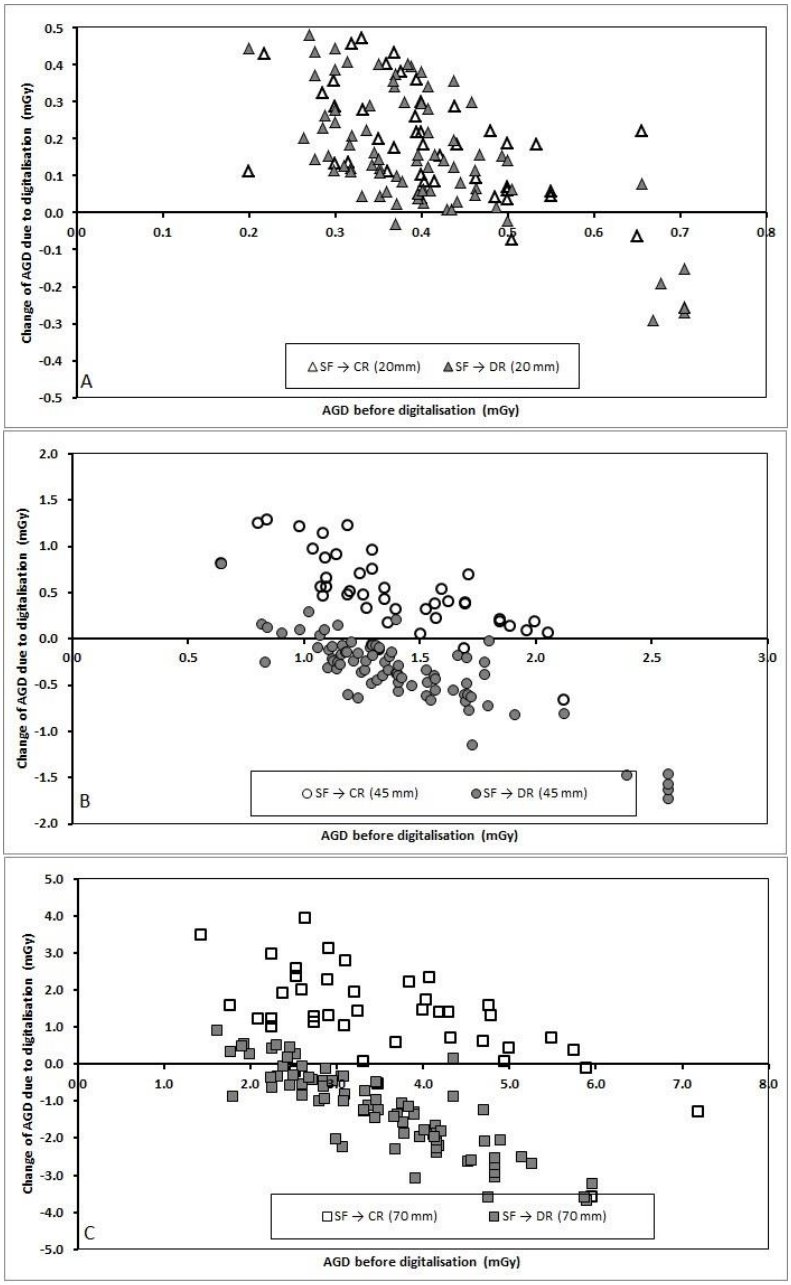

Figure 3

Graph shows shift in the mean glandular dose (MGD) after digitalization for the individual mammographic units, resulting from PMMA measurements. (A) Phantom dose study using 20mm PMMA. (B) Phantom dose study using 45mm PMMA. (C) Phantom dose study using 70mm PMMA.

Discussion

In which direction and how strong the transition from conventional screen-film mammography towards digital mammography has changed breast dose and performance characteristics in the Flemish Breast Cancer Screening Programme, is an important issue in the continuity of the quality of the programme over the years. This study analysed a cohort of screening examinations before and after digitalization during a period of 7 years. The digital transitions to both CR as DR systems are investigated since both modalities are used in the Flemish screening programme.

Our investigation showed after digitalization no effect in CDR, a higher PPV and a lower recall rate and percentage false positive results. Also after the digital transition, breasts are estimated to be less dense but no differences were found in the number of DCIS or cancers that are smaller than 1cm. These effects are similar for both CR as DR systems. When the mean glandular dose was studied, major differences between CR and DR have been found. When conventional screen film mammography was traded for a digital device, a dose increase was found for CR while a dose decrease for DR occurred.

Several studies have compared performance parameters of conventional and digital mammography screening before, but contradictory results were reported [20-34]. However, the comparative design of present study is original: parameters before and after digitalization are compared for the same mammographic units. The same teams of radiologists have read the mammograms before and after digitalization, in this way both regional differences in the patient population and individual differences in the interpretation process of the mammograms are reduced to a minimum. Most comparative studies investigating the impact of digitalization on performance parameters and breast dose in breast cancer screening programmes, studied only DR systems. Just a few also assessed CR systems [35-39]. In present paper the transition from SFM to DR and CR systems was studied separately .

Our analysis showed no effect of digitalization on the CDR neither for DR, nor for CR. These results support conclusions of other studies showing also no impact on CDR for DR [26,28]. A higher CDR after digitalization for DR [31,32], or the lower CDR after digitalization for CR reported in the French screening programme and in Canada was not confirmed in present study [36,39]. However, CDR values of present study are in line with the European Guidelines requiring CDR to be higher than 3 times the breast cancer incidence rate for the first round and 1.5 times for the subsequent rounds [5]. The baseline incidence rate is approximately equal to 1.25 per 1000 women [4]. The unchanged CDR

after the transition from SFM to digital systems is possibly related to the continuous quality assurance of the Breast Cancer Screening Programme. The mammographic units, both conventional as digital, are obliged to perform a daily quality control test for the mammographic device as well as the monitors. This daily test is under supervision of technical physical quality assurance organisations who verify that the system is stable and reliable at a daily basis. This can explain the unchanged CDR: an optimal adjusted conventional device already gave his best possible CDR. Digital devices, who are also adjusted according to optimal settings will generate approximately the same CDR but the breast dose will change according to the type of digital device.

The recall rates were found to be systemically lower after transition towards a digital device. These rates, after digitalization, meet the European Guidelines which states that these should be less than 7% in the first rounds and 5% in the subsequent rounds. In the subsequent rounds, the rates even comply with the desirable level of less than 3% [5]. This decrease is almost completely related to a reduction of BI-RADS III. In recent years, readers were advised to think twice before selecting this class as the BI-RADS class III is the grey zone between cancer and no cancer. As a consequence, the chosen BI-RADS classes by radiologists are more forethoughtful which has a positive effect on the screening programme parameters. The percentage false-positives, which are associated with the recall rates, are also systematically and significantly reduced. These significant reductions after digitalization are not always in line with previous studies. Divergent results were reported on the effect of digitalization on recall rate in other studies: some report a significant increase [20,29,31,33,40] others a significant decrease [22,30] and finally some indicate no differences [28,32,37]. The divergent results can be due to a substantially different study design and other factors like age of the population, size of the data set, single versus double reading, reading environment, hard versus soft copy reading. However, these effects of lowering are not due to the digitalization alone as it is also present in our control screen film group. The time dependence of the recall rates and false positives of our study points to the increased experience of the radiologists involved in the screening, and the improvement of the entire programme. The lower percentages found in subsequent screening rounds compared to the first screening round points to the importance of the availability of the images of previous rounds which are always available in conventional and digital mammography. The percentage third readings showed completely the same

trends as the percentage false positives. The control group data of non-digitalised mammographic units showed also that the higher PPV for digital mammography was again an effect of time which also points to the improvement of the programme. Also for this parameter, the PPV tendencies related to digitalization reported in other studies are divergent with higher PPV in favour of digital mammography in some studies [30,32] and in favour of conventional mammography in others [33].

An analysis of the data over the years show that the improvement of the studied performance parameters above can be attributed to the increase of the quality of the screening programme. This can be related to the learning curve of radiologists in the interpretation of mammograms and the continuous efforts of medical physicists in the physical-technical quality assurance. In the Flemish breast cancer screening programme a lot of attention is paid to the training of the radiologists teams involved which include both theoretical as practical training.

	First Screening Round								
Percentages (%)	SFM n = 37 327	CR n = 21 204	P*	SFM n = 99 178	DR n = 43 103	P*	SFM 2005-2008 n = 30 264	SFM 2009-2011 n= 19 061	P*
Recall rate	7.51	5.81	**0.00**	6.28	5.47	**0.00**	6.45	6.00	**0.05**
BI-RADS III	6.52	5.00	**0.00**	5.31	4.68	**0.00**	5.49	5.19	**0.17**
BI-RADS IV	0.83	0.66	**0.03**	0.77	0.64	**0.01**	0.81	0.68	**0.12**
BI-RADS V	0.16	0.17	**0.86**	0.19	0.15	**0.12**	0.18	0.14	**0.35**
	Subsequent Screening Round								
Percentages (%)	SFM n = 82 491	CR n = 74 043	P*	SFM n = 271 796	DR n = 167 848	P*	SFM 2005-2008 n = 64 581	SFM 2009-2011 n= 64 777	P*
Recall rate	3.85	2.69	**0.00**	3.02	2.56	**0.00**	3.22	2.44	**0.00**
BI-RADS III	3.20	2.16	**0.00**	2.44	2.00	**0.00**	2.63	1.89	**0.00**
BI-RADS IV	0.55	0.45	**0.01**	0.48	0.46	**0.36**	0.49	0.45	**0.31**
BI-RADS V	0.10	0.09	**0.58**	0.10	0.10	**0.96**	0.10	0.09	**0.62**

* Chi-Square test

Table 2

Recall rates and the results of BI-RADS classification resulting in a recall (III, IV, V) before and after digitalization are summarized. Mammograms interpreted as probably benign are class III, interpreted as suspicious are class IV and highly suggestive of malignancy are class V. N= number of mammographic screening examinations used to calculate the percentages.

The radiologists involved in the programme are obliged to participate on a regular basis to peer-based reading tests of sets of mammograms. The observed improvement of the programme quality in time emphasizes the need for retrospective rereading of mammograms of women, classified for recall and for which follow up data are known. The availability of images in digital mammography combined with the Heracles database facilitate this self-learning process in the Flemish breast cancer screening programme. That follow up data are not always available hampers this process and this is also a limitation of present study. An important recommendation is that in the future larger efforts should be made to complete follow up data in the database.

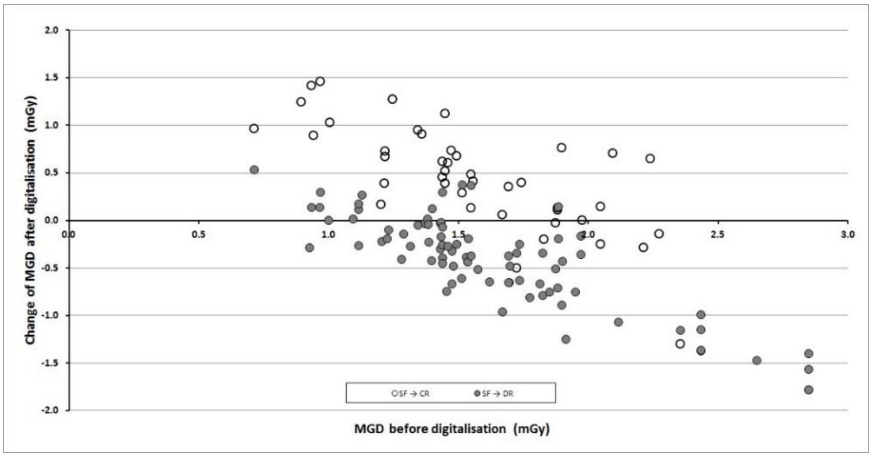

Figure 4

Graph shows shift in mean glandular dose (MGD) after digitalization for the individual mammographic units, resulting from measurements of a representative patient population.

	Average SFM	Average CR	Normalized Difference	P*	Average SFM	Average DR	Normalized Difference	P*
MGD @ 20 mm PMMA (mGy)	0.41 (±0.10)	0.61 (±0.12)	48%	**0.00**	0.40 (±0.11)	0.55 (±0.12)	38%	**0.00**
MGD @ 45 mm PMMA (mGy)	1.40 (±0.36)	1.89 (±0.28)	35%	**0.00**	1.43 (±0.39)	1.06 (±0.22)	-26%	**0.00**
MGD @ 70 mm PMMA (mGy)	3.58 (±1.31)	4.83 (±1.16)	35%	**0.00**	3.51 (±1.02)	2.25 (±0.56)	-36%	**0.00**
Median MGD Patient Dosimetry	1.56 (±0.41)	2.02 (±0.38)	29%	**0.00**	1.64 (±0.47)	1.20 (±0.27)	-26%	**0.00**

* Wilcoxon Signed Rank test

Table 3

MGD values resulting from PMMA phantom measurements (thickness 20mm, 45mm and 70mm) averaged over the mammographic units pre- and post-digitalization for computed radiography (CR) and direct radiography (DR). In addition the median MGD of a representative patient group averaged over the mammographic units pre- and post-digitalization for CR and DR is also given. Uncertainties indicated are the standard deviations.

In previous studies, it has already been proven that digital mammography is better in detecting breast cancer in young women and women with dense breasts [37]. We found for both CR and DR systems after digitalization, that breasts are estimated to be less dense and this effect was not found over time. This can be related to the better cancer detection capacity of digital mammography in dense breasts but further investigation in this regard is necessary.

