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Time Trends in Histopathological Findings in Mammaplasty Specimens in a Dutch Academic Pathology Laboratory

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Background: Reduction mammaplasties are often performed at a relatively young age. Necessity of routine pathological investigation of the removed breast tissue to exclude breast cancer has been debated. Past studies have shown 0.05%–4.5% significant findings in reduction specimens, leading to an ongoing debate whether this is cost-effective. There is also no current Dutch guideline on pathological investigation of mammaplasty specimens. Because the incidence of breast cancer is rising, especially among young women, we re-evaluated the yield of routine pathological investigation of mammaplasty specimens over three decades in search of time trends.

Methods: Reduction specimens from 3430 female patients examined from 1988 to 2021 in the UMC Utrecht were evaluated. Significant findings were defined as those that may lead to more intensive follow-up or surgical intervention.

Results: Mean age of patients was 39 years. Of the specimens, 67.4% were normal; 28.9% displayed benign changes; 2.7%, benign tumors; 0.3%, premalignant changes; 0.8%, in situ; and 0.1%, invasive cancers. Most patients with significant findings were in their forties ($P < 0.001$), the youngest patient being 29 years. Significant findings increased from 2016 onward ($P = 0.0001$), 86.8% found after 2016.

Conclusions: Over three decades, 1.2% of mammaplasty specimens displayed significant findings on routine pathology examination, with an incidence rising to 2.1% from 2016 onward. The main reason for this recent increase is probably attributable to super-specialization by the pathologists. While awaiting formal cost-effectiveness studies, the frequency of significant findings for now seems to justify routine pathological examination of mammaplasty reduction specimens.
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INTRODUCTION

A reduction mammaplasty can be performed for multiple reasons. Most women undergo this type of surgery for symptomatic breast hypertrophy or for cosmetic reasons; lastly, some opt for contralateral breast cancer surgery, aiming for symmetrization. A key question is what to do with the removed breast tissue. On the one hand, one may argue that all tissue should be subjected to histopathological investigation because it may bear clinically relevant lesions (further denoted "significant findings"), despite negative results on palpation and possibly imaging, that require information on completeness of resection (benign tumors), more intensive follow-up (premalignant lesions) or further clinical treatment (in situ or invasive cancer).[1–3] Past studies showed that the incidence of premalignant or malignant changes in mammaplasty specimens ranges from 0.05% to 4.5%.[1] On the other hand, one may argue that the resulting strain on health care and incurred costs are too high in view of the low prevalence of such significant findings.[4] Guidelines to this end, therefore, vary from country to country, and the (no longer valid but not yet updated) guidelines of the Dutch Society for Plastic Surgery only advise to submit

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mammaplasty specimens for histopathological investigation above the age of 40.

At the University Medical Centre Utrecht (UMC Utrecht), every mammaplasty reduction specimen is submitted for histopathology, and several private breast clinics routinely submit their reduction specimens to the laboratory. This has led to a large database of findings from breast reduction specimens spanning three decades where we can reevaluate the yield of histopathology of reduction specimens and analyze time trends.

To the best of our knowledge, the latter has not been investigated, but is interesting because the incidence of breast cancer is rising, especially among younger women.[5,6] While analyzing time trends, changes in workflow that may influence the frequency of significant findings need to be considered. At the pathology department of the UMC Utrecht, two factors may have played a role. The UMC Utrecht switched to a fully digital diagnostic workflow in 2015.[7] Another change occurred in 2016 when the pathologists started working as super-specialists, and a team of four dedicated breast pathologists evaluated all breast specimens. The aims of this study were therefore to search for time trends in histopathological findings in mammaplasty specimens over the past 33 years of UMC Utrecht breast pathology practice, and to analyze the underlying reasons for these trends.

METHODS

The UMC Utrecht pathology archive holds electronic records of all patients and their pathological findings since 1988, in conjunction with the Dutch National Pathology Registry. For this study, all records starting with the year 1988 to June 2021 were selected that contained the keyword mammaplasty and variants. Year of surgery, clinical information, laterality, and the pathological findings were extracted, and the age at time of diagnosis was calculated. All information was processed anonymously in compliance with the General Data Protection Regulation.

