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REDUCTION MAMMAPLASTY- PRE- AND POSTOPERATIVE DETECTION OF BREAST CANCER AND LESIONS ASSOCIATED WITH INCREASED RISK

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ACADEMIC DISSERTATION

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TO MY FAMILY

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1 LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original publications. These are referred to in the text by their Roman numerals.

I Merkkola-von Schantz P, Jahkola T, Carpelan A, Krogerus L, Hukkinen K, Kauhanen S. Adverse Histopathology and Imaging Findings in Reduction Mammaplasty Day-surgery Patients. Scand J Surg. 2014 Mar 12;103(3):209-214.

II Merkkola-von Schantz PA, Kauhanen SMC, Jahkola TA, Krogerus LA, Hukkinen KS. Breast Cancer Detection by Preoperative Imaging in Reduction Mammaplasty Patients: A Single Center Study of 918 Patients. World J Surg. 2017 Aug;41(8):2013-2019.

III Merkkola-von Schantz PA, Jahkola TA, Krogerus LA, Hukkinen KS, Kauhanen SM. Should we routinely analyze reduction mammaplasty specimens? J Plast Reconstr Aesthet Surg. 2017 Feb;70(2):196-202.

IV Merkkola-von Schantz PA, Jahkola TA, Krogerus LA, Kauhanen SMC. Reduction mammaplasty in patients with history of breast cancer: The incidence of occult cancer and high-risk lesions. Breast. 2017 Oct;35:157-161.

2 ABBREVIATIONS

ACR	American College of Radiology
ADH	Atypical ductal hyperplasia
ALH	Atypical lobular hyperplasia
BC	Breast cancer
BI-RADS	Breast Imaging Reporting and Data System
BMI	Body mass index
CC	Craniocaudal
CNB	Core needle biopsy
D	Breast density
DCIS	Ductal carcinoma in situ
FNAB	Fine needle aspiration biopsy
G	Grams
HER2	Human epidermal growth factor receptor 2
IDC	Invasive ductal cancer
ILC	Invasive lobular cancer
LCIS	Lobular carcinoma in situ
LN	Lobular neoplasia
ML	Medio-lateral
MLO	Medio-lateral-oblique
MMG	Mammogram
MRI	Magnetic resonance imaging
N/A	Not applicable
NS	Not significant
NST	Invasive cancer of no specific type
SD	Standard deviation
SERM	Selective oestrogen receptor modulator
SNB	Sentinel node biopsy
TNM	Tumour, node, metastases
US	Ultrasound
WHO	World Health Organization
2D	Two-dimensional
3D	Three-dimensional

3 ABSTRACT

Background

Reduction mammaplasty is one of the most common plastic surgery procedures. Variation exists between preoperative imaging and histopathology protocols in different countries and institutions. The aim of this study was to analyse the incidence of occult breast cancer and lesions associated with increased risk in reduction mammaplasty specimens, both in patients with or without a previous history of breast cancer. This study assessed whether patients with abnormal histopathology differed from the study population in terms of demographics. In addition, in patients with a previous history of breast cancer, it was analysed if timing of reduction mammaplasty with respect to oncological treatment influenced the incidence of abnormal findings in the specimens. This study described the imaging process and its ability to catch disease preoperatively. In addition, the association between imaging and histopathological findings in reduction mammaplasty specimens was examined.

Materials and Methods

The 1255 women that underwent reduction mammaplasty between 1/2007 and 12/2011 were retrospectively reviewed for demographics, preoperative imaging, further preoperative examinations, histopathology reports, and postoperative follow-up.

Results

Among women with no previous history of breast cancer (n=918), abnormal histopathological findings were revealed in 88 (10.4%) patients. The incidence of breast cancer was 1.2% (n=10), and the incidence of high-risk lesions (atypical ductal hyperplasia, atypical lobular hyperplasia, and lobular carcinoma in situ) was 5.5% (n=47). Age ($p<0.001$) and specimen weights ($p<0.001$) were significantly higher in patients with abnormal histopathology. Eighty-one percent of patients with abnormal histopathology had normal preoperative imaging. Preoperative examinations revealed only two high-risk and two cancer findings. Two patients later developed breast cancer in the same breast where the high-risk lesion was originally revealed.

Among women with a history of breast cancer (n=329), abnormal histopathological findings were revealed in 68 (21.5%) patients. High-risk lesions were revealed in 37 (11.7%), and cancer in six (1.9%) patients. Abnormal histopathology correlated with higher age ($p=0.0053$), heavier

specimen ($p=0.0491$), and with no previous breast surgery ($p<0.001$). Abnormal histopathological findings were also more frequent in patients with reduction mammaplasty performed prior to oncological treatment ($p<0.001$), and in patients undergoing immediate reconstruction ($p= 0.0064$).

Conclusions

Reduction mammaplasty specimens reveal a considerable number of malignant and high-risk lesions. The incidences are doubled in patients with a previous history of breast cancer and abnormal findings are strikingly frequent if reduction mammaplasty is performed prior to oncological treatment. In addition, abnormal histopathology correlates with higher age and heavier specimen. To date, preoperative imaging and demographics do not sufficiently detect cancer or high-risk lesions. Therefore, histopathological analysis of the specimens should be thoroughly considered.

4 INTRODUCTION

Reduction mammaplasty involves many breast and plastic surgeons. Common indications for the surgery are symptomatic macromastia, breast asymmetry or contralateral symmetrisation during or after breast cancer surgery. Despite preoperative evaluation and imaging of the patients, occult breast cancer, in situ cancer, and benign breast disease associated with an increased risk of breast cancer may appear in reduction mammaplasty specimens.

The incidence of occult breast cancer in reduction mammaplasty specimens has been under study in several countries with incidences ranging from 0.05% to 4.0% (Acevedo et al. 2018; Ambaye et al. 2009; Ambaye et al. 2017; Boice et al. 2000; Clark et al. 2009; Colwell et al. 2004; Cook et Fuller 2004; Desouki et al. 2013; Freedman et al. 2012; Goodwin et al. 2013; Hassan et Pacifico 2012; Ishag et al. 2003; Jansen et al. 1998; Kakagia et al. 2005; Pitanguy et al. 2005; Slezak et Bluebond-Langner 2011; Tadler et al. 2014; Tang et al. 1999; Viana et al. 2005; Waldner et al. 2018). The incidence of occult cancer in reduction mammaplasties aimed at symmetrisation in patients with a history of breast cancer varies from 0.94% to 5.45% (Colwell et al. 2004; Freedman et al. 2012; Goyal et al. 2011; Hassan et Pacifico 2012; Ishag et al. 2003; Li et al. 2014; Petit et al. 1997; Slezak et Bluebond-Langner 2011; Sorin et al. 2014; Sorin et al. 2015; Tadler et al. 2014).

Benign breast disease is typically found in reduction mammaplasty specimens (Acevedo et al. 2018; Akintayo et al. 2017; Ambaye et al. 2009; Ambaye et al. 2017; Blansfield et al. 2004; Clark et al. 2009; Desouki et al. 2013; Freedman et al. 2012; Ishag et al. 2003; Kececi et al. 2014; Samdanci et al. 2011), and a group of these women are at higher risk for breast cancer (Carter et al. 1988; Coopey et al. 2012; Dupont et Page 1985; Dupont et al. 1993; Dyrstad et al. 2015; Fitzgibbons et al. 1998; Hartmann et al. 2005; Hartmann et al. 2014; King et al. 2015; London et al. 1992; McEvoy et al. 2015; Morrow et al. 2015; Page et al. 1985). Proliferative breast lesions without atypia cause slightly increased risk (1.5-2.0 times), and atypical ductal hyperplasia (ADH) as well as atypical lobular hyperplasia (ALH) cause moderately increased risk (4.0-5.0 times) of breast cancer (Fitzgibbons et al. 1998; Lakhani et al. 2012). In addition, ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) cause markedly increased risk (8.0-10.0 times) of breast cancer (Fitzgibbons et al. 1998; Lakhani et al. 2012). LCIS is considered to be a high-risk lesion, together with ADH and ALH, whereas DCIS is regarded as a true precursor lesion and thus is managed differently (Morrow et al. 2015).

The question of routine preoperative imaging in reduction mammaplasty patients is an ongoing one, which has not yet come to a consensus. Mammogram is variously recommended for different age groups (Ambaye et al. 2009; Blansfield et al. 2004; Campbell et al. 2010; Colwell et al. 2004; Freedman et al. 2012; Hage et Karim 2006; Hassan et Pacifico 2012; Hennedige et al. 2011; Slezak et Bluebond-Langner 2011; van der Torre et Butzelaar 1997; Waldner et al. 2018; White et al. 2012). The association between results of preoperative imaging and abnormal histopathological findings in reduction mammaplasty specimens has not been studied to date in Finland, and also the literature covering this is limited. In addition, the feasibility of different imaging modalities in reduction mammaplasty patients remains unsolved.

The aim of this study was to analyse the incidence of occult breast cancer and lesions associated with increased risk in reduction mammaplasty specimens, and to compare these incidences between patients with and without a history of breast cancer. This study also analysed whether patients with abnormal histopathology differed from the study population in terms of demographics. In patients with a previous history of breast cancer, it was studied if timing of reduction mammaplasty with respect to oncological treatment influenced the incidence of abnormal findings in reduction mammaplasty specimens. This study also aimed to retrospectively describe the use of different imaging modalities, and investigated the association between preoperative imaging, needle biopsies, and final histopathological findings in reduction mammaplasty patients.

5 REVIEW OF THE LITERATURE

5.1 Reduction mammaplasty and typical indications

Reduction mammaplasty is one of the most common plastic surgical procedures. In 2016, the number of Finnish women operated was 1571 (National Institute for Health and Welfare 2013). Reduction mammaplasty is performed for both functional as well as aesthetic purposes (Thorne et al. 2014). In the public sector, typical indications for the surgery are symptomatic macromastia, breast asymmetry due to congenital causes, or contralateral symmetrisation during or after breast cancer surgery (Ambaye et al. 2017; Clark et al. 2009; Thorne et al. 2014).

Macromastia, or mammary hypertrophy, is a benign condition of breast hypertrophy that can cause physical and psychological symptoms (Clark et al. 2009; Grotting et Neligan 2013). The pathophysiology of macromastia is considered to be the consequence of an abnormal response of the breast to circulating oestrogens, causing breast proliferation which is mainly fibrous tissue, fat, and to a lesser degree glandular tissue (Grotting et Neligan 2013). Most women with macromastia have normal levels of circulating oestrogen and normal numbers of oestrogen receptors in the breast tissue (Grotting et Neligan 2013). Women seeking the operation typically express neck pain, shoulder or back pain, headache, excoriation from bra straps, intertrigo in breast skin folds, difficulties to find clothing and limitations of exercise, as well as psychological burden due to large breasts (Atterhem et al. 1998; Singh et Losken 2012). It has been shown that after the surgery women have better quality of life, less breast-associated symptoms, less depression and anxiety, and better self-esteem when compared with the preoperative situation (Saariniemi et al. 2011). In addition, benefits from the surgery remain at follow-up (Cabral et al. 2018; Nuzzi et al. 2017; Saariniemi et al. 2011).

Reduction mammaplasty is frequently used to improve asymmetry (Ambaye et al. 2009; Thorne et al. 2014). Treatment of congenital anomalies of the breast, such as tuberous breast, Poland's syndrome and virginal hyperertrophy, may require reduction mammaplasty techniques (Thorne et al. 2014). In patients with a history of breast cancer, contralateral reduction mammaplasty can be performed to balance asymmetry caused by cancer surgery (Ambaye et al. 2017; Grotting et Neligan 2013). In addition, some breast cancer patients operated with breast conservation therapy still suffer from symptomatic macromastia, and may benefit from bilateral reduction mammaplasty (Spear et al. 1998; Weichman et al. 2015).

5.2 Presurgical evaluation of reduction mammaplasty patients

Women seeking reduction mammaplasty are clinically evaluated. A history of symptoms associated with mammary hypertrophy, as well as a personal and family history of breast cancer and breast surgery should be recorded (Grotting et Neligan 2013). Attention must be paid to comorbidities, medications, weight, smoking habits, obstetric history, and previous hypertrophic scarring or keloids (Shestak et Davidson 2016). All of these are important factors, when assessing the overall risk for complications (Shestak et Davidson 2016). In addition, the results of any testing, such as imaging, should be obtained prior to surgical intervention (Grotting et Neligan 2013). It is not always possible to avoid complications, therefore it is of utmost importance to manage the expectations of the patients by preoperatively discussing the risks associated with the procedure (Shestak et Davidson 2016).

A systematic examination of the breast, axilla and supra- and infraclavicular fossae, as well as assessment of the nipple-areolar complex and the skin is mandatory (Grotting et Neligan 2013; Shestak et Davidson 2016). Scars may affect pedicle and skin resection choices, and therefore are important when planning the surgery (Grotting et Neligan 2013). Specific breast measurements, such as the sternal notch to nipple distance, are documented as a part of patient evaluation (Grotting et Neligan 2013; Shestak et Davidson 2016). They can be used to estimate pedicle length, and thus help in surgical planning. In addition, anteroposterior, oblique, and lateral photographs are documented (Shestak et Davidson 2016).

5.3 Preoperative imaging

Preoperative imaging is typically assigned before reduction mammaplasty. Two-dimensional (2D) mammogram, with craniocaudal (CC) and medio-lateral-oblique (MLO) projections, is considered to be the most important imaging method in breast diseases, and as the first line of imaging modality for diagnostic purposes in women over the age of 30 (Kopans 2007). A mammogram can be compared with a previous one, and any change is likely to be detected. According to the Finnish national mammogram screening program, women aged 50-69 years are invited to screening mammogram every second year (Ministry of Social Affairs and Health 2015). However, the sensitivity of mammogram for cancer detection varies (Price et al. 2013; Saarenmaa et al. 2001). It has been shown that in dense breasts, the sensitivity of mammogram is diminished (Carney et al. 2003; Price et al. 2013; van Gils et al. 1998). The density of breast parenchyma decreases with age, and therefore sensitivity of mammogram is increased by age and with

fattiness of the breast (Saarenmaa et al. 2001). Thus, reduction in mammographic sensitivity highly impacts to the need of supplementary imaging modalities (Price et al. 2013).

Ultrasound is considered as an adjunct imaging modality in the breast imaging process and is typically used to guide percutaneous biopsies and to evaluate abnormal findings (Kopans 2007). Nevertheless, in women under the age of 30 years, ultrasound is used as the primary imaging modality in Finland according to the national recommendation (Finnish Breast Cancer Group 2018). Another supplemental modality, magnetic resonance imaging (MRI), is a highly sensitive diagnostic modality to detect invasive breast cancer, with the capacity to detect small tumours in dense breasts, but its specificity is low (Gonzalez et al. 2014; Peters et al. 2008). In some cases, such as patients with high risk of breast cancer, or if there is incongruity between clinical and imaging findings, MRI may be indicated (Mann et al. 2008).