Digitalization in mammography does not always necessarily lead to a breast dose reduction. Several studies report a dose increase when a conventional screen film mammography is replaced by CR technology [43-45]. This phenomenon is confirmed in present study. On the average, the MGD is 30% higher for the CR equipped systems than in screen-film (Table 3, Figure 4). Indeed, all mammographic devices equipped with CR are set this high in MGD in order to keep the image quality at an acceptable level and to meet the limits of the European Guidelines for image quality in the CDMAM analysis. On the contrary, in literature it is also reported that after digitalization towards DR, this detector system can produce images with at least an equivalent image quality and with a lower dose than replaced screen film combinations [42-45]. Also this was confirmed in present research. Reliable parameters that reflect both the image quality and radiological performance are the percentage DCIS, percentage invasive breast cancers smaller than 1cm and invasive cancers with negative lymph nodes since these types are in an early stage breast cancer and result in smaller differences compared to the normal tissue on a mammogram. In present study, no significant differences of these parameters were observed between DR, CR and SFM

which indicates no major image quality difference, but only a major dose difference for DR. The dose reduction is pronounced most clearly for larger breast sizes but is not visible in small breasts (Table 3, Figure 3, 4).

The risk for a radiation induced breast cancer is considered as one of the disadvantages of breast cancer screening programmes based on mammography, especially for large volume breast women. As we are dealing with asymptomatic women in mammography screening, radiation risks related to breast doses are a matter of concern. Detection over induction ratio (DIR) is considered a good indicator of the benefit/risk ratio [46]. Because the CDR did not make any considerable change from SFM to DR or CR in our study, the change in DIR after digitalization is reflected entirely by the change in breast cancer induction rate which is dependent of the breast dose. The DIR is hereby estimated to decrease from 48 to 36 for CR and to increase from 48 to 64 for DR. These estimations are based on a RBE value of 4 and a DDREF of 2. In other investigations sometimes a RBE of 2 or unity were used resulting in higher DIR values, but on the other side some authors propose DDREF values of 1.5 or 1.0 based on the more high LET nature of mammography X-rays. This would yield lower DIR values [19]. Anyway, the DIR remains all times above the value of 10 which is the critical threshold for screening programmes as shown in previous studies. This suggest that the risks are small in proportion with the years of life saved as a result of the screening programme and from this point of view mammography screening remains justified in the studied age category (50-69 years) for as well SFM as CR and DR [47].

In the near future digital mammography will replace screen film mammography entirely in a screening setting. Present study has shown that quality performance parameters of the Flemish Breast Cancer Screening Programme were not affected by the transition towards digitalization. Though, a positive change over time of these parameters indicates an improvement of the entire Screening Programme. Every mammographic device allowed in the screening programme complies with the EUREF standards but differences are found in MGD whereas CR implicates a higher breast dose and an associated higher radiation risk while the transition to DR means a change in the opposite direction.

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ARTICLE 2

Screen-detected versus interval cancers: Effect of imaging modality and breast density in the Flemish Breast Cancer Screening Programme

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European Radiology 2017; 27:3810-3819

Abstract

Objectives: To investigate if Direct Radiography (DR) performs better than Screen-Film mammography (SF) and Computed Radiography (CR) in dense breasts in a decentralized organised Breast Cancer Screening Programme. To this end screen detected versus interval cancers were studied in different BI-RADS density classes for these imaging modalities.

Methods: The study cohort consists of 351,532 women who participated in the Flemish Breast Cancer Screening Programme in 2009 and 2010. Information on screen detected and interval cancers, breast density scores of radiologists second readers, and imaging modality was obtained by linkage of databases of the Centre of Cancer Detection and the Belgian Cancer Registry.

Results: Overall, 67% of occurring breast cancers are screen detected and 33% are interval cancers with DR performing better than SF and CR. Interval cancer rate increases gradually with breast density, regardless of modality. In the high density class, interval cancer rate exceeds cancer detection rate for SF and CR, but not for DR.

Conclusions: DR is superior to SF and CR with respect to cancer detection rate for high density breasts. To reduce the high interval cancer rate in dense breasts use of an additional imaging technique in screening can be taken into consideration.

Introduction

European registry data show that Belgium has the highest breast cancer incidence rate in Europe [1]. In 2001, a Breast Cancer Screening Programme was started in Flanders [2]. This is a decentralized screening programme inviting all women in Flanders aged between 50 and 69 years for a completely reimbursed two-view mammogram every two years. The imaging modalities used are screen-film (SF) mammography, as well as digital mammography, including both computed radiography (CR) and direct radiography (DR), with digital mammography replacing gradually conventional SF [3].

Mammographic breast density (BD) refers to the proportion of radiodense fibroglandular tissue in the mammogram and is ranked in classes according to a system developed by the American College of Radiology (Breast Imaging-Reporting and Data System, or BI-RADS) [4]. BD is recognized as a risk factor for breast cancer, with women with a high breast density having a 4-6 times enhanced risk compared to women with completely fatty breasts [5-8]. Furthermore, there is ample evidence that the sensitivity of cancer detection in mammography is decreased in high density breasts [9-13]. This is related to the masking effect of dense breast tissue since both fibroglandular tissue and tumours appear as radio-opaque structures, which leads to an increasing amount of interval cancers [9]. The study of Kavanagh et al. shows that women with high BD have a fivefold increased risk of interval cancer compared to low BD women [14].

Interval cancers (ICs) are tumours diagnosed in women participating in the screening programme after a negative screening result and before the next planned screening mammography. As defined in European guidelines, ICs include “true” ICs or occult cases, which are cancers that could not be detected in the previous mammogram, “missed” cancers or false-negatives, and the minimal signs [15]. ICs are considered to be more aggressive than screen detected cancers (SDCs) [16].

According to a recent review of breast density and lesion detection, an increased performance can be obtained in high density breasts by digital mammography [17]. In the Digital Mammographic Imaging Screening Trial (DMIST), the AUC of the ROC curve was significantly larger for digital mammography than for SF for pre- or perimenopausal women younger than 50 years, who had dense breasts at SF mammography [18]. Up to now, a systematic comparative study of cancer detection rate (CDR) and interval cancer rate versus breast density between SF and digital mammography , with CR and DR considered separately, has not been performed. This type of study has to highlight if DR is indeed

superior for dense breasts screening. Present paper describes the results of a study of the performance characteristics of the different imaging modalities (SF, CR and DR) as a function of breast density in the Flemish Breast Cancer Screening Programme. Special attention was paid to interval cancer incidence.

Materials and methods

Population

This study is a retrospective analysis of data from the Flemish Breast Cancer Screening Programme and Belgian Cancer Registry. The considered screening period was from January 2009 till December 2010, during which 351,532 women participated in the screening programme. In this period, all three imaging modalities were still adequately present in the programme. This 2 year period also corresponds to one screening round so there are no women participating twice in the study. Participants always give permission to use their screening data for scientific studies by signature of an informed consent. A privacy committee has approved the Breast Cancer Screening Programme and data collection studies within the framework of this programme.

Flemish Breast Cancer Screening Programme

In the Flemish Screening Programme, all eligible women aging between 50 and 69 years are invited for a completely reimbursed biennial screening mammography with two mammographic views of each breast (one craniocaudal and one oblique view). It is a decentralized screening programme: mammograms of participating women are taken in qualified mammographic units spread out over Flanders. Images are interpreted by 2 independent radiologists qualified for mammography evaluation. The first reader is a radiologist of the local mammographic unit where mammograms were taken. Afterwards the images are sent to one of the five Breast Cancer Centres where a radiologist, recognised as second reader, performs a second independent reading, completely blind for the outcome of the first radiologist. In case of discordance in interpretation between the two readers, the Breast Cancer Centre organises a third independent reading. These centres also collect all data associated with each participating woman into a centralised database 'Heracles'. The mammography systems used in the screening programme are of different vendors but they all comply with the Belgian quality assurance protocol with respect to physical-technical aspects, based on European Guidelines [15].

Belgian Cancer Registry

The Belgian Cancer Registry (BCR) is a national population based cancer registry,

collecting data of all new cancer diagnoses. These data are provided by the oncological care programs and the laboratories for pathological anatomy based on the specific cancer registration law [19]. Based on its database, the BCR maps out the nature and extent of cancer in Belgium, supports and evaluates the Belgian cancer screening programmes and collaborates in different research projects. To complete the Heracles database with information on SDCs and to obtain information on ICs, the Sector Committee of Social Security and Health authorized linkage on a regular base of the Heracles database with the BCR database [20]. After linkage, an anonymous database of breast cancer patients was provided for present study. This database contains data of women who participated in the screening programme in 2009-2010 and were diagnosed with breast cancer within 24 months after screening. This database allowed differentiation in SDCs and ICs. A subdivision of ICs in true, missed and minimal signs was not performed in present study.

Density

The breast density description used in present paper consists of 4 groups according to the four category BI-RADS system developed by the American College of Radiology: BI-RADS I with less than 25% glandular tissue, BI-RADS II with 25-50% glandular tissue, BI-RADS III with 51-75% glandular tissue and BI-RADS IV, a class with extremely dense breasts with more than 75% glandular tissue [4]. The new 5th edition BI-RADS classification, that is currently used in the programme, was not employed in current research as this study handles data from 2009-2010 when previous BI-RADS classification version was in use. Within the Flemish Breast Cancer Screening Programme, the mammographic density of each breast of participating women is scored by both radiologists, first and second readers, in this four category system.

Software programmes are available to measure automatically the percentage of radiodense area in digital mammograms and to assess quantitatively breast density. Within the present study, density scores of radiologists were compared with results of the Volpara Density technology software (Volpara®SolutionsTM) for quantitative volumetric assessment of breast density for a number of images of women, participating in 2015 in the breast cancer screening programme. A set of 179 for processing digital images from different DR mammographic devices were collected and uploaded into the software programme. Processing the images with the software results in a Volpara Density Grade (VDG) for each breast, which correlates directly to a BI-RADS category. As the software requires raw data, the Volpara Density software could not be applied on screening mammograms dating from the study period

2009-2010. The Volpara Density software is also not intended for breast density assessment in CR and conventional screen-film images. The obtained VDG results for the 179 cases were compared to breast density scores reported by the first and second readers.

Statistical analysis

Statistical calculations were performed using SPSS Statistics 22. For the analysis of the SDCs and ICs, in different modalities and densities, a chi square test for the comparison of two proportions, expressed as a percentage was used. When comparing more than two proportions, a test of equal proportions was applied. In case of more than two proportions, a statistical correction according to Bonferroni was made. Density scores of the first and second readers were compared to the results of the Volpara Density programme® by assessment of the intraclass correlation. In order to test significance, for all tests a p level of 0.05 was adopted.

SF				CR				DR				TOTAL			
143293				74612				133627				351532			
SDC		IC		SDC		IC		SDC		IC		SDC		IC	
745		391		427		202		791		369		1963		692	
5.20‰ ± 0.19 ‰		2.73‰ ± 0.14 ‰		5.72‰ ± 0.28 ‰		2.71‰ ± 0.19 ‰		5.92‰ ± 0.21 ‰		2.76‰ ± 0.14 ‰		5.58‰ ± 0.13 ‰		2.74‰ ± 0.09 ‰	
SDC-IC proportion				SDC-IC proportion				SDC-IC proportion				SDC-IC proportion			
65.58%		34.42%		67.89%		32.11%		68.19%		31.81%		67.11%		32.89%	
CIS	Invasive	CIS	Invasive	CIS	Invasive	CIS	Invasive	CIS	Invasive	CIS	Invasive	CIS	Invasive	CIS	Invasive
126	616	28	363	58	367	16	186	155	634	26	343	339	1617	70	892
0.88‰ ± 0.08 ‰	4.30‰ ± 0.17 ‰	0.20‰ ± 0.04 ‰	2.53‰ ± 0.13 ‰	0.78‰ ± 0.10 ‰	4.92‰ ± 0.26 ‰	0.21‰ ± 0.05 ‰	2.49‰ ± 0.18 ‰	1.16‰ ± 0.09 ‰	4.74‰ ± 0.19 ‰	0.19‰ ± 0.04 ‰	2.57‰ ± 0.14 ‰	0.96‰ ± 0.05 ‰	4.60‰ ± 0.11 ‰	0.20‰ ± 0.02 ‰	2.54‰ ± 0.08 ‰

Table 1

Overview of the number of screen detected (SDCs) and interval cancers (ICs) for the different imaging modalities (SF-CR-DR). The number of carcinoma in situ (CIS) and invasive cancers are also presented. The data are also presented as percentage of the population screened with the imaging modality. Uncertainties indicated are standard errors of proportion.

Results

Screen detected cancers and interval cancers for the different screening modalities.

The number of SDCs and ICs occurring in the study cohort for each imaging modality are listed in Table 1. CDR is higher in the DR group (5.92‰) compared to conventional SF (5.20‰) and CR (5.72‰) mammography with statistical significance for this difference between DR and SF (p =0.013). Differences between the modalities in the percentage of ICs (2.73‰, 2.71‰, 2.76‰) are not significant. Both SDCs and ICs consist of invasive cancers and carcinomas in situ (CIS). Table 1 shows that overall, 17% of SDCs are in situ cancers while this is only 7% for ICs.

CDR in women participating in the screening programme for the first time (first round) in 2009-2010 is 6.50‰, which is significantly higher than the CDR in women of subsequent rounds in 2009-2010 (5.32‰) (p=0.00). For ICs, the difference between first and subsequent rounds women is not significant: the interval cancer rate is 2.99‰ for women participating in the first round versus 2.66‰ for women in subsequent rounds (p=0.18).

The ICs reported in the first year post-mammography for women participating in the screening programme in the period 2009-2010 is 1.00‰, which is significantly lower than the percentage ICs found in the second year (1.74‰) (p=0.00). As for the total percentage of ICs, differences between imaging modalities for the percentages of first and second year ICs are non-significant.