Pathology findings were categorized into six different groups (Table 1). Group 1 included all specimens that did not show any abnormalities apart from mild signs of fibrosis. It was chosen to group fibrosis with normal breast tissue, because in most young women "fibrotic" breast tissue likely reflects the physiological status of the breast at younger age. Findings in group 2 included benign changes like fibrocystic changes. Benign tumors like fibroadenomas, papillomas, or lipomas were included in group 3. Group 4 was made up of premalignant lesions such as adenomyoepitheliomas and atypical ductal hyperplasia. In situ lobular (LCIS) and ductal (DCIS) cancers comprised group 5. Lastly, group 6 held all invasive cancers.

Table 1. Grouping of Histopathological Findings from Mammaplasty Specimens

Group 1	No Abnormalities
Group 2	Benign changes
Group 3	Benign tumors
Group 4	Premalignant changes
Group 5	In situ cancer
Group 6	Invasive cancer

Takeaways

Question: Is routine pathological examination of mammoplasty reduction specimens justifiable?

Findings: Over three decades, 1.2% of mammoplasty specimens displayed significant findings on routine pathology examination, with an incidence rising to 2.1% from 2016 onward.

Meaning: Routine pathological examination of mammoplasty reduction specimens seems justifiable.

Medical records of the UMC Utrecht patients were reviewed for preoperative imaging. The private breast clinics that we serve have no preoperative imaging policy. To trace consequences of the diagnosis of significant lesions, we searched for follow-up pathology through the Dutch National Pathology database (www.palga.nl). No ethical approval was required because we only used anonymous existing data and did not re-use material or produce new data.

The data were statistically analyzed by Pearson chi-square test to compare frequencies and Student *t* test to compare continuous variables, and *P* values less than 0.05 were considered statistically significant. Time trends were also analyzed by linear regression analysis.

RESULTS

Overall, mammaplasty specimens were included from 3430 female patients born between 1901 and 2004, with a mean age of 39 years. The reasons for deciding to have a mammaplasty ranged from (symptomatic) hypertrophy to contralateral symmetrization after breast cancer surgery. Of the UMC Utrecht patients, 90% underwent preoperative mammography, all negative.

Histopathological Findings

Table 2 shows the frequencies of groups 1–6 findings in all patients, also broken down into age categories. Of all specimens, 67.4% were normal or showed only signs of mild fibrosis, 28.9% displayed benign changes, 2.7% had benign tumors, and 0.3% harbored premalignant changes (six atypical ductal hyperplasia, one flat epithelial atypia, two adenomyoepitheliomas). In situ cancers were found in 0.8% [19 classic LCIS, five DCIS (three grade 1, one grade 2, and one grade 3)] and invasive cancers (2 invasive lobular cancers, one grade 1 and one grade 3) in 0.1% of specimens. Most patients diagnosed with significant findings were in their forties. The youngest patient with a significant lesion was 29 years old (DCIS grade 2), and three more patients with in situ cancer were younger than 40. The patients with invasive cancer were 43 and 63 years old at the time of diagnosis. Family history of breast cancer (not systematically registered) was positive for three patients who were all diagnosed with benign changes only.

Table 2. Histopathological Findings from Mammaplasty Specimens, Also Broken Down by Age Categories

	Group	N (%)	Age <30	30–40	40–50	>50
1	No abnormalities	2312 (67.4%)	855 (73%)	440 (70.6%)	436 (58.9%)	581 (64.9%)
2	Benign changes	990 (28.9%)	282 (24.1%)	164 (26.3%)	268 (36.2%)	275 (30.7%)
3	Benign tumors	91 (2.7%)	34 (2.9%)	14 (2.2%)	20 (2.7%)	23 (2.6%)
4	Premalignant	9 (0.3%)	0 (0%)	2 (0.3%)	3 (0.4%)	4 (0.4%)
5	In situ cancer	27 (0.8%)	1 (0.1%)	3 (0.5%)	12 (1.6%)	11 (1.2%)
6	Invasive cancer	2 (0.1%)	0 (0%)	0 (0%)	1 (0.1%)	1 (0.1%)

Table 3. Numbers of Mammaplasty Specimens (with %) over the Years, Also Broken Down by Nonsignificant (Group A) and Significant Findings (Group B)

	1988–1995	1996–2000	2001–2005	2006–2010	2011–2015	2016–2021
Group A N (%)	373 (11%)	520 (15.3%)	325 (9.6%)	120 (3.5%)	540 (15.9%)	1515 (44.7%)
Group B N (%)	0 (0%)	0 (0%)	3 (7.9%)	0 (0%)	2 (5.3%)	33 (86.8%)
Overall N (%)	373 (10.9%)	520 (15.2%)	328 (9.6%)	120 (3.5%)	542 (15.8%)	1548 (45.1%)

The increase in significant findings over the years was statistically significant (2016 and up versus the other years, $P < 0.001$, chi-square test).