In case of suspicious findings in the imaging, further examinations, such as medio-lateral (ML) projection, spot magnification images, or tomosynthesis (three-dimensional, 3D), are conducted (Kopans 2007). According to current recommendations, the gold standard for breast cancer diagnostics is core needle biopsy (CNB) or vacuum-assisted biopsy, and cytological examination of breast lesions is not considered a reliable method for identifying or classifying breast lesions (Hukkinen et al. 2008; Lakhani et al. 2012).

The most commonly used approach to facilitate and standardize breast imaging reporting is the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) (D'Orsi et al. 2013). It enables radiologists to provide concise reports of mammogram, ultrasound, and MRI findings, and to communicate the results in a clear and consistent fashion with a final assessment and a specific course of action (D'Orsi et al. 2013). BI-RADS classifies imaging into seven different categories from BI-RADS 0 to BI-RADS 6. This classification is presented in Table 1. In addition, breast composition can be categorized according to the BIRADS lexicon (D'Orsi et al. 2013).

Table 1 *BI-RADS classification.*

Category	Definition	Likelihood of cancer
BI-RADS 0	Incomplete	N/A[a]
BI-RADS 1	Negative	Essentially 0%
BI-RADS 2	Benign	Essentially 0%
BI-RADS 3	Probably benign	> 0%, but ≤2%
BI-RADS 4 • 4A • 4B • 4C	Suspicious • Low suspicion • Moderate suspicion • High suspicion	> 2%, but < 95% • > 2% to ≤ 10% • > 10% to ≤ 50% • > 50% to < 95%
BI-RADS 5	Highly suggestive of malignancy	≥ 95%
BI-RADS 6	Known biopsy-proven malignancy	N/A

Adapted from ACR BI-RADS atlas (D'Orsi et al. 2013)
[a] N/A Not applicable

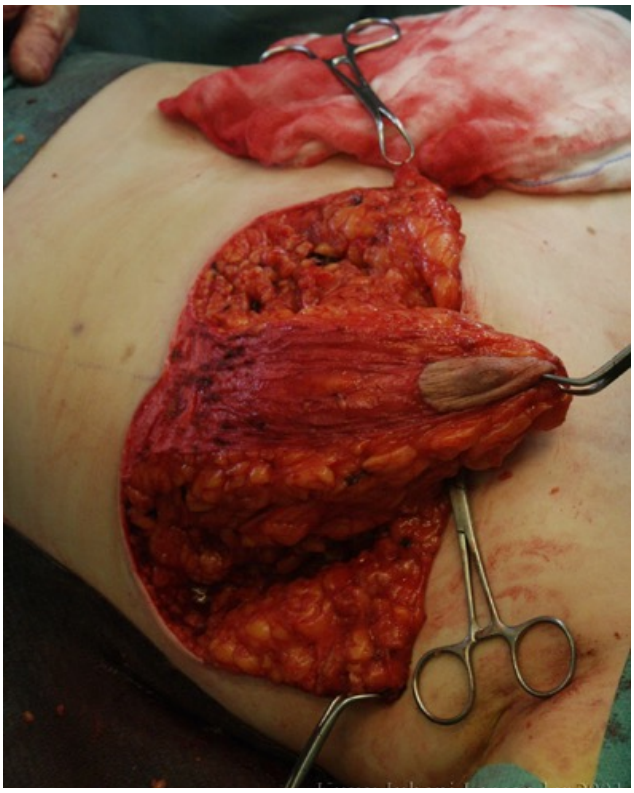
The role of preoperative imaging and the use of different imaging modalities in reduction mammaplasty patients is highly variable and controversial. No consensus exist about imaging criteria, the threshold age to start screening, or which modalities to use (Ambaye et al. 2009; Blansfield et al. 2004; Campbell et al. 2010; Colwell et al. 2004; Freedman et al. 2012; Hage et Karim 2006; Hassan et Pacifico 2012; Hennedige et al. 2011; Slezak et Bluebond-Langner 2011; van der Torre et Butzelaar 1997; Waldner et al. 2018; White et al. 2012). In general, preoperative mammogram is variously recommended from the age of 30 (Blansfield et al. 2004), from the age of 40 (Ambaye et al. 2009; Butler et al. 2003; Colwell et al. 2004; Hage et Karim 2006; White et al. 2012), or for patients over the age of 50 (van der Torre et Butzelaar 1997). Generally accepted recommendations concerning the use of ultrasound or MRI in reduction mammaplasty patients appear not to exist. In addition, the literature concerning the association between the results of preoperative imaging and abnormal findings in reduction mammaplasty specimens is limited.

5.4 Surgical procedure

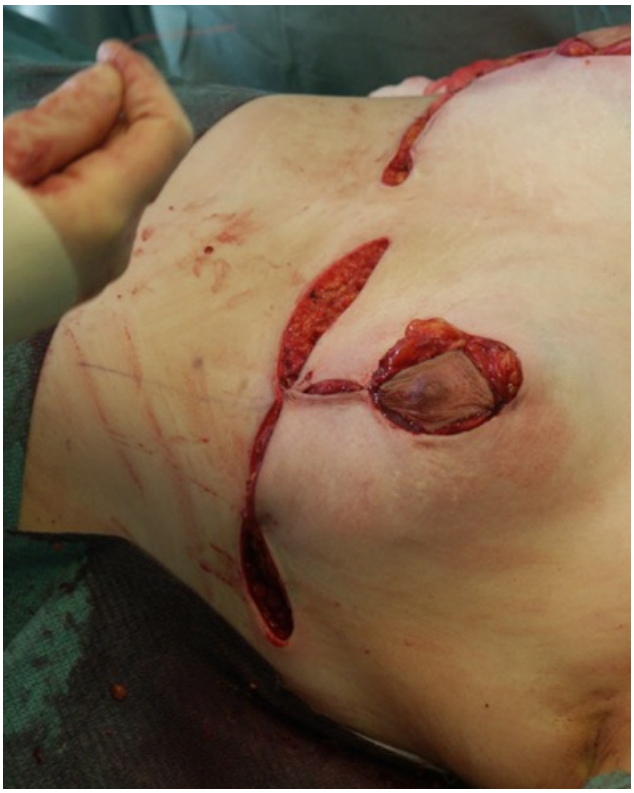
Reduction mammaplasty techniques have evolved over the years, and numerous methods currently exist for skin and parenchymal resection, as

well as pedicle selection (Grotting et Neligan 2013; Hall-Findlay et Shestak 2015). Different pedicles include superior, superomedial, medial, lateral, inferior and central pedicle, as well as vertical and horizontal bipedicle (Thorne et al. 2014). They can be combined with different parenchymal resection patterns, and both can be combined with different skin resection patterns (Thorne et al. 2014). Two of the most common techniques are inverted T (Wise pattern) and vertical approaches (Hall-Findlay et Shestak 2015; Thorne et al. 2014). Although modifications are performed intraoperatively, the procedure is based on the preoperative patient's markings in the sitting position. Location and the degree of breast hypertrophy, the amount of skin excess and its elasticity, and the position of the breast footprint on the chest wall should be considered preoperatively (Hall-Findlay et Shestak 2015).

During the surgery, the chosen pedicle is usually de-epithelialized first. Next, the skin and excess breast parenchyma is reduced, nipple-areolar complex is transposed upwards, and skin and glandular tissue are tailored to fit the new shape (Picture 1 and Picture 2) (Hall-Findlay et Shestak 2015). The goals of the procedure are weight and volume reduction, creating a pleasing shape, and, if possible, maintaining sensation and function using a skin incision pattern most optimal to the individual patient (Hall-Findlay et Shestak 2015; Thorne et al. 2014). Furthermore, the results of the surgery should be long-lasting and with acceptable scars (Shestak et Davidson 2016).



Picture 1 The skin and excess breast parenchyma is reduced. (Picture courtesy by Tiina Jahkola)



Picture 2 The skin and glandular tissue are tailored to fit the new shape. (Picture courtesy by Tiina Jahkola)

5.5 The incidence of breast cancer and benign breast disease associated with increased risk in reduction mammaplasty specimens

Breast cancer is the most frequent cancer among women; one in eight women in Finland experience it during their lifetime (Pukkala et al. 2011). It represents a quarter of all female cancers worldwide (Wyld et al. 2018). According to Finnish Cancer Registry, 5161 breast cancers were diagnosed among women in 2015 (Finnish Cancer Registry 2018). Although more women are surviving breast cancer with improved awareness, screening programs, and better treatments globally, there are differences in both incidence and mortality (Wyld et al. 2018). The five-year survival rate for patients diagnosed with breast cancer between 2013 and 2015 in Finland was 90.6%. Still, around 800 women die due to breast cancer annually in Finland (Finnish Cancer Registry 2018).

It is thus unsurprising that incidental cancers, in situ lesions, and benign breast disease associated with an increased risk of breast cancer are revealed in reduction mammaplasty specimens. Beginning with Cirkelair and Malton in 1959 (Crikelair et Malton 1959), a number of studies have demonstrated this phenomenon. According to the literature, the incidence of occult breast cancer in reduction mammaplasty specimens ranges from 0.05% to 4.0% (Acevedo et al. 2018; Ambaye et al. 2009; Ambaye et al. 2017; Boice et al. 2000; Clark et al. 2009; Colwell et al. 2004; Cook et Fuller 2004; Desouki et al. 2013; Freedman et al. 2012; Goodwin et al. 2013; Hassan et Pacifico 2012; Ishag et al. 2003; Jansen et al. 1998; Kakagia et al. 2005; Pitanguy et al. 2005; Slezak et Bluebond-Langner 2011; Tadler et al. 2014; Tang et al. 1999; Viana et al. 2005; Waldner et al. 2018), and in reduction mammaplasties aimed at symmetrisation in patients with a history of breast cancer from 0.94% to 5.45% (Colwell et al. 2004; Freedman et al. 2012; Goyal et al. 2011; Hassan et Pacifico 2012; Ishag et al. 2003; Li et al. 2014; Petit et al. 1997; Slezak et Bluebond-Langner 2011; Sorin et al. 2014; Sorin et al. 2015; Tadler et al. 2014). When only invasive cancer and DCIS are taken into account, the incidence of occult breast cancer varies between 0.05% and 2.48% in patients without a history of breast cancer (Acevedo et al. 2018; Ambaye et al. 2009; Ambaye et al. 2017; Boice et al. 2000; Clark et al. 2009; Colwell et al. 2004; Cook et Fuller 2004; Desouki et al. 2013; Freedman et al. 2012; Goodwin et al. 2013; Hassan et Pacifico 2012; Ishag et al. 2003; Jansen et al. 1998; Kakagia et al. 2005; Pitanguy et al. 2005; Slezak et Bluebond-Langner 2011; Tadler et al. 2014; Tang et al. 1999; Viana et al. 2005; Waldner et al. 2018), and between 0.94% and 3.64% in breast cancer patients (Colwell et al. 2004; Freedman et al. 2012; Goyal et al. 2011; Hassan et Pacifico 2012; Ishag et al. 2003; Li et al. 2014; Petit et al. 1997; Slezak et Bluebond-Langner 2011; Sorin et al. 2014; Sorin et al. 2015; Tadler et al. 2014).

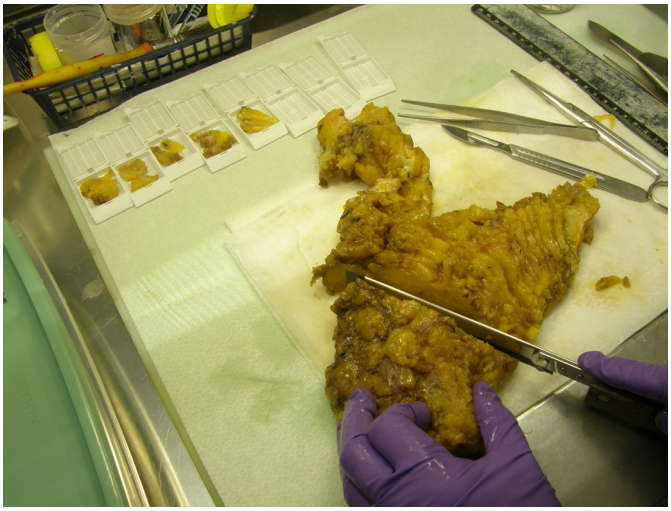
In addition to breast cancer, benign breast disease is commonly identified in reduction mammaplasty specimens (Acevedo et al. 2018; Akintayo et al. 2017; Ambaye et al. 2009; Ambaye et al. 2017; Blansfield et al. 2004; Clark et al. 2009; Desouki et al. 2013; Freedman et al. 2012; Ishag et al. 2003; Kececi et al. 2014; Samdanci et al. 2011), and a group of these women are at higher risk for breast cancer (Carter et al. 1988; Coopey et al. 2012; Dupont et Page 1985; Dupont et al. 1993; Dyrstad et al. 2015; Fitzgibbons et al. 1998; Hartmann et al. 2005; Hartmann et al. 2014; King et al. 2015; London et al. 1992; McEvoy et al. 2015; Morrow et al. 2015; Page et al. 1985). Therefore, the incidence of high-risk lesions has been an interest in a number of studies with incidences of atypical hyperplasia ranging from 1.4% to 8.4% (Acevedo et al. 2018; Ambaye et al. 2009; Ambaye et al. 2017; Blansfield et al. 2004; Clark et al. 2009; Desouki et al. 2013; Freedman et al. 2012; Ishag et al. 2003; Kececi et al. 2014; Samdanci et al. 2011).

However, comparison between studies is made difficult due to variations in study methodologies and designs, for example, institutional study, survey, population-based study, and definition of clinically relevant breast histopathology findings. Moreover, inclusion of in situ lesions, such as LCIS or unclear distinction between patients with or without a previous history of breast cancer, produces discrepancies (Desouki 2015; Hassan et Pacifico 2012; Waldner et al. 2018). The variability of the incidences of both occult breast cancer and atypical hyperplasias in reduction mammaplasty specimens is also likely to be a consequence of different tissue-sampling methods, as the number of random tissue blocks is not commonly reported. Nevertheless, it has been shown that increased sampling will increase the possibility to find significant histopathological findings (Ambaye et al. 2009; Ambaye et al. 2017; Kececi et al. 2014).