Screen detected cancers and interval cancers as a function of the breast density.

To assess the reliability of breast density scores of first and second readers, reported for the women under study, raw image data of 179 recent mammographic DR images

BI-RADS I		BI-RADS II		BI-RADS III		BI-RADS IV	
38856		177885		103955		30767	
SDC	IC	SDC	IC	SDC	IC	SDC	IC
224	43	1000	359	597	395	142	165
5.76‰ ± 0.38‰	1.11‰ ± 0.17‰	5.62‰ ± 0.18‰	2.02‰ ± 0.11‰	5.74‰ ± 0.23‰	3.80‰ ± 0.19‰	4.62‰ ± 0.39‰	5.36‰ ± 0.42‰
6.87‰ ± 0.42‰		7.64‰ ± 0.21‰		9.54‰ ± 0.30‰		9.98‰ ± 0.57‰	
SDC - IC Proportion		SDC - IC Proportion		SDC - IC Proportion		SDC - IC Proportion	
83.90%	16.10%	73.58%	26.42%	60.18%	39.82%	46.25%	53.75%

Table 2

Number of screen detected cancers (SDCs) and interval cancers (ICs) in the different BI-RADS density classes (I-IV). The data are also presented as percentage of the population in the BI-RADS category. Uncertainties indicated are standard errors of proportion.

were processed by the Volpara Density Technology software and resulting VDG scores were compared with density scores of the first and second readers. The intraclass correlation between VDG scores and scores of first readers was 0.66, which was substantially lower than the intraclass correlation between VDG scores and scores of second readers (0.82). Therefore, the density scores of second readers were retained for the study of screening parameters versus density.

In Table 2 the number of SDCs and ICs in the four BI-RADS density classes in the population of women participating in the 2009-2010 screening are presented. CDR values are of the same size in the first three density classes (5.62-5.76‰), but in the highest density class CDR is significantly lower (4.62‰) compared to the lower density classes (BI-RADS I-IV: p=0.04, BI-RADS II-IV: p=0.03, BI-RADS III-IV: p=0.02). Table 2 illustrates clearly the systematic increase of interval cancer rate with breast

density class. The percentage of cancers detected in the screening programme over the total number of cancers registered decreases from 84% for density class I to 46% for class IV.

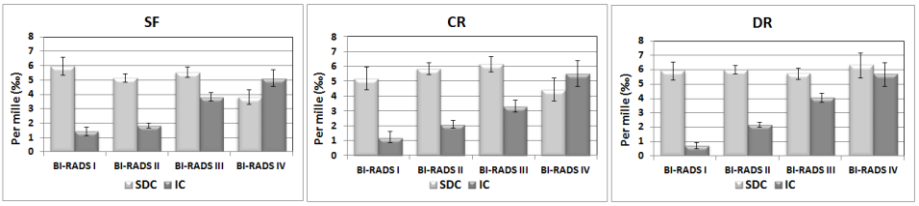

Figure 1

For each imaging modality (SF, CR, DR), screening detected cancer rate (SDC) and interval cancer rate are represented for the BI-RADS density classes. Error bars indicated in the graphs are standard errors of proportion. Statistical significance relative to DR is indicated by a black dot

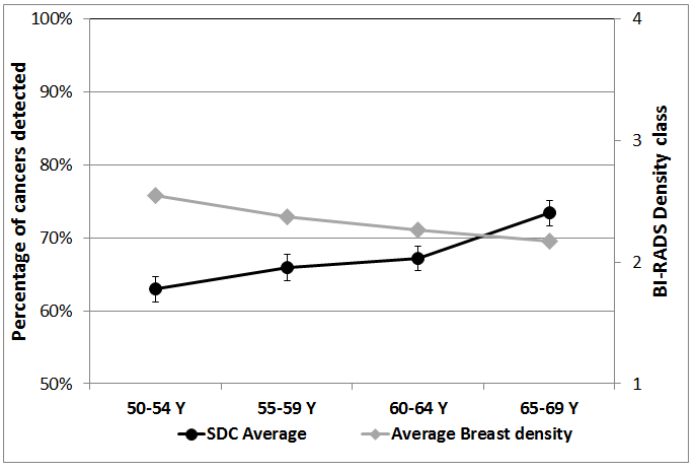

Figure 2

Percentage of breast cancers detected in the screening programme (left axis) and average BI-RADS breast density (right axis) versus five year age category. Error bars indicated in the graph are errors of proportions.

Categorization of the data, presented in Table 2, according to imaging modality allows a comparison of SDCs and ICs between SF, CR and DR for the different breast density classes, which is graphically displayed in Figure 1. For density classes I-III, the CDR is 5.00-6.16‰ irrespective of the modality. However, when comparing the CDR in the high density class IV to the lower density classes I, II and III, a significant reduction is noticed for SF (3.81‰) (p=0.01, p=0.04, p=0.01) and a non-significant reduction is observed for CR (4.44‰), while this reduction does not occur for DR (6.29‰). When comparing CDR for density class IV between the different imaging modalities, CDR is significantly larger for DR in comparison with SF (p=0.01), and larger yet not significant in comparison with CR (p=0.15). Regardless of modality, the interval cancer rate increases systematically as the density increases with no significant differences between modalities.

Breast density decreases with age in post-menopausal women. When women participating in the screening programme are categorized in 5 year categories, the mean breast density shifts to lower values with increasing age as shown in Figure 2. Calculating CDR and interval cancer rate for the different age groups shows a systematic increase of CDR with age while interval cancer rate is independent of age. This results in a higher percentage of SDCs with age, also illustrated in Figure 2.

	SF: 143293				CR: 74612				DR: 133627			
	BI-RADS I	BI-RADS II	BI-RADS III	BI-RADS IV	BI-RADS I	BI-RADS II	BI-RADS III	BI-RADS IV	BI-RADS I	BI-RADS II	BI-RADS III	BI-RADS IV
	14741	70337	42943	15228	8876	35727	22570	7430	15239	71821	38442	8109
Third readings	629	3004	2799	840	357	1484	1491	417	540	2908	2209	411
	4.27% ± 0.17%	4.27% ± 0.08%	6.52% ± 0.12%	5.52% ± 0.19%	4.02% ± 0.21%	4.15% ± 0.11%	6.61% ± 0.17%	5.61% ± 0.27%	3.54% ± 0.15%	4.05% ± 0.07%	5.75% ± 0.12%	5.07% ± 0.24%
False positives	413	1700	1736	461	240	837	880	215	396	1737	1399	219
	2.80% ± 0.14%	2.42% ± 0.06%	4.04% ± 0.10%	3.03% ± 0.14%	2.70% ± 0.17%	2.34% ± 0.08%	3.90% ± 0.13%	2.90% ± 0.19%	2.60% ± 0.13%	2.42% ± 0.06%	3.64% ± 0.10%	2.70% ± 0.18%

Table 3

Number of third readings and false positives in the different BI-RADS density classes (I-IV) for SF, CR and DR. For each modality, the data are also presented as percentage of women in each BI-RADS category. Uncertainties indicated are standard errors of proportion.

Other performance characteristics as a function of density and modality

A comparison of percentage of third readings and herewith correlated false positives between the three imaging modalities for the four BI-RADS breast density classes is presented in Table 3 and depicted graphically in Figure 3. For all

imaging modalities both performance parameters are worse for the high density classes III and IV compared to the low density classes I and II. When comparing imaging modalities, DR performs systematically better for the high density classes. The difference is statistically significant in the high density class III for third readings compared to both SF and CR (p=0.00, p=0.00) and for false positives compared to SF. Low statistical power hampers to reach statistical significance in differences between modalities for the BI-RADS IV class data.

Discussion

In former decennium, digital mammography was introduced in screening programmes. In a previous paper, the impact of the digitalisation on performance parameters and breast dose in the Flemish Breast Cancer Programme was reported [3].

In present paper we showed that in the screening period 2009-2010, CDR was significantly higher for DR (5.92‰) compared to SF (5.20‰) and higher, but not significantly compared to CR (5.72‰). Interval cancer incidence was independent of modality (2.71-2.76‰). Of all breast cancers occurring in women participating in the screening programme in this period, 67% were detected in the programme, while the remaining 33% are interval cancers. Several studies compared the diagnostic efficacy of digital mammography with SF mammography and these findings indicate that digital mammography led to better detection of breast lesions [21-29]. However, comparative studies of performance parameters of imaging modalities in organised screening programmes reported contradictory results [26,27,29-36]. In the Flemish Breast Cancer Screening programme both CR and DR are widely used as digital imaging modality. As shown in previous research, the use of CR mammographic devices results in a significantly higher mean glandular dose for the patient with even less image quality than with DR [3]. In present study CDR was lower for CR compared to DR but this difference was not statistically significant as observed in the study of Chiarelli et al. [37]. This is possibly related to the lower statistical power of the CR data in present study.

Breast density has been reported as an important factor influencing the sensitivity of mammography screening: women with dense breasts show a reduced mammographic sensitivity and higher rates of interval cancers [38-41]. Data of the present study (Table2) demonstrate a systematic strong increase of interval cancer incidence with increasing BI-RADS class (from 1.11‰ for class I to 5.36‰ for class IV), confirming conclusions of prior investigations [40,42]. On the other hand, Table 2 shows also that CDR remains constant for BI-RADS classes I to III (5.62‰-

5.74‰) but drops for the high density class IV (4.62‰). Combining these data leads to a strong decrease of the sensitivity of the mammography screening programme with increasing BI-RADS class to detect breast cancer: from 84% for class I to 46% for class IV. The observed lower sensitivity of the programme for BI-RADS IV is in line with the findings of a recent paper on this topic [43]. Generally breast density decreases gradually with age after menopause. This decrease in breast density with age involves a systematic increase of the sensitivity of the mammography screening programme to detect a present breast cancer with age: from 63% for the 50-54 year class to 74% for the 65-69 year class. The success of breast cancer screening increases with age.

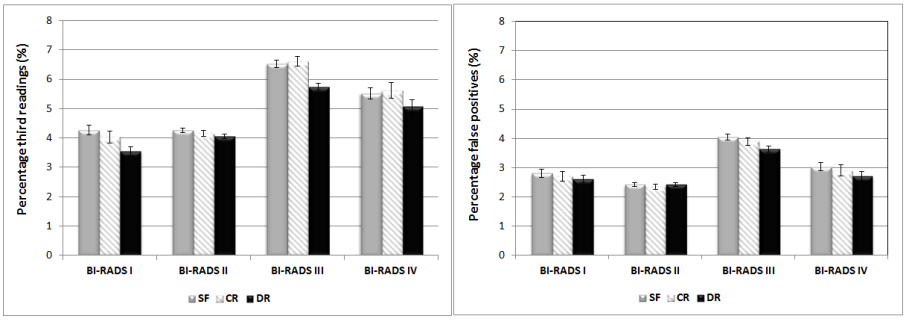

Figure 3

Comparison of percentage third readings (figure panel left) and false positives (figure panel right) between the different imaging modalities for the BI-RADS density classes. Error bars indicated in the graph are errors of proportions

Different papers indicate that DR mammography offers benefits specifically related to high breast density compared to SF, allowing better visualization of dense breast tissue [25,44] and higher screening performance [44-46]. In their review paper, Moussa et al. hypothesized that lesion detection for high mammographic breast density can be increased by using DR mammography [17]. Indeed in present study the CDR is higher for DR (6.29‰) compared to SF (3.81‰) (significantly) and to CR (4.44‰) for breast density class IV. DR is the only imaging modality for which CDR outweighs interval cancer rate for this breast density class. Also the number of third readings and false-positives for the higher breast density classes III and IV are in favour of DR: these parameters were systematically lower for DR compared to SF and CR in these groups .

Although the diagnostic accuracy in DR mammography outperforms conventional SF mammography and CR in high density breasts, present data show that only about 53% of cancer cases are detected in DR screening for breast density class IV. To

improve lesion detection in this group of extreme breast density, adjunctive screening beyond basic mammography techniques have been proposed in the literature. The STORM study [47] and an interim analysis of the Oslo trial are in favour for digital breast tomosynthesis as supplemental technique to 2D mammography for high density groups. On the other hand ultrasound has been proposed in the guidelines of the American College of Radiologists (ACR) [48].The association of higher breast density with breast cancer risk and lower detection sensitivity in mammography has also inspired authors to propose "Personalized" screening. The objectives of this risk-based screening is to reduce costs, recall rates and false-positive biopsies while maintaining the number of quality-adjusted life-years (QALYs) gained by the programme [49]. In the USA, breast density notification is becoming increasingly prevalent, mandating the reporting of breast density for women with dense breasts undergoing screening [50,51].

In conclusion, in present study a strong increase of interval cancer rate with breast density class independent of the imaging modality was observed, while for BI-RADS IV category a decrease of the CDR was noted for SF and CR but not for DR. DR is clearly superior to SF and CR for dense breasts with respect to CDR, third readings and false positives. To bring lesion detection in dense breasts to the same level as for low breast density categories, screening with an additional imaging technique adjunctive to DR mammography can be taken into consideration for this group.

Acknowledgements

We wish to thank all members of the working group research and the general working group Breast Cancer Screening of the Flemish Government for their contribution. Special thanks go to the colleagues of the physical-technical quality assurance of LUCMFR, VUB and Controlatom. We also express our gratitude to VolparaSolutions® for the use of the scientific version of VolparaDensity® software. Finally, last but not least, we wish to thank the Centres for Cancer Detection and the National Cancer Registry.