Patients who underwent unilateral symmetrization after previous contralateral breast cancer surgery were older than those undergoing bilateral mammaplasty (46.8 versus 37.7 years, $P < 0.001$), but there were no significant differences in the frequencies of significant histopathological findings.

Time Trends

For time trend analysis, the groups were further lumped into two larger groups in view of the relatively low frequencies in some individual categories: group A with no or merely benign changes (groups 1, 2, 3), making up 98.8% of cases, and group B with significant findings, meaning premalignant changes, in situ, or invasive cancers (groups 4, 5, 6), making up 1.2% of cases.

The number of cases that were examined over the decades varied. Table 3 shows the numbers of cases per year over the study period, broken down in groups A and B. An estimated 10.9% of the total number of specimens were examined until 1996; from 1996 to 2000, 15.2%; from the start of the next millennium until 2006, another 9.6%; from 2006 to 2010, 3.5%; from 2010 to 2015, 15.8%; and from 2016 to 2021, 1548 cases (45.1%) were examined. This increase over the years was statistically significant (2016 and up versus the other years, $P < 0.001$, chi-square test), even though in 2021, cases were included for only half a year.

Table 3 also shows that there was a marked increase in significant findings from 2016 onward: 33 of 38 of the significant findings (87%) were found between 2016 and 2021.

The mean age for patients with significant findings (group B) was 50.3 years, while the mean age for group A was 39.2 years ($P < 0.001$, t test). As shown in Table 4, the mean age of patients at the time of the mammaplasty increased throughout the decades. The mean age in 1988 was 31.2 years, and by 2021 it was 42.3 years. The mean age in the years 1988–2010 (34.2 years) was significantly lower than the mean age (42.8 years) in the years 2011–2021 ($P < 0.001$). Pearson linear regression analysis over the years was also significant ($P = 0.004$).

Table 4. Age (Years) of Patients Undergoing Mammaplasty over the Years, Also Broken Down by Nonsignificant (Group A) and Significant Findings (Group B)

	Group A	Group B	Overall
1988–1995	31.2		31.2
1996–2000	33.6		33.6
2001–2005	37.2	47	37.3
2006–2010	37.2		37.2
2011–2015	43.6	44.5	43.6
2016–2021	42.1	51	42.3

The mean age in the years 1988–2010 (34.2 years) was significantly lower than the mean age (42.8 years) in the years 2011–2021 (chi-square $P < 0.001$. Pearson linear regression analysis over the years $P = 0.004$).

Table 5 shows the trend over the years for mammaplasty reason (cosmetic/hypertrophy versus symmetrization). In recent years, the percentage of symmetrization tended to be higher (chi-square and Pearson linear regression analysis $P < 0.001$).

Table 6 shows the crosstable for mammaplasty reason (cosmetic/hypertrophy versus symmetrization) versus age category. With increasing age, the percentage symmetrization increased ($P < 0.001$).

Follow-up

Searching for follow-up pathology after a significant finding revealed that all invasive cancer patients underwent regular treatment, none of the LCIS underwent immediate further surgery, and one of the DCIS patients opted for ablation of the affected breast and preventive ablation of the other breast.

DISCUSSION

The aim of this study was to analyze time trends in histopathological findings in reduction mammaplasty specimens over the past 33 years of UMC Utrecht breast practice in view of the controversy of the usefulness of such investigations, and to analyze the underlying reasons for these trends.

Table 5. Reason for Mammaplasty (Cosmetic/Hypertrophy versus Symmetrization) over the Years (Chi-square *P* < 0.001, Pearson Linear Regression *P* < 0.001)

Mammaplasty Indication	1988–1995	1996–2000	2001–2005	2006–2010	2011–2015	2016–2021
Cosmetic/hypertrophy	344 (92.2%)	496 (95.4%)	294 (89.6%)	97 (80.8%)	219 (40.4%)	1418 (88.7%)
Symmetrization	29 (7.8%)	24 (4.6%)	34 (10.4%)	23 (19.2%)	323 (59.6%)	181 (11.3%)

Table 6. Crosstable for Mammaplasty Reason (Cosmetic/Hypertrophy versus Symmetrization) versus Age Category (Chi-square *P* < 0.001)