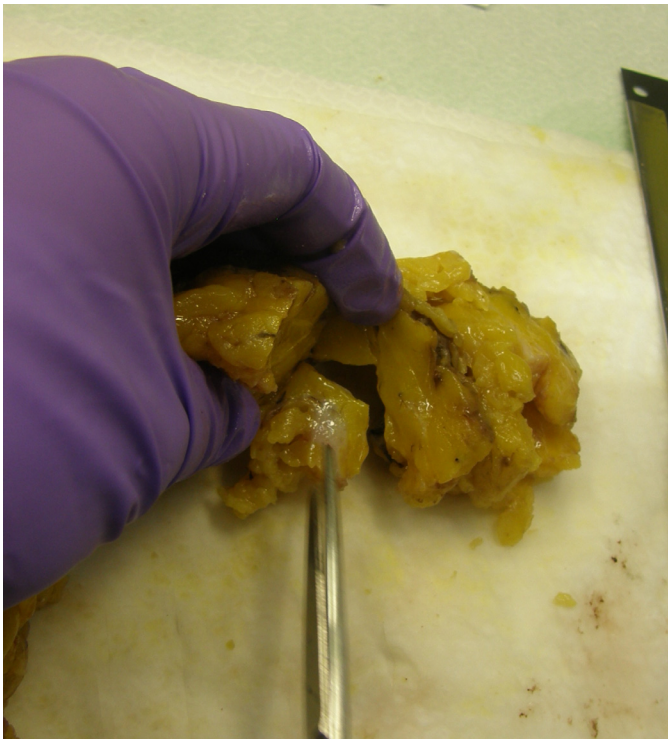
5.6 Histopathological analysis of reduction mammaplasty specimen

During the surgery, breast tissue is resected and usually sent for histopathological analysis. Samples from each breast are stored in separate containers in neutral-buffered 10% formaldehyde NBF and examined within 24 hours. Thorough gross examination is performed, and reduction mammaplasty specimens are palpated for masses and for areas of increased density. The specimens are weighed and cut into one-centimetre slices (Picture 3). Any macroscopically suspicious lesions are sampled (Picture 4). Otherwise, random samples for tissue blocks are taken. The number of tissue blocks is approximately six, and in case of suspicious findings or dense tissue, the number is increased to eight to ten. Tissue blocks are analysed histopathologically. In case of abnormal findings in histopathological analysis, the reduction mammaplasty specimen is re-evaluated, the location

of the lesion is determined, and additional tissue blocks are taken for analysis.



Picture 3 Reduction mammaplasty specimen is cut into slices. Samples for tissue blocks are taken from macroscopically suspicious areas or randomly.



Picture 4 Macroscopically suspicious areas are sampled.

However, variations exist in different countries and institutions, for example only part or none of the resected tissue may be sent for histopathological analysis. Although there are general recommendations for standardization of the macroscopic examination of surgical specimen (Rosai et Ackerman 2011),

no standardized pathology procedure for processing and examination of reduction mammaplasty specimens exists (Ambaye et al. 2017). In addition, the number of tissue blocks submitted for assessment varies between institutions (Ambaye et al. 2017).

5.6.1 Histopathological findings in reduction mammaplasty specimens

Reduction mammaplasty specimens reveal an array of histopathological findings ranging from benign lesions to invasive cancer. Clark et al. (Clark et al. 2009) showed in their study of 563 reduction mammaplasty patients that the majority (52.7%) of the breast specimens lack normal breast tissue. In addition, Degnim and et al. (Degnim et al. 2012) compared tissue samples between normal donors and women who underwent reduction mammaplasty. They showed that 87.6% of reduction mammaplasty samples had some histologic abnormality compared to 35.0% in normal donors. Recognition of abnormal lesions supports the estimation of the risk of developing invasive breast cancer (Clark et al. 2009). Thus, reduction mammaplasty specimens should be considered an opportunity to evaluate breast tissue (Ishag et al. 2003).

Benign breast disease encompasses a heterogeneous group of diagnoses typically subdivided into non-proliferative lesions, proliferative lesions without atypia, and atypical hyperplasias (Dupont et Page 1985). Since the initial report of Dupont and Page (Dupont et Page 1985), several authors have confirmed the increased risk of breast cancer associated with proliferative lesions without atypia and atypical hyperplasias (Carter et al. 1988; Coopey et al. 2012; Dupont et al. 1993; Dyrstad et al. 2015; Fitzgibbons et al. 1998; Hartmann et al. 2005; Hartmann et al. 2014; King et al. 2015; McEvoy et al. 2015; Morrow et al. 2015; Page et al. 1985). Proliferative breast lesions without atypia cause slightly increased risk (1.5-2.0 times), and ADH as well as ALH cause moderately increased risk (4.0-5.0 times) of breast cancer (Fitzgibbons et al. 1998; Lakhani et al. 2012). In addition, there are two forms of in situ breast cancer that are recognized to increase breast cancer development: LCIS and DCIS (Morrow et al. 2015). DCIS continues to be regarded as a precursor lesion to invasive breast cancer, and is managed differently form LCIS, which is most often, together with ADH and ALH, considered to be a high-risk lesion with markedly increased risk (8.0-10.0 times) of breast cancer (Fitzgibbons et al. 1998; Lakhani et al. 2012; Morrow et al. 2015). Relative risk for invasive breast cancer of these lesions is presented in Table 2. Currently ALH and LCIS are included to lobular neoplasia (LN) (Lakhani et al. 2012).

Table 2 *Relative risk for invasive cancer among benign lesions and lesions associated with an increased risk of breast cancer.*

Non-proliferative lesions/No increased risk
Adenosis (other than sclerosing adenosis)
Ductectasia
Fibroadenoma without complex features
Fibrosis
Mastitis
Mild hyperplasia without atypia
Ordinary cysts
Simple apocrine metaplasia
Squamous metaplasia
Proliferative lesions without atypia/Slightly increased risk (1.5-2.0 times)
Fibroadenoma with complex features
Moderate or florid hyperplasia without atypia
Sclerosing adenosis
Solitary papilloma without coexisting atypical hyperplasia
Atypical hyperplasias/Moderately increased risk (4.0-5.0 times)
Atypical ductal hyperplasia
Atypical lobular hyperplasia
In situ carcinomas/Markedly increased risk (8.0-10.0 times)
Ductal carcinoma in situ
Lobular carcinoma in situ

Adapted from Fitzgibbons et al. (Fitzgibbons et al. 1998; Lakhani et al. 2012).

5.6.2 Non-proliferative lesions and proliferative lesions without atypia

Non-proliferative lesions and proliferative lesions without atypia are a vast group of benign breast lesions (Dyrstad et al. 2015). They encompass diverse entities that range from reactive and inflammatory conditions to benign tumours (Lakhani et al. 2012). Some examples are listed in Table 2. Women with non-proliferative lesions of the breast have no elevation in breast cancer risk, whereas women with proliferative lesions without atypia have slightly increased risk of future breast cancer (Dupont et Page 1985; Fitzgibbons et al. 1998; Morrow et al. 2015).

5.6.3 Atypical hyperplasia: ADH and ALH

ADH is a clonal proliferation of monomorphic, evenly placed epithelial cells involving terminal-duct lobular units (Lakhani et al. 2012; Tan et Sahin 2017). It resembles microscopically low-grade DCIS, and differs from it only with regard to the extent of the atypia and proliferation of the abnormal cell population (Lakhani et al. 2012). According to many sources, two quantitative criteria that distinguish ADH from low-grade DCIS are the presence of homogenous involvement of not more than two membrane-bound spaces, or a size of ≤ 2mm (Lakhani et al. 2012; Sinn et Kreipe 2013). The atypical cell population shows high levels of oestrogen receptor expression, a low proliferative rate, and shares genetic and molecular alterations with those of low-grade DCIS and low-grade oestrogen receptor-positive (luminal type) invasive breast cancers (Lakhani et al. 2012; Morrow et al. 2015).

ALH is an atypical epithelial lesion originating in the terminal-duct lobular unit (Lakhani et al. 2012; Tan et Sahin 2017). It is characterized by a proliferation of generally small, monomorphic, discohesive cells (Lakhani et al. 2012; Tan et Sahin 2017). ALH morphologically resembles LCIS, but differs from it with regard to the extent of atypia and involvement of the lobular units: in ALH, the atypical cell population distorts and distends less than half of the acinar spaces of a lobular unit (Morrow et al. 2015).

Both ALH and ADH increase the probability for the subsequent risk of invasive breast cancer. The magnitude of the risk of breast cancer development is similar between ALH and ADH, with a relative risk of 4.0-5.0 times after a diagnosis of either lesion (Dupont et Page 1985; Dupont et al. 1993; Fitzgibbons et al. 1998; Hartmann et al. 2005; Morrow et al. 2015; Page et al. 1985). It has been pondered whether atypias represent direct precursors versus generalized risk indicators. Continued risk over the long term, including contralateral cancers, support atypia's role as a generalized risk indicator (Hartmann et al. 2014). In contrast, features supporting a precursor role, as Hartmann et al. (Hartmann et al. 2014) showed, include the tendency for cancers in the ipsilateral breast and at earlier time-points. They showed that cancers developing within five years of diagnosis of atypia were more likely to be ipsilateral (2:1 ratio) than cancers arising beyond that point (Hartmann et al. 2014). Studies have also shown common patterns of genetic alteration in ADH, low-grade in situ and invasive cancers in the same breast, suggesting that ADH may be a non-obligate precursor lesion (Lakhani et al. 2012). In addition, a recent study showed that both ADH and ALH possess advanced genomic changes that are associated with a significant risk for breast cancer, supporting a precursor role (Danforth 2018). Hartmann et al. (Hartmann et al. 2014) underscore the relevance of atypia as a premalignant lesion, or more precisely, the premalignant nature of the surrounding tissue bed. Over time, however, with advancements in imaging

and biopsy technology, smaller foci of atypical hyperplasia are being diagnosed, which may carry a lower risk for invasive breast cancer (Menes et al. 2017).

5.6.4 In situ cancer: LCIS and DCIS

The World Health Organization (WHO) Classification of Breast Tumours, 4th edition, lists both DCIS and LCIS as precursor lesions of the breast, but emphasizes their different clinical behaviour and the consequential differences in therapeutic recommendations (Lakhani et al. 2012; Sinn et Kreipe 2013).

LCIS is a non-invasive atypical epithelial lesion composed of round, monomorphic, discohesive cells in the terminal ductal lobular unit (Lakhani et al. 2012; Tan et Sahin 2017). Classic LCIS is diagnosed when more than half of the acinar spaces in a lobule are distended and distorted by a dyshesive proliferation of cells with small, uniform nuclei (Lakhani et al. 2012). Current evidence suggests that LCIS is both an indicator of an increased risk of breast cancer development and a nonobligate precursor lesion (Lakhani et al. 2012; Morrow et al. 2015). The risk of subsequent breast cancer development exists ipsilaterally to the breast with LCIS, as well contralaterally and bilaterally (King et al. 2015). More recently, pleomorphic LCIS has been recognized (Lakhani et al. 2012). It has marked nuclear pleomorphism (equivalent to that in high-grade DCIS), often with apocrine features and comedo necrosis (Lakhani et al. 2012; Tan et Sahin 2017). It is more aggressive than the classic type and is often managed as DCIS (Masannat et al. 2018).

DCIS is a non-invasive neoplastic epithelial cell proliferation that is confined within the basement membranes, arising in the terminal ductal lobular unit (Tan et Sahin 2017). It is characterized by subtle to marked cytological atypia, and has an inherent, but not necessarily obligate, tendency to progress to invasive breast cancer (Lakhani et al. 2012). DCIS shows different histological patterns, with comedo, solid, cribriform, papillary, and micropapillary being the most often diagnosed (Tan et Sahin 2017). DCIS is generally divided into three grades based on nuclear features: low, intermediate, and high (Lakhani et al. 2012). In addition, DCIS can be classified based on mammographic features according to Tabar et al. (Tabar et al. 2004; Zhou et al. 2017). Hence, DCIS is regarded as a true precursor lesion of invasive breast cancer (Morrow et al. 2015; Sinn et Kreipe 2013). The risk of breast cancer is primarily in the index breast, and management strategies are similar for those used for invasive cancer (Morrow et al. 2015).

5.6.5 Invasive cancer

The vast majority of breast malignancies arise from the epithelial cells lining the lobular unit of the terminal duct. Invasive cancer indicates a proliferation of malignant cells which penetrate through the basement membrane of ducts and lobular units (Tan et Sahin 2017). Breast cancers are broadly categorized into invasive cancers with special morphological types and invasive cancers without any special morphological features (Cardoso et al. 2017; Lakhani et al. 2012; Tan et Sahin 2017). In addition, several histological subtypes have been recognized (Lakhani et al. 2012; Tan et Sahin 2017). In clinical practice, breast cancers are classified into intrinsic subtypes (Lakhani et al. 2012) based on the immunohistochemically detected expression of oestrogen and progesterone receptors and proliferative activity (Ki-67), and human epidermal growth factor receptor 2 (HER2) amplification status identified by immunohistochemistry and in situ hybridization (Lakhani et al. 2012; Tan et Sahin 2017). Tumour grade is a predictor of clinical outcome (Cardoso et al. 2017; Elston et Ellis 2002; Tan et Sahin 2017). Three tumour characteristics — tubule formation, nuclear pleomorphism, mitotic count — are assessed using defined criteria (Elston et Ellis 2002). The staging system for breast cancer follows the TNM (tumour, node, metastases) classification (Brierley et al. 2017). The TNM system provides information about the anatomical extent of disease, which is essential for decisions on the oncological treatments and surveillance of the patients (Brierley et al. 2017; Lakhani et al. 2012) .

Invasive cancer of no specific type (invasive ductal cancer) is a heterogenic group of tumours that do not exhibit sufficient characteristics to be classified as a specific histological type (Lakhani et al. 2012). It is the largest group of invasive breast cancers comprising between 50% and 80% of all breast cancers (Lakhani et al. 2012). The wide incidence range is explained by many breast cancers showing only focal components of special types of breast cancer (Tan et Sahin 2017). There are no specific features to distinguish ductal cancer from other types of invasive breast cancer, and designation of this type is through exclusion of recognized special types (Lakhani et al. 2012; Tan et Sahin 2017). Thus, the appearance of invasive ductal cancer under the microscope is highly variable (Tan et Sahin 2017).

Invasive lobular cancer is the second most common histological type comprising 5-15% of invasive breast tumours (Lakhani et al. 2012). In the classic form, it is characterized by a proliferation of discohesive, monomorphic tumour cells that are individually dispersed or arranged in a single-file linear pattern (Lakhani et al. 2012; Tan et Sahin 2017). Variants of classic invasive lobular cancer are solid, alveolar, tubulolobular, and pleomorphic type (Lakhani et al. 2012).