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ARTICLE 3

Tumour characteristics of screen-detected and interval cancers in the Flemish Breast Cancer Screening Programme: A mammographic breast density study

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Submitted to Plos One

Abstract

Objectives: By combining data of the Flemish Breast Cancer Screening Programme with tumour information available in the Belgian Cancer Registry (BCR), a retrospective study was performed of tumour characteristics of screen-detected cancers (SDC) (n=468) and interval cancers (IC) (n=515) of 983 women who participated in the screening in 2009-2010. Applying a logistic regression model adjusting for age, density and imaging modality shows statistically significant differences between SDC and IC ($p < .05$): in IC, a larger tumour size, more nodal invasion, more expression of oestrogen receptor (ER) and progesterone receptor (PR) negativity and more grade 3 tumours are found. A molecular subtype analysis also shows this significant difference between SDC and IC where less Luminal A (LumA) and more Luminal B/HER2-negative-like (LumB/HER2-) and triple-negative (TN) cancers are found in IC.

Methods and results: A comparison of tumour characteristics of different breast density classes shows that large tumours and nodal invasion are more, but not significantly, present in the high-breast-density class for both SDC and IC. On the contrary, aggressive grade 3 tumours are more frequently found in the low-breast-density classes with significance between BI-RADS I and IV classes for SDC. A significant difference between these classes in SDC is also observed for the LumA subtype but now with a higher presence in the high breast density class. For IC, the analysis shows a three times higher presence of TN tumours in low-density BI-RADS I class compared to the high-density BI-RADS IV class for IC.

Conclusions: In conclusion, present data demonstrate that IC have less favourable features compared to SDC. Furthermore, the analysis highlights that the difficult to treat TN tumours subtype is less present in high density breasts compared to low-density breasts. This supports changes in the protocols of a breast cancer screening programme towards a more individualised approach to improve sensitivity of the programme in order to increase survival of the breast cancer patients and reduce breast cancer mortality.

Introduction

Registry data show that Belgium has the highest breast cancer incidence rate in Europe [1]. A screening programme was started in Flanders in 2001 [2] which offers all women between the ages of 50 and 69 a completely reimbursed two-view mammogram every two years. Image modalities used are screen-film (SF) mammography and digital mammography, including computed radiography (CR) and direct radiography (DR). Digital mammography gradually replaced conventional SF with a resulting digital use only [3].

Some participants are diagnosed with breast cancer in the two-year interval after a negative screening result but before the next planned screening mammography. These are called interval cancers (IC). Breast cancers with a positive screening result but a negative work-up are also categorised as IC. As defined in European guidelines, IC include 'true' IC or occult cases, 'missed' cancers or false negatives, and cancers representing only minimal signs [4].

Breast cancer is a heterogeneous disease with a large variety of clinical, pathological and molecular features. Although gene-profiling models to predict outcomes are available, conventional tumour characteristics, such as expression of oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status are routinely investigated in breast cancer biopsies and/or resection pieces for therapeutic decision-making [5]. Based on hormone/HER2 receptors and tumour proliferation markers, breast cancers are categorised in molecular subtypes which have a strong prognostic value [6].

The majority of breast cancers detected in screening exhibit favourable tumour characteristics, such as small tumour size, negative nodal invasion and oestrogen/progesterone positivity [7, 8]. On the other hand, IC tend to be more aggressive than screen-detected cancers (SDC) [9] and are more likely to have less favourable molecular features [10-13]. Some studies even report a higher proportion of triple-negative (TN) cancers among IC [10, 14]. These tumours lack the benefit of specific antihormonal therapy and are associated with an aggressive behaviour pattern and poor prognosis [15].

Mammographic breast density reflects the proportion radiodense fibroglandular tissue in the mammogram which is scored and categorised in BI-RADS breast density classes [16]. Women with a high breast density are considered to have a four to six times enhanced risk for breast cancer compared to women with completely fatty breasts [17-20]. High-density breasts are also associated with a decreased sensitivity of cancer detection in screening

programmes [21-24]. Consequently, women with dense breasts are more likely to be diagnosed with an interval cancer [22, 25, 26] but the role of breast density has not yet been completely elucidated [25, 27]. A masking effect related to hiding tumours by fibroglandular tissue as well as a biological effect related to tumour growth has been proposed [27, 28]. Previous research showed a strong increase of IC rate with breast density [29].

Because breast density influences both risk and detection of breast cancer as well as the likelihood of developing certain pathological subtypes [30, 31], studying tumour characteristics in breast density classes of SDC and IC is of great interest. A Swedish study concluded that when comparing tumour characteristics in women of the lowest- and highest-breast-density groups, IC in women with low mammographic density have a more aggressive phenotype [32].

The aim of the present study is to compare tumour characteristics and molecular subtypes of IC versus SDC in a cohort of women who participated in the Flemish Breast Cancer Screening Programme and to assess the association of tumour aggressiveness with the breast density classes in both groups.

Materials and methods

Study set up

This study concerns a retrospective analysis of characteristics of SDC and IC based on a combination of the dataset from the Center for Cancer Detection, who organises the Flemish Breast Cancer Screening Programme, and information available at the Belgian Cancer Registry (BCR).

In this screening programme, all eligible women are invited for a screening mammography, except women with bilateral mastectomy or women diagnosed with breast cancer in the past ten years as well as women with a mammographic examination in the past two years. Images are interpreted by two independent radiologists qualified for mammography evaluation. The first radiologist is from the unit where the mammograms are taken. Afterwards the images are sent to one of five departments of the Center for Cancer Detection where another radiologist, recognised as second reader, performs an independent reading, completely blind for the outcome of the first radiologist. All screening data associated with each participating woman are collected into the centralised database 'Heracles'.

BCR is a national population-based cancer registry collecting tumour characteristics of all new cancer diagnoses. These data are provided by oncological care programmes and laboratories for anatomical pathology as stated in the specific cancer registration law [33]. BCR maps out the nature and extent of cancer in Belgium, supports and

evaluates Belgian cancer screening programmes and collaborates in different research projects.

The combination of Heracles with the structured BCR database allows to complete screening data with information on SDC and IC (fig 1). Linkage on a regular basis of these databases was authorised by the Sector Committee of Social Security and Health within the framework of the Flemish Breast Cancer Screening Programme and allows SDC and IC to be identified and characterised. Participants are aware that their personal data are protected, collected and processed in the framework of quality assurance of the programme and coded when processed for statistical and scientific purposes, this by signature of an informed consent [34].

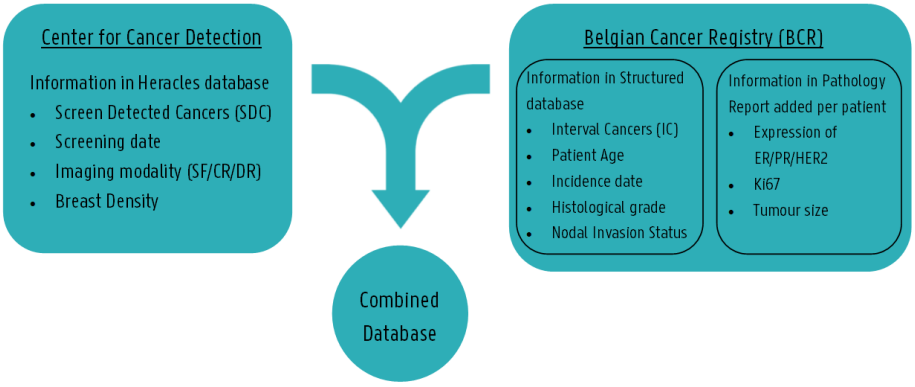

Figure 1

This is a schematic presentation of the combined database used for the study by linkage of data from the Heracles and BCR databases, complemented with information from individual pathology reports.

Breast density

Breast density is scored for each patient by all radiologists involved according to the four-category BI-RADS system developed by the American College of Radiology: BI-RADS I category comprises breasts with less than 25% glandular tissue, BI-RADS II 25-50%, BI-RADS III 51-75% and BI-RADS IV refers to a class with extremely dense breasts with more than 75% glandular tissue [16]. The currently used 5th edition BI-RADS classification was not applied as the present study handles data from 2009 to 2010 when the previous BI-RADS classification version was applied.

Former research showed an intraclass correlation of 0.82 between breast density estimations of second readers and quantitative volumetric density measurements applying dedicated software (Volpara®SolutionsTM) [29]. In contrast, this intraclass correlation was substantially lower for first readers (0.61). Based on these correlation data and because of more steadfast decision-making, only data of breast density from second readers are retained for present study.

Population

Women who participated in the screening programme from January 2009 to December 2010 and who were diagnosed with an invasive breast cancer through screening in the period up to 24 months post negative screening were included. The two-year period corresponds to one screening round so every woman is only present once in the study. All three imaging modalities, SF(41%), CR(21%) and DR(38%), were still adequately used in the programme.

	SCREEN DETECTED CANCERS (SDC)	INTERVAL CANCERS (IC)
BI-RADS I	107	33
BI-RADS II	120	162
BI-RADS III	120	163
BI-RADS IV	121	157
TOTAL	**468**	**515**

Table 1

The number of patients in the different breast density categories with a screen detected or an interval cancer included in present study.

The study was set up this way that the number of women in four breast density classes was roughly the same to study the effect of breast density on different tumour characteristics. All women in the extreme BI-RADS I and IV categories, representing only 20% of cancer cases, were included. For BI-RADS category II and III, a similar number of cancer cases as for density IV category was selected at random (table 1). Including all cancer cases of BI-RADS II and III was, due to the large amount of cancer cases, not possible. This because practical issues and its time-consuming character. However, three pilot studies of partial data were conducted with random cases before implementing the final study and all showed similar results. Applying this

procedure for SDC and IC resulted in a total population of 983 invasive breast cancer patients. Ductal carcinoma in situ cases were not considered. Out of 515 IC, 184 (36%) patients were diagnosed in the first year after the last screening and 328 (64%) in the second year. An analysis showed that for the IC no relation exist between last screening-diagnosis time and breast density.

Tumour characteristics

In the combined database, mammography date, imaging modality and breast density originated from Heracles. Information on patient age, nodal invasion, histological grading and incidence date were deduced directly from the BCR database as these variables are stored systematically in this database. Information of tumour size, expression of ER, PR, HER2 as well as Ki67 positivity, was retrieved from pathology reports of a tumour biopsy and/or resection specimen added per patient to the standardised BCR database (fig 1). When findings from biopsy and resection did not match, (in 0.9%, 3.4% and 2.6% of patients for respectively ER-, PR- and HER2-receptor status), they were not included in the analysis. According to St. Gallen International Expert Consensus recommendation 2011 [35], five molecular subtypes of invasive breast cancer can be differentiated by expression of their tumour markers. As information on Ki67 positivity was only available for 41.8% of patients, histological grade (available in 99.6% of patients) was used to differentiate between LumA and LumB/HER2- molecular subtypes following Brouckaert et al [36] (table 2).

MOLECULAR SUBTYPE	ER AND/OR PR	HER2	GRADE
Luminal A-like *(LumA)*	+	-	1-2
Luminal B/HER2 negative-like *(LumB/HER2-)*	+	-	3
Luminal B/HER2 positive-like *(LumB/HER2+)*	+	+	Any
HER2-type *(HER2)*	Both -	+	Any
Triple Negative *(TN)*	Both -	-	Any

Table 2

Criteria used in present work to categorize breast tumours into molecular subtypes

Statistical analysis

Statistical calculations were performed using SPSS Statistics25 (IBMcorp, USA). For analysing the risk of having a large tumour, nodal invasion, ER-/PR-negative cells, HER2 positivity, grade 3 tumours and TN tumours, briefly all binary endpoints between SDC and IC, a binomial logistic regression was used. This analysis was adjusted for breast density (BI-RADS I-IV), screening modality (SF vs CR vs DR) and patient age.

For each group separately (SDC vs IC) a multinomial logistic regression was applied with tumour characteristics (tumour size, nodal invasion, ER negativity,...) as outcome variable and breast density as a categorical predictor, corrected for patient age and image modality (SF vs CR vs DR).

In order to test significance, a p value of .05 was adopted. For differences in tumour size, a Mann-Whitney U test was applied.

Results

Comparison of tumour characteristics between SDC and IC

Tumour characteristics of SDC and IC are presented in Table 3. This table shows important differences between IC and SDC applying a binary logistic regression model adjusting for age, density and imaging modality. Odds ratios are given.

PARAMETER	SDC N = 468	IC N = 515	ODDS RATIO (95% CI)
Tumour size (>20mm)	(102/447) 22.8% ± 2.0%	(220/469) 46.9% ± 2.3%	3.05 (2.24-4.16)*
Nodal invasion	(114/442) 25.8% ± 2.1%	(184/472) 39.0% ± 2.2%	1.76 (1.30-2.40)*
ER negative	(50/414) 12.1% ± 1.6%	(78/468) 16.7% ± 1.7%	1.72 (1.12-2.65)*
PR negative	(80/401) 20.0% ± 2.0%	(115/455) 25.3% ± 2.0%	1.50 (1.05-2.16)*
HER2 positive	(48/390) 12.3% ± 1.7%	(68/453) 15.0% ± 1.7%	1.36 (0.87-2.12)
Grade 3	(123/443) 27.8% ± 2.1%	(210/477) 44.0% ± 2.3%	2.51 (1.85-3.41)*
Luminal A	(240/373) 64.3% ± 2.5%	(213/419) 50.8% ± 2.4%	0.48 (0.35-0.65)*
TN	(22/373) 5.9% ± 1.2%	(49/419) 11.7% ± 1.6%	2.58 (1.44-4.61)*

Table 3

Tumour characteristics of SDC and IC. Data are presented as fractions with missing values not included. The percentages are given with standard error of proportions as uncertainties. Odds ratio for IC with SDC as reference

is also given with a 95% confidence interval. Parameters with a statistical significance between SDC and IC are indicated with an * symbol.