		Age			
Mammaplasty Indication	N (%)	<30	30–40	40–50	>50
Cosmetic/hypertrophy	2867 (82.4%)	1127 (92.3%)	528 (84.6%)	589 (79.5%)	623 (69.6%)
Symmetrization	614 (17.6%)	94 (7.7%)	96 (15.4%)	152 (20.5%)	272 (30.4%)

Of all specimens 67.4% showed no abnormalities, 28.9% displayed benign changes, 2.7% had benign tumors, and 0.3% harbored premalignant changes. In situ and invasive cancers were found in 0.8% and 0.1% of specimens, respectively. The overall rate of significant findings was thereby 1.2%. This rate of significant findings is lower than those from most other hospitals. In 2009, the Virginia Mason Medical Center published their findings of 562 patients who underwent a mammaplasty between the years of 2001 and 2005. They found 1.8% in situ cancers during their examinations. When comparing these with the same time period in this study, the rate of significant findings at UMC Utrecht is 0.9%. They also found 4.4% premalignant lesions compared with 0% in at UMC Utrecht during that time period.[8] Another study by the Helsinki University Hospital published their data from the years between 2007 and 2011. While at UMC Utrecht there were no significant findings during this period, the Helsinki University Hospital found 5.5% of what they called "high risk lesions,"[1] equal to what in this study is defined as premalignant (group 3) or in situ (group 4). Massachusetts General Hospital published a study in 2019 that included 995 reduction mammaplasty specimens from 572 patients that were analyzed between the years 2000 and 2012.[9] They found 16.1% of lesions that in this study equal the qualifications for group B, while the rate at UMC Utrecht during these years was 0.67%. Slezak and Bluebond-Langner reported 10 cases of occult carcinoma among 866 women (1.15%) who underwent reduction mammaplasty between 1990 and 2009.[10] Lastly, a multi-site study that summarizes the results of 16 different European institutes comes closest to the percentage of UMC Utrecht. Between the years of 2000 and 2010, the rate of significant findings (group B) was 0.67% at UMC Utrecht, whereas the cohort study using similar grouping recognized 0.8% significant findings in their altogether 5781 patients.[11]

It is interesting to speculate on the reasons for these differences in incidence of significant findings. First, they could reflect differences in breast cancer incidence, which is most likely not the reason for our lower rate of significant findings, because the World Cancer Research Fund states that the Netherlands has the third highest breast cancer rate in the world.[12] Second, the study populations could differ, some focusing on academic cohorts with a higher risk, while our cohort contains many patients from private breast clinics. Third, there could be differences in grossing and sampling, some taking more tissue blocks than others or using specimen radiography-directed sampling. The various published studies do not, however, provide information on sampling strategies, not allowing analysis of this potential confounder. At UMC Utrecht, the grossing sampling strategy for many years has been to do intensive slicing of the fixed specimens, embed all macroscopic abnormalities and otherwise, the two least fatty blocks from each breast, while not routinely performing specimen radiography-directed sampling. Because patients undergoing unilateral symmetrization after previous contralateral breast cancer surgery may be assumed to have an inherently higher risk of (pre)malignancies in the other breast, we compared frequencies of significant findings between unilateral and bilateral patients but found no significant differences. Breast cancer screening was implemented in the Netherlands in 1990, spanning almost the full period of our study window (1988 onward), so this is unlikely to have resulted in an increased rate of significant findings. Grossing is highly standardized in the Netherlands, and grossing of reduction specimens has not changed over the years. So this factor can also be ruled out. Preoperative mammography that was done in 90% of the UMC Utrecht patients did not reveal abnormalities; so this factor is also not confounding.

We found a significant difference in incidence of specimens with either premalignant, in situ, or invasive cancer findings over the span of the study. The vast majority (87%) of cases with significant findings occurred since 2016. The age of patients gradually increased over the study years with a 10-year age increase between the periods 1988–2010 and 2011–2021, which probably does not explain the rise in incidence of significant findings. At 41 years of age, patients are still relatively young, and age in the 2011–2016 subgroup (43.6 years) was even higher than in the 2016–2021 subgroup (42.3 years), while the latter subgroup contained more significant findings than the former group (33/1548 = 2.1% versus 2/542 = 0.4%).

Therefore, the question needs be asked, what changed at the pathology laboratory at the UMC Utrecht around the year of 2016 that may have influenced this change? First, the UMC Utrecht pathology department implemented a

digital workflow for primary diagnostics in 2015. According to Stathonikos et al, a survey that was carried out 6 months after the implementation of the digital system revealed that 74% of pathologists at UMC Utrecht felt rather or very confident working with the system and also that the turnaround time per case decreased by 7% compared with glass slides.[7] Various studies have shown that digital diagnostics is about as accurate as microscope-based diagnostics but not clearly better,[13,14] so it seems unlikely that this change in workflow explains this time trend.