Other histological types of invasive breast cancer are relatively rare. The most common include tubular, cribriform, apocrine, metaplastic, mucinous,

papillary, and micropapillary cancer, as well as cancer with neuroendocrine, medullary, and salivary gland/skin adnexal type features (Sinn et Kreipe 2013).

5.7 Breast cancer risk associated with high-risk lesions and risk management options

Breast cancer risk associated with high-risk lesions (ADH, ALH, and LCIS) is well demonstrated in several studies. Hartmann et al. (Hartmann et al. 2014) showed that the cumulative incidence of breast cancer at 25 years was 29.0% in women with ADH or ALH. King et al. (King et al. 2015) also demonstrated a two percent annual incidence of breast cancer among women with LCIS and an overall cumulative cancer incidence of 26% at 15 years. Coopey et al. (Coopey et al. 2012) showed estimated 10-year cancer risks with ADH, ALH, and LCIS to be 17.3%, 20.7%, and 23.7%, respectively. In addition, the study by Degnim et al. (Degnim et al. 2007) showed that the 20-year cumulative risk of breast cancer with atypical hyperplasias was 21%. The risk exists also in younger women. McEvoy et al. (McEvoy et al. 2015) evaluated breast cancer risk in women under the age of 35 with ADH, ALH, and LCIS, and discovered that 12.1% developed breast cancer after a mean of 7.5 years, and the average age of cancer detection was 41 years. They concluded that young women with atypical lesions are at a markedly increased risk for breast cancer. Similarly, Hartmann et al. (Hartmann et al. 2014) showed in their Mayo Clinic cohort study that breast cancer risk is increased in young women with atypia. The younger a woman is when she receives a diagnosis of atypical hyperplasia, the more likely is the breast cancer to develop (Hartmann et al. 2005; Hartmann et al. 2014; Hartmann et al. 2015). There has been a controversy, however, regarding whether a family history of breast cancer has an effect on the breast cancer risk among women with atypical hyperplasia. Dupont and Page (Dupont et Page 1985) first described that a risk of breast cancer was higher in women with atypical hyperplasia and a family history of breast cancer. However, subsequent data have shown that family history of breast cancer does not increase the risk of breast cancer in patients with atypia beyond that of atypia itself (Degnim et al. 2007; Hartmann et al. 2014; Hartmann et al. 2015). It has been shown that greater numbers of atypical hyperplasia foci are associated with higher risk of breast cancer (Degnim et al. 2007; Hartmann et al. 2015). Degnim et al. (Degnim et al. 2007) demonstrated that with a single focus of atypical hyperplasia, the cumulative incidence of breast cancer was 18% at 25 years compared to 40% at 25 years with two or more foci of atypia.

The growing public awareness of breast cancer and its risk factors has led to many women consulting their doctors regarding their breast cancer risk (Boughey et al. 2010). At present, standard breast cancer risk prediction

models do not provide accurate estimates when assessing risk for women with atypical hyperplasias (Boughey et al. 2010; Degnim et al. 2016; Hartmann et al. 2015; Pankratz et al. 2008). However, accurate assessment of the risk of breast cancer development associated with atypical hyperplasia and LCIS has become more clinically relevant with the improved availability of advanced imaging technologies to screen women at increased risk of the disease, and with the approval of drugs for breast cancer risk reduction (Morrow et al. 2015). Current risk-management options for women with ADH, ALH, and LCIS include active surveillance, chemoprevention, and more rarely bilateral prophylactic mastectomy (Coopey et al. 2012; Hartmann et al. 2015; Hunt et al. 2017; King et al. 2015; McEvoy et al. 2015; Morrow et al. 2015; Visvanathan et al. 2013).

Active surveillance relies on screening mammogram. Houssami et al. (Houssami et al. 2014) found no difference in the sensitivity of screening mammogram for breast cancer detection among women with ADH, ALH, or LCIS compared with a control group lacking a history of these lesions. However, they stated that these patients may benefit from adjunct (ultrasound or MRI) screening due to lower mammogram specificity and higher interval cancer rates. Berg et al. (Berg et al. 2012) also suggested that in women with an increased risk of breast cancer, supplementation of ultrasound or MRI resulted in a higher cancer detection, but also an increase in false positive findings. For women under the age of 35 with ADH, ALH, and LCIS, McEvoy et al. (McEvoy et al. 2015) recommended MRI starting at age 25 through 29, and screening mammograms for those over the age of 30. At present, the guidelines for breast cancer screening of high-risk women state that there is insufficient evidence to make recommendations for or against MRI screening, and there are no prospective data that address the value of screening MRI for women with atypical hyperplasia (Hartmann et al. 2015). However, as Hartmann et al. stated, given the recently published data on the cumulative risk of breast cancer in patients with atypical hyperplasia, which is a level of risk that meets the current standard for MRI screening, it is important that guidelines are updated to include a recommendation for MRI screening in addition to mammogram in patients with atypical hyperplasia (Hartmann et al. 2015).

The use of chemoprevention as a risk management has been shown to reduce breast cancer incidence among women with atypical hyperplasia and LCIS at 10 years from 21.3% to 7.5% (Coopey et al. 2012). King et al. (King et al. 2015) also showed a reduction in breast cancer incidence at 10 years from 21% to 12% in women with LCIS taking chemoprevention compared to women with no chemoprevention. Current guidelines by the American Society of Clinical Oncology (Visvanathan et al. 2013) recommend considering tamoxifen (selective oestrogen receptor modulator, SERM) as an option to reduce the risk of breast cancer in pre- and postmenopausal women

at increased risk of breast cancer or with LCIS, as well as raloxifene (SERM) and exemestane (aromatase inhibitor) for postmenopausal women. Morrow et al. (Morrow et al. 2015) concluded that substantial and persistent elevation in breast cancer risk in these women is sufficient to justify a discussion of chemoprevention with those in good health, particularly pre-menopausal women.

Bilateral prophylactic mastectomy reduces the risk of developing a primary breast cancer, and the reduction from this procedure is greatest in healthy, unaffected women with a known genetic predisposition or a strong family history of breast and ovarian cancer (Hunt et al. 2017). It is also likely to confer a survival advantage when it is performed at a relatively early age in women at very high risk for breast cancer (Hunt et al. 2017). In the average-risk woman, or women with a small increase in risk, there is no evidence it improves survival (Hunt et al. 2017). However, atypical hyperplasia or LCIS are generally not indications for bilateral prophylactic mastectomy (Hartmann et al. 2015).

6 AIMS OF THE STUDY

The aim of the thesis was to analyse the incidence of occult breast cancer and lesions associated with an increased risk of breast cancer in reduction mammaplasty specimens in patients both with and without a history of breast cancer.

The specific aims were:

I To assess the incidence of invasive and in situ cancer, and benign breast disease associated with an increased risk of breast cancer in reduction mammaplasty specimens in day-surgery patients.

II To describe the imaging process in a single centre regarding modality selection, age, and timing, in addition to the association between imaging and histopathological findings in reduction mammaplasty specimens.

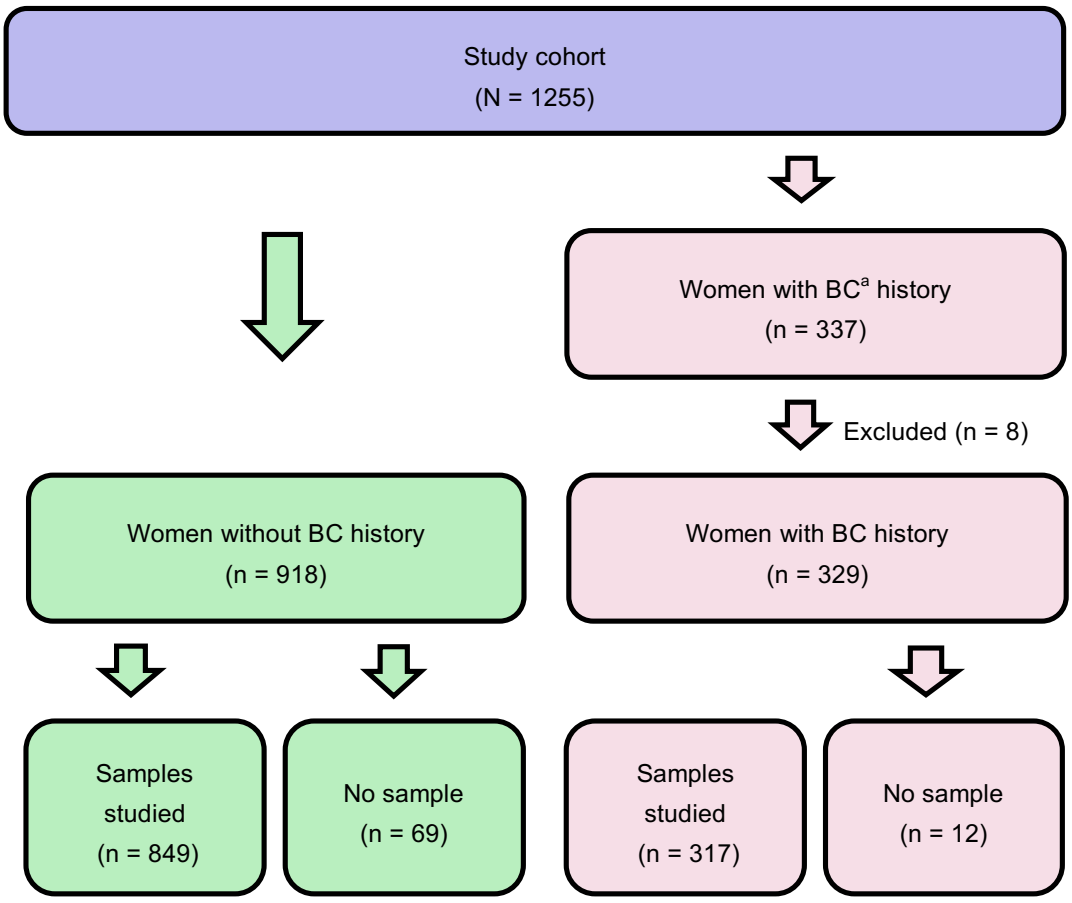
III To analyse the incidence of occult breast cancer and lesions associated with an increased risk of breast cancer in reduction mammaplasty specimens in patients without a previous history of breast cancer. Also, to analyse whether patients with abnormal histopathology differ from patients with normal histopathology in terms of demographics.

IV To examine the incidence of occult breast cancer and high-risk lesions in reduction mammaplasty patients with a previous history of breast cancer. In addition, to analyse whether the timing of reduction mammaplasty with respect to oncological treatment influenced on the incidence of abnormal findings in the specimens.

7 MATERIALS AND METHODS

7.1 Patients

Reduction mammaplasty patients operated in the Department of Plastic surgery, Helsinki University Hospital, Töölö, and Jorvi Hospital units, between January 2007 and December 2011, were retrospectively reviewed. The University Hospital Research Board approved the study. A total of 1255 women underwent reduction mammaplasties during the study period. The number of patients without a history of breast cancer operated in Töölö Hospital was 466 (50.8%), and in Jorvi Hospital was 452 (49.2%). The number of patients with a history of previous breast cancer operated in Töölö Hospital was 177 (52.5%), and in Jorvi Hospital was 160 (47.5%). The number of patients and samples studied are illustrated in Flowchart 1.



[a]BC: Breast cancer

Flowchart 1 The number of patients and samples studied.

Study I

Study I represented a pilot study for the final study population. Patient material consisted of 101 consecutive patients, who underwent surgery for symptomatic macromastia in Jorvi Hospital day-surgery unit during 1.1.2007-30.4.2009. One patient was excluded because of the history of breast cancer, giving the total amount of 100 patients. Demographic data, findings in preoperative imaging, histopathology reports, postoperative follow-up, and retrospective radiologic reviewing of images were recorded.

Studies II-III

Women with a previous history of breast cancer were excluded, and the final study population amounted to 918 patients. The indications for the surgery were symptomatic macromastia or asymmetry of the breasts. Eleven patients entered the study material twice and one patient three times, due to re-reductions. Unilateral procedures were performed in 35 cases due to congenital or postoperative asymmetry, for instance, one patient had undergone mastectomy due to burn injury and reduction mammaplasty was performed for achieving better symmetry. Findings were recorded per treated patient and not per breast. Patient records were retrieved and retrospectively analysed for demographic data, preoperative imaging, operative and histopathology reports, and postoperative follow-up.

Study IV

The study population consisted of 337 breast cancer patients. Eight patients had been entered to the database indicating reduction mammaplasty, but patient records revealed that the true procedures comprised, for example, oncoplastic resection with reduction mammaplasty technique, or breast reconstruction with breast sharing technique. Thus, the final number of patients was 329. The final number of patients operated in Töölö Hospital was 175 (53.2%), and in Jorvi Hospital was 154 (46.8%). The data was retrieved from patient records and retrospectively analysed for demographics, operative and histopathology reports, oncological treatment, and postoperative follow-up.

7.2 Preoperative imaging

During the study period imaging protocols varied. Reduction mammaplasty patients without a previous history of breast cancer conducted ultrasound, mammogram or both imaging modalities depending on the imaging site, breast density, and age. Some patients were referred to undergo imaging in the private sector or in primary health care centres. Some patients

underwent no preoperative imaging. The different approaches to imaging were due to present routines at that time and thus the groups were not designed for research purposes.

Study I

A radiologist, with over ten years of breast imaging experience, reviewed and re-analysed available mammograms of those women who had abnormal findings in reduction mammaplasty specimens.

Studies II-III

Preoperative imaging findings were retrospectively classified according to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) (D'Orsi et al. 2013) as listed in Table 1. BI-RADS 1 and BI-RADS 2 were categorized as normal breast imaging findings, and BI-RADS 3 and BI-RADS 4 as suspicious of malignancy.

This study retrospectively assessed if the findings in preoperative imaging associated with histopathological diagnosis of the specimens. Those patients who had malignant postoperative histopathology had their mammogram reviewed and re-analysed by a radiologist. This study also registered the time frame in which patients had completed preoperative imaging prior to surgery, and six months or less was considered as a cut off according to the present recommendation. Breast density was retrospectively analysed for patients with malignant postoperative histopathology according to BI-RADS lexicon (D'Orsi et al. 2013).

Study IV

In breast cancer patients, preoperative imaging was not separately recorded. The reason for this was that in case of primary breast cancers, the diagnosis was typically obtained from screening mammograms, and thus the imaging was conducted for other than preoperative purposes. In addition, patients with a history of breast cancer are followed-up by a multidisciplinary team, and the imaging is part of the normal clinical regime. Therefore, preoperative imaging was not included in this study.