The present study shows that the odds ratio of having a tumour larger than 20 mm is three times larger comparing IC to SDC. For present analysis, the tumour size is dichotomised (≤ and >20 mm) but the average tumour size in SDC is 16 mm (SD ±10 mm) which is also significantly smaller than the average tumour size of IC which is 23 mm (SD ±15 mm). It is also significantly more likely to have nodal invasion, a grade 3 tumour or ER-/PR-negative phenotype, which are all characteristics of more aggressive tumours, in IC than in SDC. The probability of having a Luminal A cancer is half as likely in IC than in SDC. On the other hand, the odds ratio of having a TN tumour in IC compared to SDC is 2.5. The conclusions on the difference in tumour characteristics between SDC and IC cases presented in Table 3 hold also when excluding the first round screening participants resulting in clean incident screening data.

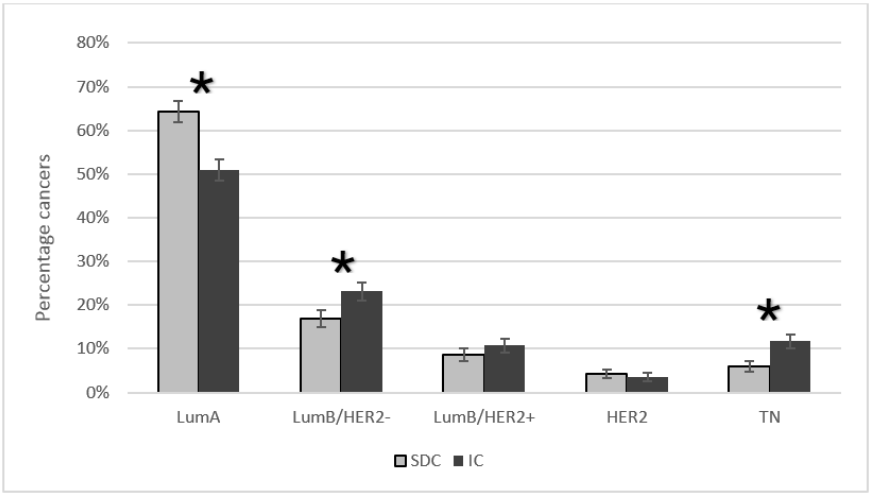

Figure 2

LumA, LumB/HER2-, LumB/HER2+, HER2 type, TN. Data is presented as percentages with standard error of proportions as uncertainties. A statistical significant difference is indicated with a *symbol

Figure 2 presents the distributions of SDC and IC with respect to molecular subtypes. This shows that Luminal A cancers occur significantly more in SDC in comparison

with IC. On the contrary, TN cancers are significantly more represented in IC. The same effect is visible for LumB/HER2- which are also more represented in IC with odds ratio 1.72 (95% CI 1.18-2.51). For LumB/HER2+ and HER2+ groups, differences between SDC and IC are not significant.

Effect of density on tumour characteristics in SDC and IC

Table 4 shows the effect of density on different tumour characteristics in SDC and IC. A multinomial logistic regression model with density I as reference, adjusting for age and imaging modality, was applied.

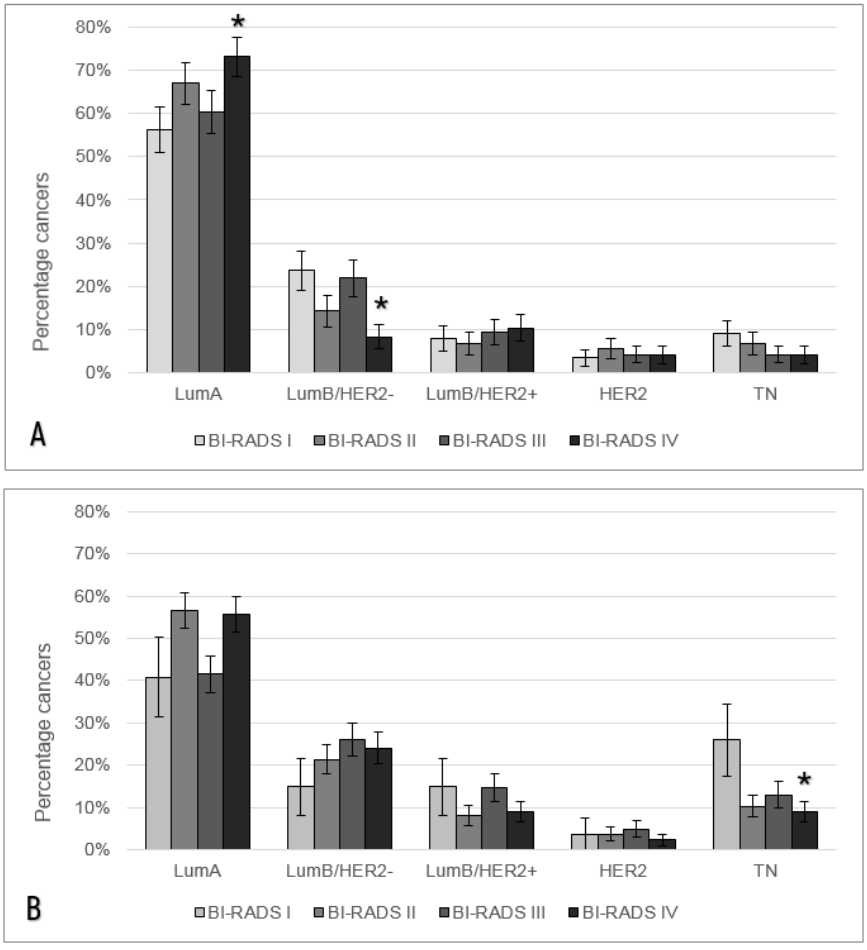

Figure 3

Distributions of (A) SDC and (B) IC with respect to molecular subtypes as a function of breast density. Data is presented as percentages with uncertainties indicated standard error of proportions. Parameters in BI-RADS classes with statistical significant differences compared to BI-RADS I are indicated with a * symbol.

Breast cancers with large tumour size (>20 mm) and nodal invasion are more frequently found in higher-density breasts compared to low density I reference group, and this for SDC as well as IC. However, resulting odds ratios are not significant. On the contrary, ER- and PR-negative phenotypes are represented less in higher-density categories for both SDC and IC. The difference between density I and IV for ER negativity reaches almost the significance limit in SDC. The aggressive grade 3 tumours are also more represented in the lower breast densities with for SDC grade 3 tumours 60% less likely in the high density BIRADS IV group compared to the low density reference group resulting in statistical significance. For HER2+ breast cancers, no significant differences were found between high- and low-density breasts. Tumour characteristics versus breast density of incidence screening obtained by exclusion of the first round participants in the dataset show the same tendencies.

The results of the analysis of molecular subtypes in different breast density groups in SDC and IC are depicted in Figure 3. In SDC, the presence of LumA subtype increases with breast density class, with an odds-ratio of 2 when comparing BIRADS IV with I resulting in a statistically significance. For LumB/HER2- subtype, this significant trend is reversed. For IC, trends in LumA and LumB/HER2- breast density data are less clear, but LumB/HER2- subtype suggests an increase with breast density class. For LumB/HER2+ and HER2+ subtypes, no systematic variation with breast density is observed for SDC or IC.

The most striking observation of molecular subtypes in SDC and IC as a function of breast density as depicted in Figure 3 is the high presence of TN tumours for low-breast-density class I compared to higher-density classes. This is especially pronounced for IC where the TN subtype is three times less likely in BI-RADS IV compared to I resulting in statistical significance.

Adjustments for imaging modality was made in these logistic regression models. However, no significant difference with respect to image modality was observed.

PARAMETER		SDC N = 468	ODDS RATIO (95% CI)	IC N = 515	ODDS RATIO (95% CI)
Tumour size (>20mm)	**BI-RADS I**	(20/103) 19.4% ± 3.9%		(13/30) 43.3% ± 9.0%	
	BI-RADS II	(27/112) 24.1% ± 4.0%	1.35 (0.68-2.70)	(66/145) 45.5% ± 4.1%	1.12 (0.48-2.60)
	BI-RADS III	(26/118) 22.0% ± 3.8%	1.29 (0.64-2.58)	(63/147) 42.9% ± 4.1%	1.10 (0.47-2.55)
	BI-RADS IV	(29/114) 25.4% ± 4.1%	1.65 (0.81-3.38)	(78/147) 53.1% ± 4.1%	1.70 (0.73-3.96)
Nodal Invasion	**BI-RADS I**	(22/103) 21.4% ± 4.0%		(8/28) 28.6% ± 8.5%	
	BI-RADS II	(28/111) 25.2% ± 4.1%	0.98 (0.50-1.92)	(58/147) 39.5% ± 4.0%	2.17 (0.81-5.80)
	BI-RADS III	(29/115) 25.2% ± 4.0%	1.06 (0.55-2.04)	(61/148) 41.2% ± 4.0%	2.32 (0.87-6.20)
	BI-RADS IV	(35/113) 31.0% ± 4.3%	1.46 (0.75-2.84)	(57/149) 38.3% ± 4.0%	2.03 (0.76-5.44)
ER neg	**BI-RADS I**	(16/97) 16.5% ± 3.8%		(8/31) 25.8% ± 7.9%	
	BI-RADS II	(13/103) 12.6% ± 3.3%	0.62 (0.25-1.54)	(22/146) 15.1% ± 3.0%	0.63 (0.22-1.79)
	BI-RADS III	(12/105) 11.4% ± 3.1%	0.60 (0.24-1.48)	(28/142) 19.7% ± 3.3%	0.80 (0.29-2.24)
	BI-RADS IV	(9/109) 8.3% ± 2.6%	0.38 (0.14-1.02)	(20/149) 13.4% ± 2.8%	0.46 (0.16-1.34)
PR neg	**BI-RADS I**	(25/98) 25.5% ± 4.4%		(9/30) 30.0% ± 8.4%	
	BI-RADS II	(17/98) 17.3% ± 3.8%	0.61 (0.29-1.32)	(34/145) 23.4% ± 3.5%	0.94 (0.36-2.49)
	BI-RADS III	(18/99) 18.2% ± 3.9%	0.74 (0.35-1.56)	(41/136) 30.1% ± 3.9%	1.37 (0.52-3.60)
	BI-RADS IV	(20/106) 18.9% ± 3.8%	0.70 (0.33-1.48)	(31/144) 21.5% ± 3.4%	0.78 (0.29-2.07)

HER2 pos	BI-RADS I	(10/95) 10.5% ± 3.1%		(6/30) 20.0% ± 7.3%	
	BI-RADS II	(11/94) 11.7% ± 3.3%	0.96 (0.34-2.73)	(16/141) 11.3% ± 2.7%	0.50 (0.16-1.56)
	BI-RADS III	(13/98) 13.3% ± 3.4%	1.23 (0.46-3.30)	(28/138) 20.3% ± 3.4%	0.88 (0.30-2.62)
	BI-RADS IV	(14/103) 13.6% ± 3.4%	1.22 (0.45-3.32)	(18/144) 12.5% ± 2.8%	0.52 (0.17-1.61)
Grade 3	BI-RADS I	(37/99) 37.4% ± 4.9%		(17/30) 56.7% ± 9.0%	
	BI-RADS II	(30/115) 26.1% ± 4.1%	0.56 (0.30-1.06)	(64/154) 41.6% ± 4.0%	0.48 (0.20-1.11)
	BI-RADS III	(34/116) 29.3% ± 4.2%	0.70 (0.38-1.30)	(66/146) 45.2% ± 4.1%	0.56 (0.24-1.31)
	BI-RADS IV	(22/113) 19.5% ± 3.7%	0.41 (0.20-0.80)*	(63/147) 42.9% ± 4.1%	0.52 (0.22-1.21)
Luminal A	BI-RADS I	(50/89) 56.2% ± 5.3%		(11/27) 40.7% ± 9.5%	
	BI-RADS II	(61/91) 67.0% ± 4.9%	1.68 (0.87-3.26)	(77/136) 56.6% ± 4.2%	1.65 (0.68-3.99)
	BI-RADS III	(58/96) 60.4% ± 5.0%	1.23 (0.65-2.32)	(51/123) 41.5% ± 4.4%	0.95 (0.39-2.33)
	BI-RADS IV	(71/97) 73.2% ± 4.5%	2.34 (1.17-4.71)*	(74/133) 55.6% ± 4.3%	1.58 (0.66-3.82)
TN	BI-RADS I	(8/89) 9.0% ± 3.0%		(7/27) 25.9% ± 8.4%	
	BI-RADS II	(6/91) 6.6% ± 2.6%	0.59 (0.18-1.94)	(14/136) 10.3% ± 2.6%	0.418 (0.13-1.34)
	BI-RADS III	(4/96) 4.2% ± 2.0%	0.45 (0.12-1.62)	(16/123) 13.0% ± 3.0%	0.38 (0.12-1.21)
	BI-RADS IV	(4/97) 4.1% ± 2.0%	0.42 (0.11-1.59)	(12/133) 9.0% ± 2.5%	0.27 (0.08-0.91)*

Table 4

Tumour characteristics of SDC and IC as a function of breast density. Data are presented as fractions with missing values not included. The percentages are given with standard error of proportions as uncertainties. Odds ratio within each breast density class with breast density class I as reference is also given with a 95% confidence

interval. Parameters with a statistical significance between the considered BI-RADS class and the reference class I are indicated with an * symbol.