Another change that occurred in 2016 at UMC Utrecht was pathologists starting to work as super-specialists. This means that all reduction mammaplasty specimens since 2016 have been diagnosed by dedicated breast pathologists. Although it is likely that super-specialist more accurately detect subtle abnormalities, the literature on this topic is sparse. Although not completely comparable, clues as to the effect of super-specialization may be found in the literature about second opinions, assuming that second opinions will usually be conducted by more specialized pathologists compared with the pathologist who established the primary diagnosis.[15] Lopez-Beltran et al stated, "the high complexity associated with the histopathologic diagnosis and eventual molecular analysis may suggest the use of a histopathologic second opinion from a specialized pathologist. Diagnostic inaccuracies and difference between primary diagnosis and second opinion are expected at the population level: however, the magnitude of this difference is remarkably high."[16] A Dutch study also attested to these discrepancies and showed that 45% of second opinions resulted in a different diagnosis than the original.[17]

To analyze whether switching to a super-specialist workflow at UMC Utrecht may have been responsible for the drastic increase in significant findings since 2016, we reviewed as a pilot experiment 92 (54.7%) of the cases from 2014, a year before super-specializing and yet close to the switch, to exclude that environmental and other factors varied much. From the 92 reviewed cases, nine showed previously undetected significant findings, including six cases of LCIS, three cases with atypical ductal hyperplasia and one DCIS. Thereby, 4.35% of the reviewed cases revealed significant findings (group B) that were previously undetected. These preliminary data make it quite likely that switching to super-specialization is the biggest factor in the rising incidence of significant findings over the last half decade.

We observed a rising number of specimens over the years, not likely due to changes in guidelines (as there are none active in the Netherlands) or submitting a higher fraction of cases (all the clinics that we serve routinely submit all specimens), but probably simply due to starting to service many more private breast clinics.

Searches for follow-up pathology revealed that all invasive cancer patients underwent regular treatment, none of the LCIS underwent immediate further surgery (so must have chosen for regular follow-up only), and one of the DCIS patients opted for ablation of the affected breast and preventive ablation of the other breast.

The controversial question regarding whether routine pathological examination of mammaplasty specimens is cost-effective remains. The University of Rochester Medical Center claimed that when adding up all costs and taking into consideration the frequency of cancerous findings, the diagnosis of one woman with breast cancer due to the evaluation after a reduction mammaplasty specimens would be $236.000.[4] The reality in the Netherlands might look different due to much lower pricing. The Helsinki University Hospital, however, stated that, "histopathological examination offers a sufficient chance of detecting cancer and risk-increasing lesions that merits the cost of histopathology."[1] Stratifying patients for histopathologic analysis according to risk factors may increase cost-effectiveness, but there are yet no obvious strategies. We are not aware of any studies stratifying on preoperative or specimen imaging, and although age of patients with significant findings was higher, as expected, the youngest patient with a significant finding was 29 years of age, so any age threshold will lead to missing some significant lesions. When an age limit of 40 would have been considered, four of 27 (15%) in situ cancers would have been missed. Also, family history may be considered, but these data were incomplete in the present study. The three patients where a positive family history was indicated on the request form all had only benign changes. For now, we therefore feel that the 1%–5% significant findings over different studies allows patients to receive treatment or more intensive follow-up as soon as possible and justifies the moderate costs of pathological routine examination of the specimens.

The advantage of this retrospective study compared with other similar studies is that the underlying data provide information about the percentage of significant pathological findings in mammaplasty specimens over multiple decades, allowing analysis of time trends. Disadvantages were incomplete information on family history and lack of preoperative imaging results.

In conclusion, over the three study decades, 1.2% of mammaplasty specimens displayed significant findings on routine pathology examination that may lead to more intensive follow-up or surgical intervention, with an incidence rising to 2.1% from 2016 onward. Most of these findings occurred in women over the age of 40. Further, 2.7% of specimens showed benign tumors. The reason for the increase in significant findings over the years 2016–2021 was probably largely attributable to super-specialization by the pathologists. While awaiting formal cost-effectiveness studies, the frequency of significant findings for now seems to justify the routine pathological examination of mammaplasty reduction specimens.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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