7.3 Histopathology

Experienced pathologists performed histopathological analysis of reduction mammaplasty specimens. After formalin fixation, weighing and macroscopic examination of the specimens were carried out. Specimens were cut into one-centimetre slices that were palpated for masses and for areas of increased

density. Samples for tissue blocks were taken from macroscopically suspicious areas or randomly and evaluated histopathologically.

Histopathological findings in reduction mammaplasty specimens were categorized based on a consensus statement outlined by the Cancer Committee of the College of American Pathologists (Fitzgibbons et al. 1998). In short, abnormal histopathological findings in this thesis included proliferative breast lesions without atypia, ADH, ALH, LCIS, DCIS, and invasive cancer.

Study I

Approximately six to eight blocks were taken from macroscopically suspicious areas and evaluated histopathologically. In Study I, LCIS was categorized as an in situ finding and calculated as a cancer finding. In 11 (11.0%) patients, no tissue sample was submitted to histopathological analysis.

Studies II-III

The number of blocks per breast varied between four and 20, five being the most common. Abnormal histopathological findings were divided into subgroups based on the relative risk of invasive breast cancer. Low risk lesions included sclerosing adenosis, intraductal papilloma, and phylloid tumour. High-risk lesions included ADH, ALH, and LCIS. Invasive cancer and DCIS were categorized as cancer findings according to their similar clinical management. All other histopathological findings were defined as normal breast tissue. In 69 (7.5%) patients, no tissue sample was submitted to histopathological analysis. The percentages of abnormal findings were calculated from the number of samples available (n = 849).

Study IV

The number of tissue blocks varied between three and 22, six being the most common. In 12 (3.6%) patients, no tissue sample was submitted to histopathological analysis. Abnormal histopathological findings were divided into subgroups based on the relative risk of invasive breast cancer. Low-risk lesions included intraductal papilloma and sclerosing adenosis. High-risk lesions included ADH, ALH, and LCIS. Invasive cancer and DCIS were categorized as cancer findings due to their similar clinical management. All other histopathological findings were defined as normal breast tissue. The percentages of abnormal findings were calculated from the number of samples available (n = 317). For statistical purposes, patients with abnormal histopathology were assigned to subgroups based on the most severe finding,

for example, a patient with both low-risk and high-risk lesions was included in the high-risk group.

Primary breast cancers of those patients, who underwent symmetrizing reduction mammaplasty, were recorded. For statistical purposes, no sub-classification of invasive carcinomas was performed.

7.4 Statistical analysis

Study I

Descriptive statistics were reported as the mean value and range between minimum and maximum. The frequency of histopathological abnormality was calculated on a patient basis (how many women were affected).

Study II

Descriptive statistics were reported as the mean value and range between minimum and maximum. Pearson's chi-squared test was applied in bivariate analyses with categorical variables. Two-sample t-test and analysis of variance were used when patient age was compared between patient groups. The sensitivity of preoperative imaging and diagnosis was calculated as cancers detected preoperatively compared to all cancers diagnosed in reduction mammaplasty specimens. The specificity was calculated as patients with normal preoperative imaging compared to patients without cancer in their specimens.

Study III

Descriptive statistics were reported as the mean value (SD). Pearson's chi-squared test was applied in bivariate analyses with categorical variables. Mann-Whitney U test was applied for difference in medians. P-values less than 0.05 were considered statistically significant.

Study IV

Mean values (SD) were reported for continuous variables. Pearson's chi-squared test was applied in bivariate analyses between categorical variables. Mann-Whitney U test was applied for testing differences in medians between two groups, when variables did not follow normal distribution. Two-sample t-test and analysis of variance were used when patient age was compared between patient groups. P-values less than 0.05 were considered statistically significant.

The statistical analysis of whether primary cancer type affected the incidence of abnormal histopathological findings in reduction mammaplasty specimens was impossible due to the small number per primary cancer type.

8 RESULTS

8.1 Demographic data

Study I

A total of 100 women underwent reduction mammaplasty in a day-surgery unit. The average age of the patients was 43.9 years (range 16 – 64 years). Reduction mammaplasty specimens from both breasts together weighed between 400 and 3119 grams (mean 1168g).

Study II and III

A total of 918 women without a previous history of breast cancer underwent reduction mammaplasty with a mean age of 44.3 ± 12.8 years (range 16 – 79 years) and a mean body mass index of 27.7 ± 3.9 (range 19.0 – 50.5). The mean age (SD), body mass index (BMI), reduction mammaplasty specimen weight (g), past medical history, previous breast surgery, and smoking habits of the patients with normal and abnormal histopathology are listed in Table 3. There was a statistically significant difference in age ($p < 0.001$) and specimen weights ($p < 0.001$) between patients with abnormal and normal histopathology such that abnormal histopathology correlated with a higher age and heavier specimen.

Table 3 *Demographic characteristics of the patients without a previous history of breast cancer. (Reproduced with permission from JPRAS, An International Journal of Surgical Reconstruction (Merkkola-von Schantz et al. 2017b))*

Demographic Data	Normal histopathology n = 761	Abnormal histopathology n = 88
Mean age[a]	44.0 ± 12.9	49.5 ± 10.2
Mean BMI	27.7 ± 3.9	28.5 ± 3.8
Previous medical condition[b]	399 (52.4%)	51 (58.0%)
Smoking	Yes: 88 (11.6%) No: 673 (88.4%)	Yes: 7 (8.0%) No: 81 (92.0%)
Previous breast surgery	66 (8.7%)	5 (5.7%)
Mean weight (g) of the specimens[a]	1136.6 ± 627.7	1331.2 ± 581.7

[a] There is a statistical difference in age ($p < 0.001$) and specimen weights ($p < 0.001$) between patients with abnormal and normal histopathology.

[b] Five most common: hypertension, asthma, depression or depressed mood, hypercholesterolemia, and hypothyroidism.

Study IV

A total of 329 women with a previous history of breast cancer and a mean age of 56.3 ± 8.2 years, underwent reduction mammaplasty. The mean age (SD), smoking history, previous breast surgery, and the mean weight (g) of the specimen of the patients with normal and abnormal histopathology are listed in Table 4. There was a significant difference in age ($p = 0.0053$), specimen weights ($p = 0.0491$), and incidence of previous breast surgery ($p < 0.001$) between patients with abnormal and normal histopathology so that abnormal histopathology correlated with higher age, heavier specimen, and with no previous breast surgery. The incidences of different forms of primary cancer in patients undergoing contralateral reduction mammaplasty and histopathological evaluation are listed in Table 5.

Table 4 *Demographic characteristics of the patients with a previous history of breast cancer. (Reproduced with permission from The Breast (Merkkola-von Schantz et al. 2017a))*

Demographic data	Normal histopathology n = 249	Abnormal histopathology n = 68
Mean age[a]	55.8 ± 8.1	58.9 ± 8.5
Positive smoking history	19 (7.6%)	2 (2.9%)
Previous breast surgery[a] • No • Yes	26 (56.5%) 223 (82.3%)	20 (43.5%) 48 (17.7%)
Mean weight (g) of the specimens[a]	342.8 ± 256.6	398.2 ± 254.9

[a] There is a statistical difference in age (p = 0.0053), specimen weights (p = 0.0491) and incidence of previous breast surgery (p < 0.001) between patients with abnormal and normal histopathology.

Table 5 *The incidences of different forms of primary cancer in patients undergoing contralateral reduction mammaplasty and histopathological evaluation. (Reproduced with permission from The Breast (Merkkola-von Schantz et al. 2017a))*

Primary cancer	Normal histopathology n = 249	Abnormal histopathology n = 68
DCIS	21 (8.4%)	12 (17.6%)
IDC	157 (63.1%)	45 (66.2%)
ILC	45 (18.1%)	8 (11.8%)
IDC and ILC	10 (4.0%)	2 (2.9%)
Other	5 (2.0%)	1 (1.5%)
Unknown	11 (4.4%)	0 (0.0%)

DCIS: Ductal carcinoma in situ, IDC: Invasive ductal cancer, ILC: Invasive lobular cancer, IDC and ILC: Both Invasive ductal and lobular cancers, Other: Malign Phylloid Tumour, Both Paget disease and DCIS, or Both Paget disease and IDC.

8.2 Preoperative imaging

Study I

Preoperative imaging had been conducted for 95.0% of the patients. The different imaging modalities and patient numbers are presented in Table 6. Ultrasound, as the only imaging modality, was carried out for one patient. In five percent of the patients neither of the imaging modalities were completed or the information about imaging could not be confirmed. The average age of the patients who did not conduct preoperative mammogram, ultrasound, or neither of the imaging was 36.2 years (range 16 – 64 years), 48.1 years (range 16 – 64 years), and 38.2 years (range 16 – 64 years), respectively. In two patients, with an average age of 50.5 years, abnormal preoperative imaging

led to further examinations. Fine needle biopsy was performed for one of them and core needle biopsy for the other. The histopathology results showed no cell atypia and mastopathia chronica, respectively.

Table 6 *The different imaging modalities in day-surgery patients. (Reproduced with permission from the Scandinavian Journal of Surgery (Merkkola-von Schantz et al. 2014))*

Imaging modality	Number of patients
Mammogram	94
Ultrasound	79
Both modalities	78
No imaging	5

Preoperative mammograms of the 13 patients with abnormal histopathological findings were retrospectively searched for and seven were retrieved and re-analysed by an experienced radiologist. Micro-calcifications existed in one of the preoperative mammograms analogous to intraductal papilloma diagnosed histopathologically. Preoperative mammograms were negative in six (46.0%) of these patients.

Study II and III

Preoperative imaging had been conducted for 89.2% of the patients (n=819) without a previous history of breast cancer. The different imaging modalities and the patient numbers are presented in Table 7. The mean age of the patients with normal (BI-RADS 1 and BI-RADS 2) imaging findings did not statistically differ from patients with imaging suspicious of malignancy (BI-RADS 3 and BI-RADS 4).

Table 7 *The different imaging modalities among patients without a previous history of breast cancer. (Reproduced with permission from the World Journal of Surgery (Merkkola-von Schantz et al. 2017c))*

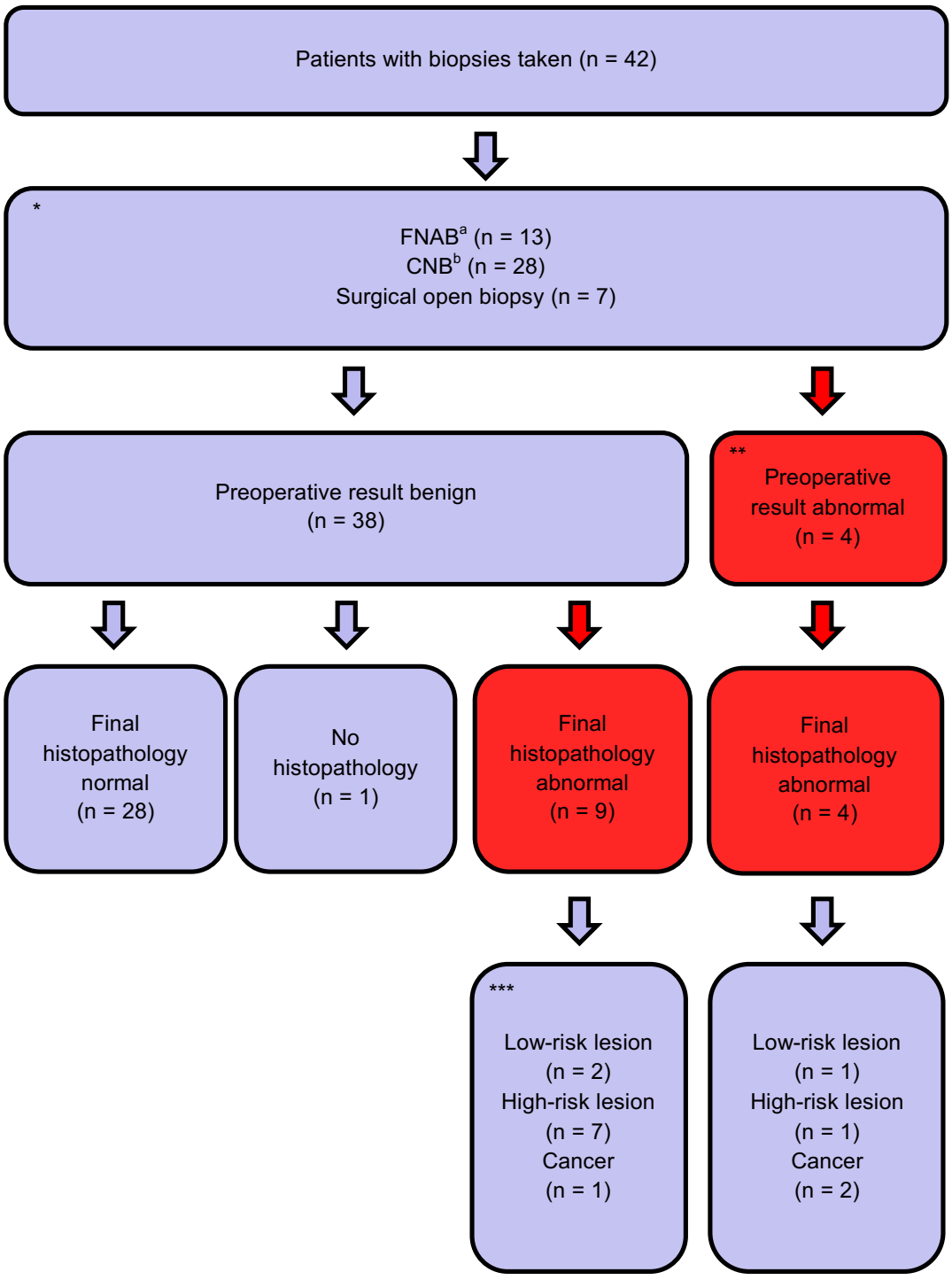
Imaging modality	Patients (%)	Mean age and range
Mammogram alone	250 (27.2%)	47.0 (18 – 73)
Ultrasound alone	15 (1.6%)	21.5 (18 – 26)
Both modalities	554 (60.3%)	43.8 (18 – 79)
No imaging	99 (10.8%)	43.2 (16 – 68)

8.2.1 Association between BI-RADS class of mammogram and ultrasound

BI-RADS classes of mammogram and ultrasound coincided in 536 (96.8%) patients with both imaging modalities (n = 554). For 18 patients (aged 32 to 67 years) adjunct ultrasound revealed suspicious lesions, which were undetectable in mammogram. These lesions were biopsied (n = 15) with benign results, or surgical open biopsy (n = 2) was performed simultaneously with reduction mammaplasty. Final histopathology revealed high-risk lesions in five patients. One patient had no further work-up despite BI-RADS 4 class in the ultrasound (left breast), and the final histopathology revealed DCIS in both breasts, sized 7mm (right breast) and 2.5mm (left breast).