Discussion

In screening, IC are a representative for the sensitivity of the programme. Investigation of IC may point to changes in protocols and imaging techniques leading to an improvement of a screening programme. In the Flemish Breast Cancer Screening Programme, 67% of breast cancers are SDC and 33% are IC [29]. Furthermore, interval cancer rate increases gradually with breast density from 1.11 ‰ for BI-RADS I to 5.36‰ for BI-RADS IV. The link between interval cancer rate and breast density may be related to masking effect and/or differences in tumour characteristics [27, 28, 37]. To elucidate this, tumour characteristics and biomarker profile of SDC and IC were studied as functions of breast density. As the final goal of screening programmes is to reduce breast cancer mortality, the collected data can also be of value to investigate if changes in the programme may represent a reduction of IC.

Our data show that IC have worse tumour prognostic features than SDC. IC have a less favourable biomarker profile with a lower frequency of hormone receptor positive cancers and a higher frequency of TN cancers. The frequency of HER2-positive tumours is also higher in IC. These findings are consistent with other breast cancer screening programmes [9, 11-14, 38-40]. A comparison of molecular subtypes shows a significantly lower percentage of LumA tumours and a significantly higher percentage of TN tumours in IC [14, 41]. As LumA tumours have the best five-year survival (e.g. 92% [6]) and TN the worst (e.g. 69% [6]), we may expect that biomarker differences will also result in worse tumour survival in IC. This is confirmed in studies of Eriksson et al [42] and Domingo et al [41] who reported a significantly higher five-year cancer-specific survival of SDC versus IC. Based on differences in biomarker profiles and these survival data, IC contain a subgroup of breast cancers with rapid growth and high aggressiveness. This conclusion holds also to symptom-detected cancers outside screening programmes [43].

Analysis of tumour characteristics versus breast density shows a larger tumour size for BI-RADS IV breasts compared to BI-RADS I breasts for both SDC and IC but the difference is not statistically significant. This larger tumour size can be attributed to a masking effect as it is well documented that high breast density is associated with a larger contribution of occult IC [37] so the increase of the masking effect will involve a delay in diagnosis. Eriksson et al [42]

observed a similar trend in tumour size with breast density as in present work but the breast density was divided in non-dense (<25%) and dense (≥25%) classes. The trend of lymph node involvement increasing with breast density can be explained in the same way by delay of diagnosis. On the other hand, grade, hormone receptor status and other histopathological tumour characteristics indicate a worse prognosis in low-density breasts for both IC and SDC. A similar conclusion of a more aggressive phenotype in IC for low-density breasts based on receptor status and grade was drawn by Holm et al [32].

Analysis of molecular subtype distributions versus breast density revealed a higher percentage of TN phenotype in BI-RADS I breasts as well in SDC as IC. However, this effect is only significant in IC. In IC, TN tumours amount to over 25% in low-density breasts which differs significantly from 9% in high-density breasts. A similar dependence of TN phenotype on breast density can be found in Spanish screening data [41]. They report TN percentages of 11.7% and 5.7% for <25%- and >75%-density classes in SDC and 28.7% and 14.3% in true IC. Also, data of Holm et al support the prevalence of TN phenotype in non-dense breasts in IC [32]. For patients with TN tumours, an effective and specific antihormonal therapy is lacking, resulting in poor survival [6].

Strengths of the present study are the completeness of information, resulting from a combination of screening data and clinical-pathological information and statistical analysis of tumour characteristics with breast density. This study also has limitations. First, no radiological review of IC was made with subdivision in true, minimal signs and missed tumours. A second limitation is that Ki67-positivity information was only available in 42% of cancer cases. Third, some important variables associated with breast density, such as body mass index, age at menarche and childbirth are not collected in screening programmes and could not be included in the statistical analysis.

Present data show that IC in the highest-breast-density class, which have the highest interval cancer rate in the Flemish Breast Cancer Screening Programme, are less likely to develop a TN tumour, which have a poor prognosis, compared to low-density breasts. The Luminal A tumours, with the best five-year survival, are also more frequently found in the highest-breast-density class compared to low-density breasts. This observation supports changes in breast cancer screening to more individualised protocols to bring lesion detection in dense breasts to the same level as for low-breast-density categories. This involves e.g. stratification of women into different breast screening strategies as part of a more personalised breast screening

programme as in the MyPeBS project funded by the Horizon 2020 programme of the European Commission [44]. In the clinical trial protocol of this project, breast ultrasound and automated breast ultrasound are additional screening techniques for women in the high-density breast group. In the future, digital breast tomosynthesis may be a valuable alternative technique for this additional screening as an overall increase of cancer detection and reduction of recall rates in screening trials are reported [45-48]. However, large scale trials devoted to the study of all practical aspects (interpretation time, projections, dose) have to confirm the added value of DBT as a secondary technique, especially in high-density-breast screening before implementation.

Conclusions

Present research confirms a significant difference of tumour characteristics in SDC and IC. Although IC express more characteristics that have properties of aggressive tumours, IC in high-density breasts are less likely to be of the TN tumour subtype compared to low-density breasts. This supports changes in screening protocols to improve sensitivity of the screening programme in order to increase survival of the breast cancer patients.

Acknowledgments

We wish to thank all members of the research working group and the general working group of the Breast Cancer Screening of the Flemish Government for their contribution. Special thanks go to the colleagues of the physical-technical quality assurance of LUCMFR, VUB and Controlatom. Finally, we wish to thank the Center for Cancer Detection and BCR.

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PART

General Discussion

III

As mammography screening reduces breast cancer mortality, increases chance of complete recovery and less aggressive treatment, a Breast Cancer Screening Programme was started in Flanders. Originally, screen-film mammographic devices were used in the programme and digital mammographic devices gradually replaced these. In our research, the impact of the digitalization on the performance parameters of the screening programme and the breast dose is investigated. Also the effect of the different imaging techniques on breast dose were examined. As breast density is recognized as a risk factor for breast cancer, we also investigated whether DR mammographic devices perform better than CR and SFM, especially in dense breast. This by analysing the interval cancers (ICs) and screen detected cancers (SDCs) within the different BI-RADS breast density classes for the various imaging modalities. ICs tend to be more aggressive and have less favourable molecular features than SDC. However, breast density influences both risk and detection of breast cancer. Therefore, we investigated the tumour characteristics and molecular subtypes of interval cancers and screen detected cancers within the different breast density classes.

1 DENSITY SCORING

During this decade, the standard in the Flemish Breast Cancer screening programme moved from screen-film mammography towards digital mammography and especially to direct radiography (DR) mammographic devices. It is reported that breast density has a different appearance between analogue and digital mammograms and this presents a first challenge in scoring breast density for a radiologist in mammography screening programmes [1, 2]. After a digital switch, breast density is assessed differently due to another visual image. Digitalisation to DR resulted in half the percentage of women with BI-RADS density class IV (the highest density class). This phenomenon is also present for the transition from SFM to CR, but the effect is less pronounced. A breast density shift with time in a control group, without a change of mammography technique, was not found so a time related effect could be excluded [3]. In the period considered in this paper, all image modalities were frequently applied in mammographic units.

While the visual method of density assessment, which is used in the Flemish Breast Cancer Screening programme, is well-established, it presents also limitations. This method relies on human judgement and is thus inherently subjective. Individual radiologists show high consistency determined by intra-reader agreement. This intra-reader agreement varies with a weighted kappa value from 0.82 to 0.87 in several density reading studies. Based on the Landis and Koch guidelines, the intra-reader reliability could thus be seen as 'very good' [4-7]. However, recent studies have highlighted a large inter-reader variability (with a weighted kappa value between 0.54 and 0.57) and demonstrated that density assessment can be highly dependent on the reader [5, 8]. Nonetheless, it is also demonstrated that training has a positive impact on the accuracy of breast density assessment by radiologists [9]. Senologists participating in the screening in Flanders are well trained, as well theoretically as practically, in protocoling mammographic images. Since the Flemish Breast Cancer Screening Programme is a decentralised programme, breast density is scored by the radiologist of the mammographic unit where the mammogram is taken (reader 1) and subsequently also by the radiologist in the Centre for Cancer Detection (reader 2). In 2010, 186 radiologists were recognised as first reader, 32 as

second reader. In 2016, the group of first readers increased to 409 whereas the total of second readers remained stable with 36 radiologists in total. The standard for a second reader is scoring 5000 mammograms per 2 years. However, there is no standard for first readers and the number of protocoled images is highly variable and ranged from 0 to 800 per 2 year in 2011 [10, 11]. Due to the large variation in the number of protocolled mammographic images between first readers, density assessment by radiologists first readers is less reliable than the assessment by radiologists second readers. This effect was also found when density scores from both readers were compared with quantitative volumetric density measurements applying dedicated software (Volpara®Solutions™). An intraclass correlation of 0.66 for first readers was obtained, whereas related to the high throughput and therefore steadfast decision-making, a satisfactory value of an intraclass correlation of 0.82 for second readers was obtained [12]. Based on this information the breast density assessment performed by the second reader is withheld as breast density in present research.

Due to the subjective character of density assessment by radiologists, several automated breast density programmes have been developed to provide objective measures of mammographic breast density. In the Flemish breast cancer screening programme, it is nor forbidden, nor obliged to apply a density programme. However, also some considerations have to be taken into account when using quantitative density assessment programmes.

The different fully automated breast density methods developed vary widely in their approaches how differences in fibroglandular tissue in mammograms are being used for breast density assessment. Programmes based on the area of dense tissue in mammograms work with images from SF, CR and DR but they cannot determine the depth of the dense tissue or overlapping regions of dense tissue in the breast (e.g. LIBRA developed at university of Pennsylvania [13]). Volumetric approaches on the other hand provide a better estimate as they take the actual depth of fibroglandular tissue into consideration as well as overlapping regions. An example of a fully automated volumetric breast density assessment programme is Volpara®Solutions™.

DR also produces two types of images: a raw image ("for processing") with grey-level intensity values proportional to the x-ray attenuation through the breast, and a vendor-processed image ("for presentation") with increased tissue contrast and lesion borders, which is used for radiological interpretations and diagnostic evaluation (Figure 1.1)

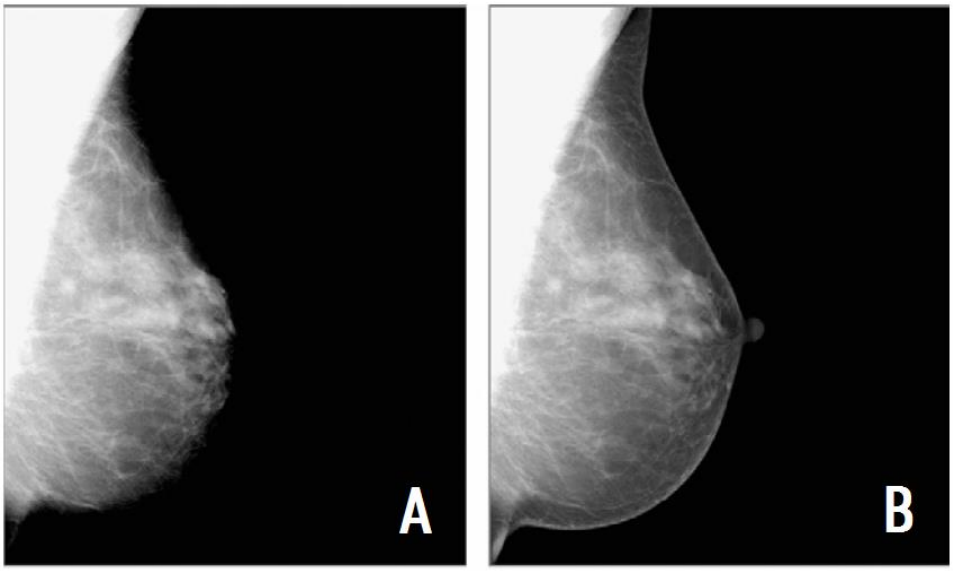

Figure 1.1

Example of a raw "for-processing" (A) and a processed "for-presentation" (B) mammogram of a mediolateral-oblique examination from a 53-year old woman. In the "for-presentation" image, contrast is enhanced and the skin line is more pronounced compared to the "for-processing" digital mammogram [14].

When using automatic density scoring programmes, it has been recommended that breast density should be assessed using the raw images because of its proportional relationship between grey-level intensity and the underlying tissue x–ray attenuation [15]. However, the majority of clinical density assessments performed by radiologists is primarily performed on the vendor-processed images because these are the ones used for clinical interpretation and archived by most clinical centres [16].

As breast density is an essential factor in the risk of developing breast cancer and the effectiveness (sensitivity and specificity) of a mammography breast cancer

screening programme, there will be a growing demand for a reliable and consistent method of assessing density in the Flemish Breast Cancer Screening Programme, guiding the subjective density assessment by the second readers. Further research to evaluate the most appropriate automated density programme for the Flemish screening programme needs to be performed.

Mammographic breast density does not remain steady during a woman's lifetime. Breasts undergo an age-related involution that has an inverse association with density [17]. Menopause, in particular, is correlated with a 2.4% – 6.8% decrease in percent area mammographic density [18, 19]. Initial breast density at the start of a measurement period also affects the overall density change: high density breasts undergo a greater total decline of density with age compared to those with lower baseline density [20].

Also dietary differences influence breast density. Women with a higher adherence on western diet patterns had higher breast density compared to women with a Mediterranean diet [21]. In addition, alcohol intake can also modulate mammographic density: women consuming more than seven alcoholic drinks per week have a 17% higher mammographic density, measured by the area-based density programme Cumulus, compared to non-drinkers [22]. However, evaluation whether decreasing alcohol intake is associated with a reduction in mammographic density still needs to be performed. This suggests that dietary factors could have an implication in the risk of breast cancer by contributing to the increase of mammographic density. Not only the dietary differences between women are substantial, also a diet change can affect breast density in a particular women. A sudden increase or decrease of body weight influences also the percentage of dense tissue in the breast [19].