8.2.2 Additional preoperative examinations

In total, preoperative imaging was suspicious of malignancy (BI-RADS 3 and BI-RADS 4 category) in 56 (6.8%) of the 819 imaged patients. No further examinations were performed in 12 of these patients. In 49 of 819 (6.0%) patients imaging led to further examinations. The mean age of these patients was 45.3 years (range 23 - 67 years). Mammographic magnification of a suspicious area had been conducted for nine patients. Flowchart 2 shows the process of patients submitted for biopsies. In total, further examinations revealed two cancers (48 and 58 years), one ADH (50 years), and one LCIS (56 years) finding. Table 8 demonstrates features and treatment of two preoperatively diagnosed cancer findings.



[a] FNAB: Fine needle aspiration biopsy, [b] CNB: Core needle biopsy * Six patients needed two simultaneous examinations, ** Cancer (n = 2), ADH (n = 1), LCIS (n = 1), *** One patient had two simultaneous lesion

Flowchart 2 Illustration of the patients submitted for biopsies. (Reproduced with permission from the World Journal of Surgery (Merkkola-von Schantz et al. 2017c))

Table 8 *Preoperatively diagnosed cancer findings. (Reproduced with permission from the World Journal of Surgery (Merkkola-von Schantz et al. 2017c))*

Patient	Imaging	Tumour size in imaging	Needle biopsy	Treatment	Tumour size in histopathology
Patient 1	MMG[a] (BI-RADS 4), US[b] (BI-RADS 4) D2[c]	14mm (MMG, US)	CNB[d]	Oncoplastic resection, SNB[e], contralateral reduction mammaplasty	13mm
Patient 2	MMG (BI-RADS 2, 4), US (BI-RADS 4) D1	11mm (MMG), 10x7x7mm (US)	CNB	Oncoplastic resection, SNB, contralateral reduction mammaplasty	12mm

[a]MMG: Mammogram, [b]US: Ultrasound, [c]D: Breast density, [d]CNB: Core needle biopsy, [e]SNB: Sentinel node biopsy

8.2.3 Association between preoperative imaging and histopathology of the specimens

There were 12 patients with no conducted preoperative imaging and with no histopathological analysis of reduction mammaplasty specimen. Among patients with abnormal histopathology (n = 88), preoperative imaging had been conducted for 78 (88.6%) patients and no imaging was conducted for 10 (11.4%) patients. Preoperative imaging was normal (BI-RADS 1 and BI-RADS 2) in 80.8% and suspicious of malignancy (BI-RADS 3 and BI-RADS 4) in 19.2% of these patients. Among patients with imaging suspicious of malignancy (n = 56; BI-RADS 3 and BI-RADS 4), reduction mammaplasty specimens revealed abnormal histopathological findings in 27.3% and normal findings in 72.7% of the patients. One patient had no histopathological analysis of reduction mammaplasty specimen despite suspicious imaging. During the study period, no mention of subsequent oncological incident was found with this patient. Final histopathology revealed 10 (1.2%) patients with invasive cancer or DCIS. The features of preoperatively undetected cancer findings are demonstrated in Table 9.

Table 9 *Preoperatively undetected cancer findings in reduction mammaplasty specimens. (Reproduced with permission from the World Journal of Surgery (Merkkola-von Schantz et al. 2017c))*

Patient	Age	Imaging modality	Further examinations	Result	Histopathological diagnosis of the specimen	Size of cancer
1	51	MMG[a], US[b] D2[c]	FNAB[d], CNB[e]	Benign	Invasive ductal cancer	40mm
2	51	MMG, US D3	None	-	DCIS[f] (both breasts)	7mm (right) 2,5mm (left)
3	49	MMG, US D3	None	-	DCIS (right) Invasive lobular cancer (left)	2mm (right) 7 lesions, 2 – 6mm (left)
4	50	MMG, US D2	None	-	Invasive lobular cancer, DCIS	7mm (cancer) unknown (DCIS)
5	67	MMG D1	None	-	Invasive ductal cancer	7mm
6	57	MMG D3	None	-	DCIS	2mm
7	62	MMG D2	None	-	DCIS	11mm + 7mm
8	62	None	None	-	DCIS	2mm

[a]MMG: Mammogram, [b]US: Ultrasound, [c]D: Breast density, [d]FNAB: Fine needle aspiration biopsy, [e]CNB: Core needle biopsy, [f]DCIS: Ductal carcinoma in situ

Preoperative imaging of the 10 patients with malignant histopathology was retrospectively searched for and eight were retrieved and re-analysed by an experienced radiologist. None of the previously undetected cancer findings could be retrospectively defined as clearly malignant.

8.2.4 Sensitivity and specificity of imaging

The sensitivity of the preoperative imaging was 20.0%, considering that the final histopathology encompasses only the operated part of the breast. There

were no false positive preoperative biopsy findings leading to specificity of 100.0%.

8.2.5 The timing of imaging

The date of imaging could be retrieved from patient records in 738 cases. The number of patients with conducted imaging within six months prior to surgery was 699 (94.7%), and the number of patients with older imaging was 39 (5.3%). Abnormal histopathological findings were detected in 9.7% in the timely imaged group and in 12.8% in the group with older imaging (ns).

8.3 Histopathology of the specimens

Study I

Abnormal histopathological findings occurred in 13 (14.6%) day-surgery patients with a mean age of 55.2 years (range 45 – 63 years) (Table 10.). In 11 patients, with a mean age of 35.6 years (range 22 – 59 years), specimens were not sent for histopathological examination. In situ cancer was diagnosed in four (4.5%) patients: DCIS in one (1.1%) and LCIS in three (3.4%). Breast lesions demonstrating increased risk of breast cancer were diagnosed in 12 (13.5%) patients. Four (4.5%) patients presented with more than one simultaneous lesion demonstrating increased risk of breast cancer. Three (3.4%) patients had findings in both breasts. Abnormal histopathological findings for different age groups are presented in Table 11.

The average age of the patients with in situ lesions was 52.0 years (range 45 – 62 years). The weight of the reduction mammaplasty specimen of these patients varied between 230 to 754 grams for the right breast and between 291 to 635 grams for the left breast. In this patient material, re-operation due to abnormal histopathological finding was not recommended in any case. Due to increased risk of future cancer, however, regular clinical and radiological follow-up was recommended.

Table10 *Subtypes of abnormal histopathological findings in day-surgery patients*. (Reproduced with permission from the Scandinavian Journal of Surgery (Merkkola-von Schantz et al. 2014))*

Finding	Numbers of patients	(%)
DCIS	1	1.1
LCIS	3	3.4
Intraductal papilloma	3	3.4
ADH	10	11.2
ALH	1	1.1
Sclerosing adenosis	1	1.1

* In four patients, more than one lesion demonstrating increased risk of breast cancer was diagnosed.

Table 11 *Abnormal histopathological findings among day-surgery patients of different age groups (y). (Reproduced with permission from the Scandinavian Journal of Surgery (Merkkola-von Schantz et al. 2014))*

Finding	≤ 40y (n = 32)	41 – 50y (n = 27)	51 – 60y (n = 23)	≥ 61y (n = 7)	Total (n = 89)
Abnormal histopathology	0 (0.0%)	2 (7.4%)	9 (39.1%)	2 (28.6%)	13 (14.6%)

All patients diagnosed with LCIS lesions had normal preoperative mammograms. Preoperative ultrasound was completed in one patient with in situ cancer findings, and it appeared normal. A patient with DCIS finding completed neither of the imaging methods. Among those patients (n=5) having neither of the imaging methods completed, final histopathology was abnormal in one patient revealing both DCIS and ADH in the same breast

Study II- III

Abnormal histopathological findings were revealed in 88 (10.4%) patients with a mean age of 49.5 ± 10.2 years. In 69 (7.5%) patients, with a mean age of 40.6 ± 12.7 years, no sample was submitted for histopathological analysis. Incidences of abnormal findings are presented in Table 12. Two simultaneous abnormal findings were revealed in nine, three simultaneous abnormal findings in one, and four simultaneous abnormal findings in two patients.

Table 12 *Abnormal histopathological findings in patients without a previous history of breast cancer *. (Reproduced with permission from JPRAS, An International Journal of Surgical Reconstruction (Merkkola-von Schantz et al. 2017b))*

Diagnosis	Number of patients	%
Sclerosing adenosis	20	2.4
Intraductal papilloma	19	2.2
Phylloid tumour	2	0.2
ADH	40	4.7
ALH	4	0.5
LCIS	8	0.9
DCIS	6	0.7
Invasive ductal cancer	4	0.5
Invasive lobular cancer	2	0.2

*Two simultaneous abnormal findings were revealed in nine patients, three simultaneous abnormal findings in one patient, and four simultaneous abnormal findings in two patients.

High-risk lesions (ADH, ALH, and LCIS) were identified in 47 (5.5%) patients and additionally in two patients together with cancer. In the subgroup of invasive cancer and DCIS, we could identify ten patients (1.2%). The mean age of these patients was 55.5 ± 6.6 years. Two patients were simultaneously identified with DCIS and lobular cancer.

The incidence of abnormal histopathological findings by age is presented in Table 13. A closer look at young women, under the age 30 years, revealed one patient (27 years) with an ADH finding. In addition, in the group of 30 to 40 years, four patients were diagnosed with ADH. Abnormal histopathological findings in total ($p < 0.001$), as well as high-risk lesions ($p < 0.001$) and cancer findings ($p = 0.003$), were more frequent with increasing age as demonstrated in Table 13. Still, in the subgroup of patients with high-risk lesions, 36.2% were under 50 years of age.

Table 13 *The incidence of abnormal histopathological findings by age groups (y). (Reproduced with permission from JPRAS, An International Journal of Surgical Reconstruction (Merkkola-von Schantz et al. 2017b))*

	Findings by age				
	< 40y n = 288	**40 – 49y** n = 240	**50 – 59y** n = 209	**≥ 60y** n = 112	**Total** n = 849
Abnormal histopathology[a]	14 (4.9%)	29 (12.1%)	28 (13.4%)	17 (15.2%)	88 (10.4%)
Low-risk lesion[b]	11 (3.8%)	15 (6.3%)	7 (3.3%)	4 (3.6%)	37 (4.4%)
High-risk lesion[c]	5 (1.7%)	12 (5.0%)	19 (9.1%)	11 (9.8%)	47 (5.5%)
Cancer[d]	0 (0.0%)	2 (0.8%)	5 (2.4%)	3 (2.7%)	10 (1.2%)

Abnormal histopathological findings in total ($p < 0.001$), as well as high-risk lesions ($p < 0.001$) and cancer findings ($p = 0.003$), were more frequent with increasing age.
[a]Two simultaneous abnormal findings were revealed in nine patients, three in one patient, and four in two patients.
[b] Sclerosing adenosis, intraductal papilloma, phylloid tumour, [c] ADH, ALH, LCIS, [d] Invasive cancer, DCIS

In cases of abnormal postoperative histopathology, a family history of breast cancer was positive in 12 patients and negative in 17 patients. The information about family history was unavailable for 59 (67.0%) patients.

Study IV

In patients with a history of breast cancer, histopathological evaluation of reduction mammaplasty specimens revealed abnormal findings in 68 (21.5%) patients (mean age 58.9 ± 8.5 years) and normal breast tissue in 249 (78.5%) patients. In 12 (3.6%) patients, with a mean age of 53.5 ± 6.5 years, no sample was obtained for histopathological analysis. The incidences of abnormal histopathological findings are presented in Table 14. Two simultaneous abnormal findings were revealed in 12 patients and three simultaneous abnormal findings in one patient.

Table 14 *Abnormal histopathological findings in patients with a previous history of breast cancer*. (Reproduced with permission from The Breast (Merkkola-von Schantz et al. 2017a))*

Diagnosis	Number of patients	%
Sclerosing adenosis	24	7.6
Intraductal papilloma	12	3.8
ADH	30	9.5
ALH	5	1.6
LCIS	4	1.3
DCIS	5	1.6
Invasive ductal cancer	1	0.3
Invasive lobular cancer	1	0.3

*Two simultaneous abnormal findings were revealed in 12 patients and three simultaneous abnormal findings in one patient. One patient had both ductal cancer and DCIS finding at the same time in reduction mammaplasty specimen.

In total, low-risk lesions (sclerosing adenosis, intraductal papilloma) were revealed in 35 (11.0%) patients, high-risk lesions (ADH, ALH, and LCIS) in 37 (11.7%) patients, and cancer in six (1.9%) patients. The incidence of abnormal histopathological findings by age is presented in Tables 15a and 15b. In age comparisons, for statistical purposes, patients with abnormal histopathology were categorized to subgroups based on the most severe finding, for example, a patient with both low-risk and high-risk lesions was included in the high-risk group. Abnormal histopathological findings in total were more frequent with increasing age ($p = 0.0088$). Statistical analysis for smaller subgroups was not reliable due to low number of findings per different age groups.

Table 15a *Abnormal histopathological findings by age groups (y). (Reproduced with permission from The Breast (Merkkola-von Schantz et al. 2017a))*

Finding	<40y (n = 10)	40 – 49y (n = 46)	50 – 59y (n = 143)	>60y (n = 118)	Total (n = 317)
Normal histopathology	9 (90.0%)	37 (80.4%)	122 (85.3%)	81 (68.6%)	249 (78.5%)
Abnormal histopathology*	1 (10.0%)	9 (19.6%)	21 (14.7%)	37 (31.4%)	68 (21.5%)

*Abnormal histopathological findings were more frequent with increasing age ($p = 0.0088$).

Table 15b *Abnormal histopathological subgroups presented in age groups (y)*. (Reproduced with permission from The Breast (Merkkola-von Schantz et al. 2017a))*

Finding	<40y (n = 10)	40 – 49y (n = 46)	50 – 59y (n = 143)	>60y (n=118)	Total (n=317)
Normal histopathology	9 (90.0%)	37 (80.4%)	122 (85.3%)	81 (68.6%)	249 (78.5%)
Low-risk lesion	1 (10.0%)	1 (2.2%)	13 (9.1%)	11 (9.3%)	26 (8.2%)
High-risk lesion	0 (0.0%)	7 (15.2%)	7 (4.9%)	22 (18.6%)	36 (11.4%)
Cancer	0 (0.0%)	1 (2.2%)	1 (0.7%)	4 (3.4%)	6 (1.9%)

* For statistical purposes, patients with abnormal histopathology were categorized to subgroups based on the most severe finding, for example a patient with both low-risk and high-risk lesions was included in the high-risk group.