Extrinsic hormones and medications also affect density in several ways. Hormone replacement therapy (HRT), used to relieve menopausal symptoms, particularly combination HRT that uses estrogen and progesterone, leads to increased density [23-27]. It is shown that combination HRT is associated with increased breast cancer

risk and this risk is reflected by the increased breast density [28]. In contrast, intake of tamoxifen, an estrogen antagonist, decreases breast density [29, 30].

Apart from these factors changing during life, breast density is also shown to be heritable [31, 32]. This highlights the importance of genetic components in breast density. However, it is still unknown whether this heritable effect is influenced by non-heritable environment factors, as well as factors related to behaviour [32].

In addition, race also influences breast density. In a large study including Asian, Caucasian, African American and "other ethnicities", the highest breast density was seen in Asian women and the lowest in African American [33].

Race and heredity may be the driving factors for native breast density, however, the differences in breast cancer risks in the different racial groups are not yet fully understood [33].

2 INTERVAL CANCERS

Interval cancers play a major role in a cancer screening programme. The interval cancer rate is an indicator to evaluate the effectiveness of a screening programme but it can also be used as an audit tool to improve screening quality. The rate of interval cancers in mammography breast cancer screening is related to factors inherent to mammography such as the mammography equipment, the quality of radiographic positioning and the interpretative skills of the radiologist [34]. The proportion interval cancers in Flanders is 33% [12]. The occurrence is associated with the organization of the screening programme [35-37]. According to several studies, the ICs are lower for annual (14.7%) and higher for triennial (32-38%) screening intervals [38]. Follow-up of the interval cancer rate throughout the years is a good indicator to provide information on the impact of screening, which can be used to provide a long-term balance between benefits and harms [39].

In case of a high interval cancer rate, a revision of the quality of the programme is required. However, interval cancers consist out of a combination of true interval cancers, false negatives (missed) and minimal signs. The category "minimal signs" consists of cancers that show detectable but non-specific signs on the prior screening mammography. A total elimination of the interval cancers is impossible due to the presence of fast growing occult tumours, the true interval cancers. Categorization of interval cancers in the three subtypes can only be achieved after a radiological review of both screening and diagnostic mammograms. In the Flanders Breast Cancer Screening programme, this categorization has not yet been performed on a large scale. However, other mammography screening programmes reported a range between 13 and 35% of breast cancers in the screening population to be false-negative cancers (missed). The vast majority of interval cancers were not missed at screening and comprises both true interval cancers (about 50%) as minimal signs (about 20%) [38]. Failure to detect these tumours is caused by the limitations of the screening methodology and is inherent to an organized screening process [39].

Performing a radiological review of interval cancers can also be part of a quality improvement of the screening programme. This results in a training set used for radiologists during their education, and in an additional training set for senologists

involved in mammography screening to reduce the amount of interval cancers, specifically false-negatives. These initiatives occur in the Flemish Breast Cancer Screening Programme.

A main risk factor for the false-negatives category of interval cancers was a previous false-positive result, suggesting that some misinterpreted follow-up examinations may result in false-negatives [40-42]. Another risk factor for interval cancers is a high breast density, mainly for the group of occult tumours or minimal signs, but also for false-negatives due to a masking effect. However, the effect of masking is found to be less in false-negatives compared to overall interval cancers. This reinforces the hypothesis that tumours are stimulated by growth factors found in dense breasts which results in true interval cancers [43]. Understanding the role of breast density is important in a breast cancer screening programme as it is one of the variables proposed to tailored screening.

When we look at the SDCs and ICs in the four breast density classes in Flanders, the cancer detection rate (CDR) in BI-RADS density classes I-III remains similar (5.62 – 5.76‰). The CDR in dense breast class IV on the other hand drops to 4.62‰ (SD ± 0.4‰). In addition, 16% of all breast cancers in low density breasts (class I) are interval cancers and this proportion rises to 54% in the high density breasts (class IV). Combining these data leads to a strong decrease in the sensitivity of the mammography screening programme with increasing BI-RADS density class [12].

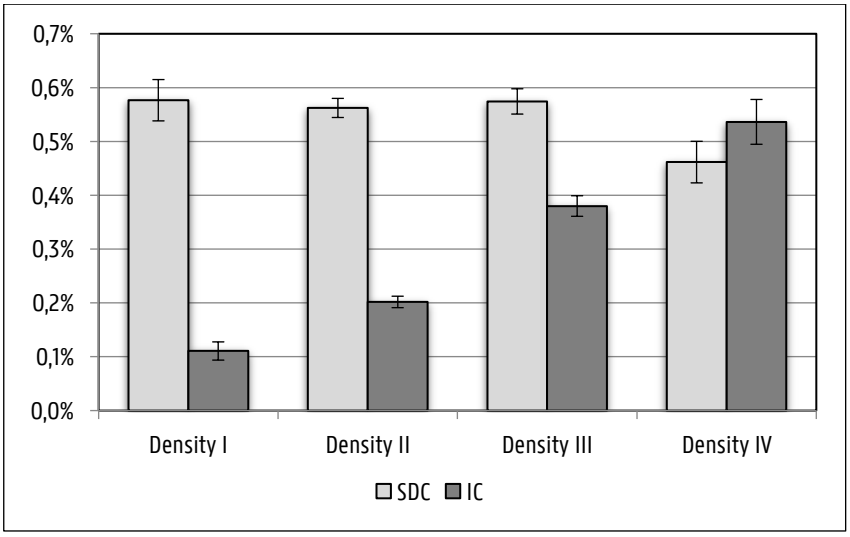

Figure 2.1

Cancer detection rate and interval cancer rate with density class. Cancer detection rate (CDR) remains similar in density classes I-III. The CDR in density class IV drops to 4.62‰. The interval cancer rate increases gradually with density class.

As stated above, density assessment is different on a digital mammographic device than with screen-film mammography. This has an impact on the rate of interval cancers with breast density. Regardless of modality, the interval cancer rate increases systematically as the density increases with no significant differences between modalities. However, in DR, the CDR exceeds the interval cancer rate in high density breasts of the BI-RADS IV class, which does not occur in CR or SF.

These findings are in line with different papers that indicate that DR mammography offers benefits specifically related to high density breasts allowing better visualization of dense breast tissue [44-46]. Although the diagnostic accuracy in DR mammography outperforms conventional SFM and CR in high density breasts, only 53% of cancer cases are detected with DR in women of the high density BI-RADS IV class in the Flemish Breast Cancer Screening programme while in low density breasts, this proportion was still 89%.

To improve lesion detection in this extreme breast density group, adjunctive screening beyond basic mammography techniques has been proposed for this group. Some authors are in favour of adding digital breast tomosynthesis (DBT) to 2D-mammography [47], others propose ultrasound [48]. The association of high breast density with breast cancer risk and lower sensitivity has inspired authors to propose a 'tailor-made' screening based on breast density. The objectives of this risk based screening is to reduce costs, recall rates, false positives and unnecessary biopsies while maintaining the number of quality-adjusted life-years (QALYs) gained by the programme [49]. In the USA, breast density notification is becoming widespread, mandating to report breast density for women with dense breasts who participate in breast cancer screening [50, 51].

3 TUMOUR CHARACTERISTICS

As stated above, according to the data of present work, the interval cancer rate increased gradually with breast density class [12]. The link between interval cancers and breast density class may be related to a masking effect and/or differences in tumour characteristics between breast density classes.

Breast cancer is a biologically heterogeneous disease. Analysis of tumour characteristics shows that interval cancers are more likely to have less favourable molecular features than screening detected cancers, such as a larger tumour size, more nodal invasion, higher proportion ER and PR negative tumours, more HER2 positive tumours and higher grade, which is in line with other published studies [35, 36, 52-54].

Five molecular subtypes have been differentiated by their expression of ER, PR and HER2 markers. To differentiate between Luminal A and Luminal B/HER2 negative-like subtypes, tumour grade was used following Brouckaert et al [55]. Ki-67 can also be used as proliferation marker to differentiate. However, the validity and robustness of Ki-67 is still controversial as the cut-off recommendation of 14% has been viewed critically due to a large inter- and intraobserver variability. Therefore, Ki-67 is still not a routine test in all laboratories in Flanders. The collected tumour characteristics (article 3) only show an availability of 42% for Ki67. This is because the pathology examinations of the biopsies and/or resection specimens were performed in laboratories spread throughout Flanders.

The distribution of molecular subtypes was different for SDC and IC. A higher presence of luminal A type cancers, which have the best prognosis, was found in SDC whereas a higher proportion of TN cancers with the worst prognosis was found among interval cancers [52, 53, 56]. The latter observation is even more pronounced if only the subset of true interval cancers is considered [35]. The association between IC and TN subtype could explain the rapid onset and aggressive character of these cancers. As luminal A-type tumours have the best 5-year survival (92% [57]) and TN the worst (69% [57]), we can expect this will also result in a worse tumour survival in IC. Several studies already reported a significantly higher 5-year cancer specific

survival of SDC versus IC [58, 59]. Based on differences in biomarker profiles and the published survival data, IC contain a subgroup of breast cancers with rapid growth and high aggressiveness.

According to the data of present work, tumour characteristics also tend to show differences among BI-RADS breast density groups. According to the performed analysis, breast cancers of women in the BI-RADS IV category have a larger tumour size compared to the BI-RADS I category in both SDC and IC (see Figure 3.1). As it is well documented that high breast density is associated with a larger contribution of occult tumours, this tumour size effect can be probably attributed to a masking effect. The larger amount of dense tissue will involve an increased masking effect, which results in a delay of diagnosis [39, 43]. Lymph node involvement also increases with breast density, which can be explained also by the larger masking effect postponing the timing of diagnosis. On the other hand, tumour grade, hormone receptor status and other histopathological tumour characteristics show the worst specifications in low density breasts.

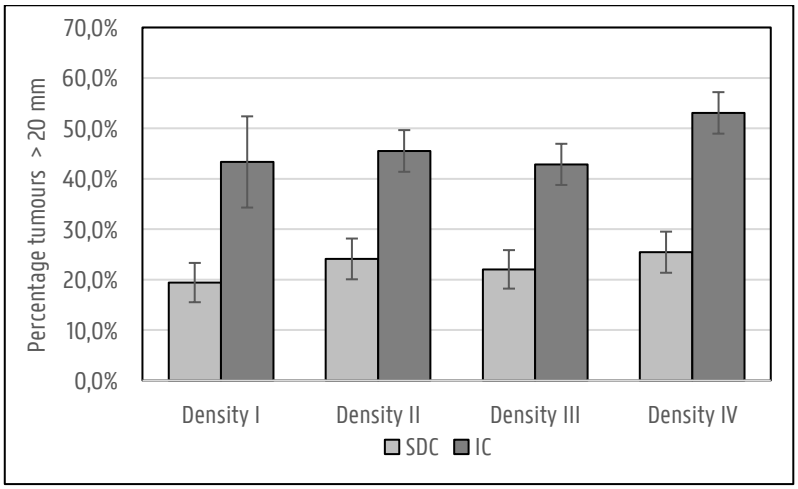

Figure 3.1

Screen detected cancers and interval cancers in the breast density classes. BI-RADS IV category has a larger tumour size compared to the BI-RADS I category in both SDC and IC.

Differentiation in molecular subtypes versus breast density revealed a significant association between Luminal A cancers and the high density BI-RADS IV class. This

association is in line with published research reporting an association between ER positivity and higher breast density [60]. However, other authors mention a negative association [61]. Our study also revealed a higher proportion of TN cancers in BI-RADS I breasts as well in IC as in SDC. This observation was especially prominent in IC where more than 20% of tumours in the low breast density BI-RADS I class are TN, which differs significantly from the 9% in high density breasts. This correlates with another study where the TN phenotype was more likely to occur in predominantly fatty breasts rather than in extremely dense breasts (see Figure 3.2) [37]. This may reflect the aggressive behaviour, rapid carcinogenesis and nonlinear progression of this tumour phenotype.

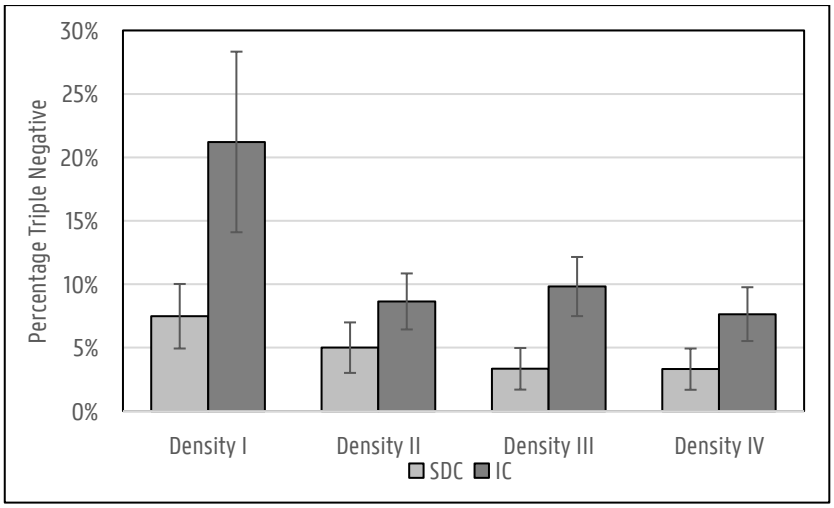

Figure 3.2

Screen detected cancers and interval cancers in the breast density classes. Graph shows a higher proportion of TN tumours in density class I in both SDC and IC.

In summary, investigation of tumour characteristics resulted in a significant difference between SDC and IC with IC showing less favourable molecular features. However, the tumour characteristics in the highest breast density class, in both SDC and IC, have a better prognostic tumour biomarker profile when compared to low density breasts.

4 STRATIFICATION ACCORDING TO BREAST DENSITY

Up till now, age has been the only parameter considered for inviting women to a mammography screening programme. This “one size fits all” strategy is effective in reducing breast cancer mortality [36, 54]. However, it is not ideal as women have their own individual risk of developing breast cancer based on genetic profile, family history and hormonal status. Our research demonstrated that high breast density leads to a higher chance of developing an interval cancers. However, according to the performed tumour characteristics study, interval cancers in women with high breast density tend to have a better prognostic tumour biomarker profile compared to low density breasts. This information supports the change from a “one size fits all” strategy to a tailor-made screening programme.

Customized prevention strategies are effective in individuals with very high breast cancer risk due to inherited mutations as BRCA1 and BRCA2 mutations [62]. However, this concerns only about 1 over 500 women. The large majority of women does not belong to this population at increased risk of breast cancer and is recommended to follow national screening guidelines. Developing a tailored approach in the screening programme, requires risk estimation models and eventually has to lead to a better screening, which would be more effective, less morbid and more health economically beneficial.

To estimate a woman’s’ breast cancer risk, several mathematical models have been developed which use clinical variables based on family history, hormonal variables and history of benign breast disease [63]. Breast density is also acknowledged as an important breast cancer risk factor and recent breast cancer risk models integrate mammographic breast density as a factor [64].

Implementation of the knowledge that we gained from our research to decrease the interval cancer rate in breast cancer screening programmes leads to: additional imaging in the group of women with high breast density to improve sensitivity on the one hand and on the other hand to outline a customized screening trajectory with different intervals according to the woman’s risk estimation.

In the MyPeBS project, funded for a 8 year period by the Horizon 2020 programme of the European Commission, women are stratified into different breast screening strategies as part of a more personalized screening programme [65]. The breast cancer risk is determined through DNA extraction and genotyping from a saliva sample together with application of risk estimation software. Women will be categorized in four groups with associated screening trajectory: low risk women get a mammogram every 4 year, average risk women get a mammogram every 2 year, high risk women get a mammogram every year and very high risk women get a yearly mammogram and MRI. The average and high-risk women with dense breasts also get an additional ultrasound.

This project is the beginning of a tailor-made approach of a screening programme and will clarify some ongoing questions. However, regarding the proposed protocol, some questions remain and further investigation is still necessary. Ultrasound is used as an additional imaging technique for high density breasts in the project. Time-effectiveness still needs to be investigated as well as some practical issues as second reading and quality control, which is not obvious for ultrasound. Adding ultrasound also adds costs. It is a necessity that extra costs of the screening programme are limited to maintain a high quality screening programme. When the overall costs of a screening programme are too high, the government would omit the programme and invest the money in something other besides preventive medicine. In the near future, digital breast tomosynthesis may also be a valuable alternative technique. Screening trials have shown an increase in cancer detection rate and a reduction of recall rate for DBT compared to 2D mammography [66-69]. However, large scale trials devoted to study all practical aspects have to confirm the added value of DBT as secondary technique especially in high density breasts before implementation. The use of DBT as stand-alone technique to replace mammography in high density breasts or together with ultrasound also needs to be studied.

Not only are the practical aspects of tailored screening of value, it is also important that professionals pay attention to the state of mind of women, who participate in the screening, towards a customized approach. [70]. In general, women had positive attitudes towards a screening programme with a more tailored approach based on

risk calculations. However, women only tend to accept this approach if they can be sure of a periodic mammographic examination even when they are at low risk [71, 72]. Additionally, subsequent anxiety and the potential for stigma in case of categorization in the high risk groups are concerns women have expressed regarding a tailor-made screening programme [73, 74].

The MyPeBS project is a beautiful project to investigate the tailor-made approach for a screening programme. However, a screening programme based on an individualized genetic risk profile is only based on one parameter. Other risk factors e.g. environmental, BMI, physical activity, are also important in assessing a woman's individual risk for breast cancer. Breast density, as seen in this PhD-thesis, is definitely a parameter that should be taken into account when implementing a tailor-made screening programme due to its many cancer-promoting characteristics. However, a tailor-made screening programme with different trajectories based on solely breast density is as ordinal as current programme.

Therefore, a tailor-made breast cancer screening programme based on many risk models, many environmental factors and (according to this thesis) including breast density, can result in an evidence-based screening programme with high sensitivity and specificity, high efficiency and a balanced economical cost-effectiveness. However, some pitfalls need to be solved before a tailor-made breast cancer screening can be realised in practice.

5 CONCLUSION

In this PhD dissertation, breast density was investigated in the Flemish Breast Cancer Screening Programme. A first purpose was to evaluate the impact of digitalisation of mammography on performance parameters, breast density and dose of the screening programme as a foundation of further research. We found that the performance parameters were not affected by the digital transition however, a significant lower MGD was found in mammography with DR devices. Regarding breast density, when a digital DR mammographic device was used as imaging technique, the density assessment was estimated lower in comparison with a conventional screen-film device or digital CR mammographic device.

The performed study of interval cancers in the screening programme showed a strong dependence of the BI-RADS breast density class. We found that the percentage interval cancers of screened women is 16% in the density I category women and this amount rises to 54% in the high breast density class IV. This illustrates a strong decrease in the sensitivity of the mammography screening programme with increasing BI-RADS density class

The link between interval cancers and breast density may be related to a masking effect and/or differences in tumour characteristics. Analysis of tumour characteristics showed that interval cancers have less favourable characteristics than screen detected cancers and this applies also to the molecular subtype classification. However, when investigating the tumour characteristics as a function of BI-RADS breast density class, tumour grade, hormone receptor status and other histopathological tumour characteristics have worse specifications in low density breasts compared to high density breasts. Molecular subtype analysis support also a better prognosis for the high density breasts.

In conclusion, we demonstrated that breast density has a large impact on the interval cancer rate in women who participated in the Flemish Breast Cancer Screening programme. Based on this observed relation, additional measures focussing on the group of women with dense breasts, are indicated to bring the effectiveness of the screening programme in this group to the same level as to other

women. This is supported by the tumour characteristics data indicating a better prognosis for interval cancers in dense breasts. At the moment, a population based Screening Programme is a very good initiative and using mammography is widely acknowledged as the most effective method of detecting early stage breast cancer and reducing breast cancer mortality. The Flemish Breast Cancer Screening Programme has been successful for many years. However, this 'one-size'-fits-all' approach does not take breast density, nor other risk factors, into account. With this research in mind, it may be time for a 'tailor-made' Flemish Breast Cancer Screening Programme.

An immediate developed stratified model of the screening programme does not yet exist. We believe that a 'tailor-made' screening approach will guide the next years of research. A stratified trajectory for every participating woman based on risk models and environmental factors, without any shortcomings for low risk women, can result in an evidence-based screening programme with high sensitivity and specificity, high efficiency and a balanced economical cost-effectiveness. However, some pitfalls need to be solved before a tailor-made breast cancer screening can be realised in practice.

6 FUTURE PROSPECTS

6.1 Evolution in the Flemish Breast Cancer Screening Programme

Combining the experience of many years of a population based screening programme together with new knowledge gained from research, a stratified screening approach based on risk models and environmental factors will probably be the future. Based on this stratified screening model, not only mammographic devices will probably be used as imaging technique, but this will be expanded with MRI, ultrasound and digital breast tomosynthesis. Different interval periods will also occur according to the probability of developing breast cancer in each woman. However, before implementing this tailor-made breast cancer screening programme in practice, some large scale studies need to be performed.

6.2 Evolution in breast cancer detection

Not only the way of participation and the use of imaging techniques in the screening programme will change in the coming years, but there will also be a change in detection of breast cancers.

Human readers evaluate screening mammograms. The reading process is tiring, lengthy, monotonous and most importantly, prone to errors [75]. Multiple studies reported that 20-30% of screening detected cancers could also be found retrospectively on the prior negative screening mammogram by blinded reviewers [76-80]. In addition, the problem of missed cancer persist, where in Flanders, 1/3 of all breast cancer cases in the screened population is an interval cancer.

Computed-aided detection (CAD) solutions were developed to help radiologists to read mammograms. These programmes analyse mammographic images and indicate suspicious regions, which should be reviewed by radiologists. Although several studies showed promising results [78, 81-85], multiple studies led to the conclusion that CAD technologies do not improve the performance of radiologists [86-88]. These results indicate that CAD can be of great help for radiologists when

implemented in a screening programme but that the reading quality of radiologists is the determining factor for the success of the screening.

Several large studies have established that mammographic breast density is a risk factor for breast cancer [89-91]. High density breasts have also a higher risk of masking tumours and the associated reduction of sensitivity [92-96]. The assessment of breast density by radiologists-second readers is subjective with considerable inter- and intrareader variability, however it is the standard in current clinical practice [91, 97]. Improving the accuracy and consistency of breast density assessment is a clinical need and can be obtained by using automated density programmes. Cumulus software [98] and LIBRA programme [99] estimate an area based percent density, Quantra [100] and Volpara [101] are volume based methods. These methods objectify the density assessment and can be of great assistance for radiologists in a screening programme. However, the volume based methods function only on raw 'for processing' images, which are not routinely stored.

These conventional classification algorithms are based on strong engineering, which required knowledge of data and a crafting process to build descriptive features. Conversely, deep learning can extract features automatically and directly from original data [102]. Since 2012, deep convolution neural networks (CNN) have reached the level of human performance in image classification and object detection and even outperformed traditional hand-crafted imaging descriptors [103, 104]. In recent years, deep learning has attracted great attention in artificial intelligence due to its successes in pattern recognition and has shown promising capability in medical image analysis [105]. Studies already investigated deep learning in breast anatomy classification, diagnosis of lesions and discrimination of masses and microcalcifications. Deep learning can also be applied for classifying breast density [104, 106-108].

Deep learning is not yet applied in routine in mammography screening, although the possibilities of this application in the future will be endless. Replacing conventional CAD software, with his controversially efficiency, by recently developed deep learning based software can result in increasing sensitivity and specificity as well as

increased efficiency in reading mammographic images, especially in an asymptomatic population based screening programme.

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Work Experience

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Publications

1. Timmermans L, De Hauwere A, Bacher K, Bosmans H, Lemmens K, Bleyen L, Van Limbergen E, Martens P, Van Steen A, Mortier G, Van Herck K, Thierens H. Impact of the digitalisation of mammography on performance parameters and breast dose in the Flemish Breast Cancer Screening Programme. European Radiology (2014); 24:1808-1819.

2. Timmermans L, Bleyen L, Bacher K, Van Herck K, Lemmens K, Van Ongeval C, Van Steen A, Martens P, De Brabander I, Goossens M, Thierens H. Screen-detected versus interval cancers: Effect of imaging modality and breast density in the Flemish Breast Cancer Screening Programme. European Radiology (2017); 27:3810-3819.

3. Timmermans L, De Brabander I, Van Damme N, Bleyen L, Martens P, Van Herck K, Depyere H, Thierens H*, Bacher K*. Tumour Characteristics of screen-detected and interval cancers in the Flemish Breast Cancer Screening Programme: A mammographic breast density study. Plos One, article submitted (PONE-D-18-27361).

** These authors contributed equally tot his work*

Conferences

Symposium Radioprotection, AZ Delta

Roeselare, Belgium, 15/09/2018

Oral Presentation: Screen detected versus interval breast cancers: Impact of breast density on tumour characteristics in the Flemish Breast Cancer Screening Programme.

Symposium 15 years of Breast Cancer Screening in Flanders

Brussel, Belgium, 26/10/2017

Attendance

Symposium Radiation Protection in Radiology, FANC

Brussel, Belgium, 21/10/2017

Attendance

Symposium Radioprotection, Sint-Lucas

Gent, Belgium, 26/04/2017

Oral Presentation: Screen detected versus interval cancers: Effect of image modality and breast density in the Flemish Breast Cancer Screening Programme.

ECR – European Congress of Radiology

Vienna, Austria 1-5/02/2017

Poster Presentation: Comparison of physical technical parameters in mammographic devices from different manufacturers used in the Flemish Breast Cancer Screening Programme.

BHPA – Annual Symposium of the Belgian Hospital Physicist Association

Gent, Belgium, 3-4/02/2017

Oral Presentation: Screen detected versus interval cancers: effect of image modality and breast density in the Flemish Breast Screening Programme.

Senological Congress
Oostduinkerke, Belgium, 28/05/2016
Oral Presentation: Interval Cancers and breast density in the Flemish Breast Cancer Screening Programme.

ECR – European Congress of Radiology
Vienna, Austria 2-6/02/2016
Oral Presentation: Screen detected cancers vs. interval cancers: Influence of image modality and breast density.

BHPA – Annual Symposium of the Belgian Hospital Physicist Association
Luik, Belgium, 26-27/01/2016
Attendance

Belgian Breast Meeting
Brussels, Belgium, 20/11/2015
Attendance

Breast Tomosynthesis QC protocol and workshop
Vienna, Austria, 11/09/2015
Attendance

EFOMP digital mammography and quality Control
Prague, Tsjechië, 29-31/01/2015
Attendance

PhD-day
Gent, Belgium, 27/01/2015
Oral presentation: Performance characteristics versus breast density in the Flemish Breast Cancer Screening Programme.

Symposium Dose registration and optimization: More than just CT – UZA
Antwerp, Belgium, 24/04/2014
Attendance

Science day
Gent, Belgium, 13/03/2014
Oral Presentation: Impact of the digitalization of mammography on performance parameters and breast dose in the Flemish Breast Cancer Screening Programme.

BHPA – Annual Symposium of the Belgian Hospital Physicist Association
Mechelen, Belgium, 01-02/02/2013
Attendance