8.4 The timing of reduction mammaplasty and breast reconstruction

Study IV

Reduction mammaplasty was performed before oncological treatment in 77 (23.4%) patients and after oncological treatment in 252 (76.6%) patients. Abnormal histopathological findings were statistically more frequent ($p < 0.001$) in patients with reduction mammaplasty performed before oncological treatment (42.1%) compared to 14.9% if surgery was performed after oncological treatment. The patients receiving neoadjuvant therapy (n = 5) were assigned to the latter group.

Breast reconstruction was performed in 159 (48.3%) patients, of which immediate reconstruction took place in 33 (20.8%) and delayed reconstruction in 126 (79.2%). The patients undergoing immediate reconstruction after neoadjuvant therapy (n = 2) were assigned to the first group. In breast reconstruction patients, contralateral reduction mammaplasty revealed abnormal histopathological findings in 31 (20.3%) patients, and histopathology was normal in 122 (79.7%). There was a statistical difference ($p = 0.0064$) in patients with abnormal histopathology between immediate and delayed reconstruction so that histopathology was abnormal in 15.7% with delayed reconstruction versus 37.5% with immediate reconstruction.

8.5 Long-term postoperative follow-up

Study III

Long-term postoperative surveillance of the patients with abnormal histopathology was counted until October 2015. The mean follow-up period for patients with abnormal histopathology and for patients with no histopathological analysis was 6.2 ± 1.4 years. In this study material, two patients developed breast cancer in the same breast as the high-risk lesion revealed in reduction mammaplasty specimens (Table 16.). Active surveillance with both mammogram and ultrasound every two years was recommended for the majority of the patients with high-risk lesions (ADH, ALH, and LCIS). In 12 patients, information about surveillance could not be found.

Table 16 *Patients with subsequent cancer. (Reproduced with permission from JPRAS, An International Journal of Surgical Reconstruction (Merkkola-von Schantz et al. 2017b))*

	Patient 1	**Patient 2**
Age at reduction mammaplasty	55	58
Preoperative imaging	MMG[a]+US[b] BI-RADS 2	MMG+US BI-RADS 2
Histopathology of the specimen	ADH	LCIS
Postoperative surveillance	MMG + US every two years	Recommended: screening MMG
		Realized: symptomatic liponecrosis -> annual imaging and several biopsies
Cancer diagnosis method	Screening MMG	Skin biopsy
Time of cancer diagnosis	4 years, 10 months	6 years, 8 months
Treatment	Mastectomy + SNB[c] + axillary clearance, hormone therapy	Mastectomy, axillary clearance, preoperative neoadjuvant chemotherapy, postoperative radiotherapy and hormone therapy
Type of cancer	Bifocal invasive ductal cancer, gr I, pT1 (20+2mm), pN0 (i+)	Bifocal invasive lobular cancer, gr I, pT2 (30+15mm), pN3a (14/21)

[a] MMG: Mammogram, [b] US: Ultrasound, [c] SNB: Sentinel node biopsy
TNM classification of malignant tumours, 7th edition. Wiley Blackwell, Oxford UK 2009

Of 69 patients with no histopathological analysis, preoperative imaging had been conducted for 57 (82.6%), all with a normal result. Retrospective survey of patient records showed no indication of future oncological treatment.

Study IV

Long-term postoperative follow-up until the end of December 2016 was included. The mean follow-up time was 7.4 ± 1.4 years. During this time, three patients were diagnosed with a new cancer in the reduced breast. Reduction mammaplasty specimens had revealed ADH in one, and mastopathia chronica in one of these patients. In the third case, no sample for histopathological analysis had been taken. The patient with ADH in the specimens was later diagnosed with DCIS. The other two were diagnosed with DCIS and invasive cancer, respectively.

9 DISCUSSION

9.1 The incidence of breast cancer and benign breast disease associated with increased risk in reduction mammaplasty specimens

Reduction mammaplasty continues to be a frequent procedure in plastic and breast surgery. Despite thorough preoperative evaluation and imaging, occult breast cancer and lesions associated with an increased risk of breast cancer are revealed in the specimens. The incidences have been studied elsewhere, however, data on this subject is lacking in Finland. In addition, variations exist in criteria for submitting the specimen for analysis and how the specimen is examined both nationally and internationally.

In this thesis, a considerable number (10.4%) of abnormal findings was detected in reduction mammaplasty specimens in patients without a previous history of breast cancer, the number doubling (21.5%) in patients with prior breast cancer. The same trend could be observed for high-risk lesions as well as in actual cancers. The incidence of occult breast cancer in patients without a history of breast cancer was 1.2%, compared to patients with a history of breast cancer for whom the incidence rises to 1.9%. Similarly, others have noticed that previous history of breast cancer increases the incidence of abnormal findings in reduction mammaplasty specimens, and in many cases multiplies the incidence of occult breast cancer (Colwell et al. 2004; Freedman et al. 2012; Goyal et al. 2011; Hassan et Pacifico 2012; Ishag et al. 2003; Li et al. 2014; Slezak et Bluebond-Langner 2011; Sorin et al. 2014; Sorin et al. 2015; Tadler et al. 2014). It is worth noting that in breast cancer patients the incidence of abnormal findings in contralateral reduction mammaplasty is calculated per one breast compared to macromastia patients with the incidence calculated per both breasts. Still, the incidence of abnormal findings, with findings from only one breast, often multiplies in breast cancer patients. Thus, this supports the importance of histopathological evaluation of reduction mammaplasty specimens. According to previous studies, when only invasive cancer and DCIS were taken into account, the incidence of occult breast cancer varies between 0.05% and 2.48% in reduction mammaplasty patients (Acevedo et al. 2018; Ambaye et al. 2009; Ambaye et al. 2017; Boice et al. 2000; Clark et al. 2009; Colwell et al. 2004; Cook et Fuller 2004; Desouki et al. 2013; Freedman et al. 2012; Goodwin et al. 2013; Hassan et Pacifico 2012; Ishag et al. 2003; Jansen et al. 1998; Kakagia et al. 2005; Pitanguy et al. 2005; Slezak et Bluebond-Langner 2011; Tadler et al. 2014; Tang et al. 1999; Viana et al. 2005; Waldner et al. 2018), and between 0.94% and 3.64% in breast cancer patients with the surgery aimed at symmetrisation (Colwell et al. 2004; Freedman et al. 2012;

Goyal et al. 2011; Hassan et Pacifico 2012; Ishag et al. 2003; Li et al. 2014; Petit et al. 1997; Slezak et Bluebond-Langner 2011; Sorin et al. 2014; Sorin et al. 2015; Tadler et al. 2014). In this thesis, the incidences of occult breast cancer correspond to previous studies in both patient groups.

Benign breast disease together with in situ cancer findings are important predictors of future breast cancer risk (Carter et al. 1988; Coopey et al. 2012; Dupont et Page 1985; Dupont et al. 1993; Dyrstad et al. 2015; Fitzgibbons et al. 1998; Hartmann et al. 2005; Hartmann et al. 2014; King et al. 2015; London et al. 1992; McEvoy et al. 2015; Morrow et al. 2015; Page et al. 1985), and they are common findings in reduction mammaplasty specimens (Acevedo et al. 2018; Akintayo et al. 2017; Ambaye et al. 2009; Ambaye et al. 2017; Blansfield et al. 2004; Clark et al. 2009; Desouki et al. 2013; Freedman et al. 2012; Ishag et al. 2003; Kececi et al. 2014; Samdanci et al. 2011). In this thesis, the incidence of high-risk lesions (ADH, ALH, and LCIS) doubled (11.7% versus 5.5%) in patients with prior breast cancer compared to patients without a history of breast cancer. Li et al. (Li et al. 2014) showed that the frequency of detecting atypical proliferative lesions in reduction mammaplasty specimens in patients with a history of breast cancer is significantly higher than in patients without previous breast cancer (12.8% versus 4.3%). Ishag et al. (Ishag et al. 2003), and Freedman et al. (Freedman et al. 2012), have demonstrated a higher incidence of high-risk lesions in breast cancer patients compared to patients without a history of breast cancer, 7.1% versus 0.97%, and 17.9% versus 3.3%, respectively. Thus, in this thesis, the incidence of high-risk lesions follows the same pattern as seen in previous studies, both in patients with and without a history of breast cancer.

In this study, there were patients with no histopathological analysis conducted, thus eliminating the possibility of data collection from the specimens. In day-surgery patients, histopathological evaluation of reduction mammaplasty specimens had not been performed for 11.0% of the patients. The mean age of these patients was markedly younger (mean 35.6 years) than the mean age of the study population. Still the oldest patient of this group was 59 years old. In patients without a previous history of breast cancer, there were 69 (7.5%) patients, with a mean age of 40.6 ± 12.7 years, with no sample submitted for histopathological analysis. However, there were also older patients in this group (range 19 – 66 years). In addition, there were 12 patients with no preoperative imaging or histopathological analysis of their reduction mammaplasty specimen, eliminating all pre- and postoperative diagnostics. In patients with prior breast cancer history, in 12 (3.6%) patients, with a mean age of 53.5 ± 6.5 years, no sample was obtained for histopathological analysis. An explanation for this may be that some surgeons might have based their decision for not sending the specimens for histopathological analysis on the young age of the patients, perhaps regarding them as low-risk patients due to their young age. The reason for

not sending older, for instance > 40 years-of-age, patients' samples for histopathological analysis remains unclear. In the public sector, the cost of histopathological analysis of the specimens is hardly the deciding factor, but it may be an issue in the private sector.

9.2 The influence of demographic features on the incidence of abnormal histopathological findings

In this thesis, there was a statistically significant difference in age and specimen weights between patients with normal and abnormal histopathology, both in patients with and without a history of breast cancer. Patients with abnormal histopathology were older and the specimens were heavier. Similarly, others have noticed that age is significantly associated with abnormal histopathological findings (Acevedo et al. 2018; Ambaye et al. 2009; Ambaye et al. 2017; Clark et al. 2009; Desouki et al. 2013; Freedman et al. 2012; Hassan et Pacifico 2012; Li et al. 2014; Samdanci et al. 2011; Tadler et al. 2014). Nevertheless, in this study high-risk lesions were distributed among all age groups in patients without a previous history of breast cancer, and among all age groups except under 40 years-of-age in patients with prior breast cancer history. Cancer was found in all age groups, except under 40 years-of-age, both in patients with and without breast cancer history. In addition, in patients with a history of breast cancer, there was a statistically significant difference in the incidence of previous breast surgery between patients with normal and abnormal histopathologies, so that if previous breast surgery was conducted, the histopathological examination more often showed normal histology. Other variables did not differ between these groups. Despite these findings, it seems difficult to define a certain cut-off age or threshold to preoperatively catch patients with abnormal histopathology or to securely say that histopathological examination can be ruled out based on a certain age group. In addition, recent studies (Hartmann et al. 2014; King et al. 2015) have shown that family history of breast cancer does not increase the risk of breast cancer in patients with atypia beyond that of atypia itself. This indicates that based on demographics and, for example, family history, histopathological analysis should not be preoperatively ruled out. However, based on this study, it is recommended that the heavier specimen of older patients might benefit from more frequent sampling. Similarly, Ambaye et al. (Ambaye et al. 2009; Ambaye et al. 2017) concluded that increased sampling was associated with a significantly greater frequency of abnormal pathologic findings, but only in patients 40 years and older. Notably, sending reduction mammaplasty specimens to histopathological analysis also in young women captures a certain population for closer future surveillance, as the importance of high-risk lesions for the patients is clear over time (Coopey et al. 2012; Hartmann et al. 2014; King et al. 2015; McEvoy et al. 2015). The majority of the patients

with previous breast surgery were operated for breast cancer and received postoperative oncological treatment before contralateral reduction mammaplasty. This may explain the protective effect of previous breast surgery.

9.3 Preoperative imaging

Preoperative imaging before reduction mammaplasty remains controversial, and to date no consensus exists. This study allows analysis of the imaging process in regard to modality selection, age, and timing, and of the association between imaging and histopathological findings in reduction mammaplasty specimens.

In this study, the majority of the patients, 95.0% in Study I and 89.2% in Studies II and III, underwent preoperative imaging. The patients who did not conduct preoperative imaging were younger (Study I mean 38.2 years and Studies II-III mean 43.2 years) than the mean age in these studies. Also, in Studies I-III there were patients with no mention about imaging in the patient records or the information about imaging could not be confirmed. Pending information on imaging may be due to a large number of patients who conduct imaging in the private sector with no mention about imaging in the patient records. In addition, younger patients may symbolize low-cancer-risk patients and therefore imaging was not performed, but this fails to explain the lack of imaging in older patients. This focuses attention on the importance of a preoperative routine. That is patients with no preoperative imaging are precluded preoperative diagnostics.

During the study period, imaging protocols varied and the different approaches to imaging were due to present routines at that time. Some of the younger patients, under the age of 30, also conducted mammogram, which nowadays is not recommended. In addition, according to current recommendations, FNAB by itself is not a sufficient diagnostic method.

The existing literature shows variation between imaging protocols in different countries. In the UK, 92.0% of breast surgeons and 41.0% of plastic surgeons routinely performed radiological screening for reduction mammaplasty patients. The majority chose age as an indicator for screening (Hennedige et al. 2011). A survey conducted in the Netherlands (Hage et Karim 2006) showed that only 3.0% of the responders routinely required preoperative mammogram, and only one responder routinely required preoperative ultrasound. In addition, a more recent study evaluating the incidence of occult malignancies in reduction mammaplasty specimens revealed that only 16% of patients underwent preoperative mammogram and 0.5% underwent ultrasound (Waldner et al. 2018). In general, preoperative

mammogram is variously recommended from the age of 30 (Blansfield et al. 2004), from the age of 40 (Acevedo et al. 2018; Ambaye et al. 2009; Butler et al. 2003; Colwell et al. 2004; Hage et Karim 2006; White et al. 2012), or for patients over the age of 50 (van der Torre et Butzelaar 1997). In this study, patients were imaged in all age groups, the mean age of these patients being over 40 years.

In this thesis, 80.8% of the patients with abnormal findings in reduction mammaplasty specimens had normal preoperative imaging. Similarly, others (Ambaye et al. 2009; Campbell et al. 2010; Colwell et al. 2004; Kakagia et al. 2005; Slezak et Bluebond-Langner 2011) have noticed that incidental discovery of atypical hyperplasia, LCIS, or cancer were not associated with abnormal imaging. Moreover, in patients without a previous history of breast cancer, only two out of 10 cancers were detected preoperatively. It seems that preoperative imaging does not sufficiently detect high-risk or cancer findings. Therefore, histopathological evaluation of reduction mammaplasty specimens seems difficult to bypass.

In Study II, among the patients with preoperatively undetected cancers, one patient (ductal cancer 40mm) had fine and core needle biopsies taken with benign results. Either biopsies were targeted incorrectly, or more likely the biopsy material was suboptimised. In three patients, both mammogram and ultrasound could not detect cancer or DCIS preoperatively despite bilateral malignancies in two of them. Why these were not detected, may be explained by the growth pattern of DCIS and lobular cancer, as well as the small size of lesions. In three patients with malignant outcome, preoperative mammogram alone, with breast densities varying from D1 to D3, was conducted. In theory, the false negative ductal cancer, sized 7mm, might have been found with additional ultrasound. In one patient, no preoperative imaging was conducted, which precludes the possibility of preoperative diagnostics. Nevertheless, small invasive cancers, DCIS, or high-risk lesions may remain undetected with all imaging modalities, including MRI. In Study II, the sensitivity of the imaging was 20.0%, which may be explained by the small size of undetected cancers. The specificity was 100.0%. There were no false positive cancers.

Study II revealed 18 patients with incoherent imaging. Despite normal mammogram, ultrasound was conducted and showed BI-RADS 4 unexpectedly. Eventually, 33.3% of the patients had either DCIS or a high-risk lesion in the specimens. Although actual cancer findings in the reduction mammaplasty specimens were rare in this patient group, a considerable number of findings demonstrating increased risk of breast cancer were detected. There is data indicating that both imaging modalities are warranted in some cases. In screening situations (Houssami et al. 2014) patients with a history of ADH, ALH, or LCIS may benefit from adjunct (ultrasound or MRI)

screening due to lower mammogram specificity and higher interval cancer rates. In women with an increased risk of breast cancer, supplementation of ultrasound can result a higher cancer detection, but also an increase in false positive findings (Berg et al. 2012). Ultrasound also has the ability to detect small, mammographically occult breast cancers in women with dense breast tissue (Crystal et al. 2003; Korpraphong et al. 2014), as sensitivity of mammogram is lower among young women and in dense breasts (Saarenmaa et al. 2001). However, in this study, a substantial amount of work with false positive imaging raises the question of the use of routine ultrasound in combination with mammogram, as opposed to ultrasound only in dense breasts or in addition to suspicious mammogram.

The importance of screening mammogram has been debated lately and guidelines re-assessed. For example in the USA, breast density notification legislations have been introduced, and women with dense breasts have the choice to conduct further screening with additional imaging modalities (Price et al. 2013). There are differences in target age between countries. Currently, routine mammographic screening is not recommended for women under the age of 40. However, breast cancers in very young women are typically aggressive (Narod 2012), and DCIS in young women is often multifocal and multicentric (Alvarado et al. 2012). These studies support preoperative imaging also in very young women. Based on this, preoperative ultrasound is recommended prior to major breast surgery for women under 30 years of age in our unit, and mammogram is recommended for patients older than that. At present, there are no national guidelines available for reduction mammaplasty patients.

Reduction mammaplasty changes the architecture of the breast and complicates the exact localization of abnormal findings. In case of occult cancer in the specimens, breast-conserving options may be limited. Therefore, emphasis should be placed on preoperative diagnosis, hence the surgery can be altered into oncoplastic resection in case of preoperatively detected cancer (Butler et al. 2003; Keleher et al. 2003; van der Torre et Butzelaar 1997; White et al. 2012). It has been suggested that precise segments of the breast are identified and marked, which would allow better localization of the occult lesion (Blansfield et al. 2004; Butler et al. 2003; Jansen et al. 1998; Slezak et Bluebond-Langner 2011). Specimen radiography has also been suggested for further assistance. (Clark et al. 2009; Colwell et al. 2004; Ozmen et al. 2001). In our department, marking of the specimens is not a common practice, and is used only when macroscopically suspicious lesions are found intraoperatively.

To summarize, a large number of patients (n = 819) without a previous history of breast cancer, were imaged with only two cancers and two high-risk lesions detected preoperatively. Still, these operations could be planned

and performed as oncoplastic resections, which supports the role of preoperative imaging. On the other hand, in this thesis, all other abnormalities went undetected in the imaging. This highlights the value of histopathological analysis as the method to detect cancer and risk-increasing lesions. Ideally improved preoperative imaging and targeted needle biopsies may increase the rate of preoperatively detected abnormal findings leading to tailored oncoplastic surgery in selected cases.

9.4 Breast cancer risk management options

Ideally, women with an increased risk of breast cancer could be detected early and individual strategies for risk management could be offered. Current risk management options for women with high-risk lesions (ADH, ALH, or LCIS) include active surveillance, chemoprevention, and less commonly bilateral prophylactic mastectomy (Coopey et al. 2012; Hartmann et al. 2015; Hunt et al. 2017; King et al. 2015; McEvoy et al. 2015; Morrow et al. 2015; Visvanathan et al. 2013).

During the study period, mammogram and ultrasound were recommended every two years for the majority of high-risk patients in our department. The current surveillance protocol in our unit for women under 50 years includes both mammogram and ultrasound and clinical examination annually. For women between 50 and 69 years, mammogram is recommended annually, and for women over 69 years, mammogram is recommended every two years. The surveillance is ended when a woman reaches 80 years-of-age or even earlier if her general condition deteriorates. This protocol differs from a comprehensive national government-funded breast cancer screening protocol, with mammogram performed every two years only for age groups 50 to 69 (Ministry of Social Affairs and Health 2015). Given the cumulative risk of breast cancer development among patients with atypical hyperplasia or LCIS, active surveillance with tailored imaging is justified. It remains to be seen, if imaging guidelines are updated to include MRI screening in addition to mammogram in high-risk patients.

Despite the fact that the use of chemoprevention strategies has been shown to reduce breast cancer incidence among women with atypical hyperplasia and LCIS (Coopey et al. 2012; Hartmann et al. 2015; King et al. 2015), only a small minority of high-risk women take these drugs. The low rate of the use of chemoprevention in these women may result from an insufficient understanding of their cumulative risk of breast cancer, as well as a fear of side effects (Hartmann et al. 2015). In my experience, in our health care system, chemoprevention is rarely offered to patients with an increased risk of breast cancer.

Over the past years, there has been an increasing rate of bilateral and contralateral prophylactic mastectomies (Hunt et al. 2017; Wong et al. 2017), and awareness of these procedures has risen also in Finland. The surgery may be indicated in women with the highest risk, such as gene mutation carriers or women with a strong family history of breast cancer. However, in current practice, atypical hyperplasia and LCIS are generally not indications for prophylactic mastectomy (Hartmann et al. 2015).

Results from the present research suggest that women with high-risk lesions in reduction mammaplasty specimens should be appropriately counselled regarding their future breast cancer risk. Active surveillance with imaging, perhaps a discussion of chemoprevention, as well as patient education regarding different alternatives, are key points in patients with high-risk lesions. This thesis demonstrated that reduction mammaplasty specimens reveal a considerable number of malignant and high-risk lesions, and the incidence is commonly doubled in patients with prior breast cancer history. The specimens reveal abnormal findings, especially frequently if reduction mammaplasty is performed prior to oncological treatment. In light of these results, contralateral reduction mammaplasty followed by histopathological evaluation in breast cancer patients offers a sophisticated tool to catch those patients whose contralateral breast requires increased attention. This works without conducting unnecessary skin-sparing risk-reducing bilateral mastectomies and implant-based reconstructions advocated by patients fears for cancer and industry-led insurance policies, increasing in popularity in many countries.

Reduction mammaplasty lowers the subsequent risk of breast cancer (Tarone et al. 2004). Boice et al. (Boice et al. 2000) showed 28% reduction in breast cancer risk after reduction mammaplasty, and the decreased risk was most evident in women 50 years and older. In women operated before the age of 40, the risk was lowered in the long run (Boice et al. 2000). Although reduction mammaplasty diminishes the risk of breast cancer, a notable amount of breast tissue remains after surgery. Thus, it cannot be compared to prophylactive mastectomy in prevention strategies. However, histopathological evaluation of the reduction mammaplasty specimens can provide an estimate of the future breast cancer risk.

9.5 The timing of reduction mammaplasty and breast reconstruction

In patients with a previous history of breast cancer, the majority (76.6%) of reduction mammaplasties were performed after oncological treatment. However, abnormal histopathological findings were statistically more frequent in patients with surgery performed before oncological treatment.

This may be explained by oncological treatment that lowers the incidence of contralateral cancer (Coopey et al. 2012; King et al. 2015; Wong et al. 2017). In patients undergoing breast reconstruction, abnormal histopathological findings were statistically more frequent, if reconstruction was performed immediately. Thus, it seems that oncological treatment plays a role in the incidence of abnormal findings in reduction mammaplasty specimens. To conclude, this places emphasis on histopathological evaluation of reduction mammaplasty specimens in breast cancer patients with reduction mammaplasty performed before oncological treatment.

9.6 Long-term postoperative follow-up

Long-term postoperative follow-up periods in Studies III and IV were alike, but rather short. In Study III, two patients developed breast cancer. Both cancers were ipsilateral to the high-risk lesion. As Hartmann et al. (Hartmann et al. 2014) showed, cancers developing within five years of diagnosis of atypia were more likely to be ipsilateral than cancers arising beyond that point. In Study IV, three patients were diagnosed with a new cancer on the reduced breast. With a longer follow-up period, the number of new breast cancers might have been increased.

9.7 Cost-effectiveness

It has been advocated that routine histopathological analysis of reduction mammaplasty specimens is not cost-effective since the incidence of occult cancers in the specimens is low (Hassan et Pacifico 2012; Koltz et Girotto 2010). The burden on histopathology laboratories in processing and analysing the specimens is also substantial (Hassan et Pacifico 2012). However, as Kececi et al. (Kececi et al. 2014) suggested, these figures are usually calculated per cancer detected, and do not take into account risk-increasing lesions. High-risk lesions should be considered in determining whether histopathological analysis of specimens is cost-effective or not, as they pose life-long consequence for the patients.

During the study period, approximately 184 reduction mammaplasties for symptomatic macromastia were performed per year in the Department of Plastic Surgery, Helsinki University Hospital. In this annual cohort approximately two cancers and 10 high-risk lesions were found. We could, as an example, hypothesize that histopathological analysis of reduction mammaplasty specimens costs 140 euros per breast amounting to 51,520 euros per year for these patients. This investment detected 12 patients, who will benefit from altered clinical management. In patients with a previous history of breast cancer, the annual field comprised one detected cancer and

eight detected high-risk lesions with an input of 9,240 euros. In this context, one could mention as a rough example, the calculated mean annual cost of one breast cancer patient, approximately 23,000 euros (Torkki et al. 2018). Thus, these investments seem reasonable. When concentrating on patient's benefits, sending reduction mammaplasty specimens for histopathological analysis seems financially justified.

9.8 Limitations

The limitations of this study are mostly due to the inability to control preoperative routines and histopathological sampling in a retrospective study. In addition, the retrospective study compels us to rely on patient files, which were originally not intended for research purposes. Nevertheless, this study cohort represents common plastic surgery practice. In a large institution and between facilities, breast imaging and the threshold to conduct additional imaging or examinations may vary. Also, patients requiring mastectomy or more extensive oncological treatment may have been referred to the Breast Unit and therefore the data is missing from the study material. It remains uncertain as to whether the unoperated part of the breast contains cancer or risk-increasing findings. Therefore, the sensitivity of mammogram is calculated for the operated part of the breast, and the true sensitivity may be even lower. The follow-up time is short, which probably effects on the number of subsequent cancers. With longer follow up, more cancers may be detected in high-risk patients.

In the literature, there is a variability in the definition of clinically relevant breast histopathology findings (Hassan et Pacifico 2012). Some publications, addressing the incidence of occult breast cancer in reduction mammaplasty specimens, include LCIS as a cancer finding in calculations (Ambaye et al. 2009; Petit et al. 1997; Sorin et al. 2015; Tadler et al. 2014). In this thesis, the first study (Study I) included LCIS as an in-situ cancer finding together with DCIS affecting on the incidence of cancer. Subsequent publications regarded LCIS as a high-risk lesion.

9.9 Recommendations and future perspectives

According to this study, reduction mammaplasty specimens reveal a considerable number of malignant and high-risk lesions. The incidences are doubled in patients with a previous history of breast cancer, and abnormal findings are found especially frequently if reduction mammaplasty is performed prior to oncological treatment. To date, preoperative imaging, further examinations, and demographics do not sufficiently detect cancer or high-risk lesions. However, based on this study, it appears that heavier specimens of older patients, as well as those from patients with a previous

history of breast cancer, may benefit from more frequent sampling. Hopefully, in the future, more defined guidelines for examining reduction mammaplasty specimens are developed.
The role of preoperative imaging is supported even though the majority of malignant findings remained undetected in the imaging. Still, those that are revealed can be treated with tailored oncoplastic surgery. Thus, preoperative ultrasound is recommended prior to major breast surgery for women under 30 years of age, and mammogram is recommended for patients older than that.

Reduction mammaplasty combined with subsequent histopathological examination offers a sufficient chance of detecting cancer and risk-increasing lesions that justifies the cost of histopathology. In addition, contralateral reduction mammaplasty offers a sophisticated tool to catch breast cancer patients whose contralateral breast needs increased attention. At best, reduction mammaplasty specimens can enlighten both the patient and the physician in regard to the future breast cancer risk, and therefore, gives the opportunity to choose the best method to treat and follow-up the patients. This knowledge can only be gained if the samples are examined histopathologically.

10 CONCLUSIONS

I In day-surgery patients, reduction mammaplasty specimens reveal a marked number of important histopathological findings that have prognostic value for the patient.

II The majority of patients without a previous history of breast cancer underwent imaging, with only two cancers and two high-risk lesions detected preoperatively. To date, preoperative imaging and further examinations do not sufficiently detect cancer or high-risk lesions. Therefore, histopathological analysis of reduction mammaplasty specimens should be thoroughly considered.

III Reduction mammaplasty specimens reveal a considerable number of malignant and high-risk lesions. Abnormal histopathology correlates with higher age and heavier specimen. However, at present, demographic features of the patients cannot preoperatively detect patients with cancer or high-risk lesions.

IV The incidences of occult breast cancer and high-risk lesions are doubled in patients with a previous history of breast cancer compared to those without. Abnormal histopathological findings are found especially frequently if reduction mammaplasty is performed prior to oncological treatment.

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