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Pathologic findings in reduction mammoplasty specimens: a surrogate for the population prevalence of breast cancer and high-risk lesions

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Abstract

Purpose Mammoplasty removes random samples of breast tissue from asymptomatic women providing a unique method for evaluating background prevalence of breast pathology in normal population. Our goal was to identify the rate of atypical breast lesions and cancers in women of various ages in the largest mammoplasty cohort reported to date.

Methods We analyzed pathologic reports from patients undergoing bilateral mammoplasty, using natural language processing algorithm, verified by human review. Patients with a prior history of breast cancer or atypia were excluded.

Results A total of 4775 patients were deemed eligible. Median age was 40 (range 13–86) and was higher in patients with any incidental finding compared to patients with normal reports (52 vs. 39 years, $p = 0.0001$). Pathological findings were detected in 7.06% (337) of procedures. Benign high-risk lesions were found in 299 patients (6.26%). Invasive carcinoma and ductal carcinoma in situ were detected in 15 (0.31%) and 23 (0.48%) patients, respectively. The rate of atypias and cancers increased with age.

Conclusion The overall rate of abnormal findings in asymptomatic patients undergoing mammoplasty was 7.06%, increasing with age. As these results are based on random sample of breast tissue, they likely underestimate the prevalence of abnormal findings in asymptomatic women.

Keywords Breast · Mammaplasty · Breast neoplasm · Epidemiology · Breast diseases

Introduction

Breast cancer (BC) is the most common cancer affecting women. In 2018, the American Cancer Society estimates that 268,670 new cases of invasive BC will be diagnosed in the US and that there will be 41,400 BC associated deaths [1]. Certain nonmalignant lesions place patients at higher risk of developing this disease. These "high-risk lesions" include atypical lobular hyperplasia (ALH), lobular carcinoma in situ (LCIS), atypical ductal hyperplasia (ADH), and "severe ADH" (also known as "Borderline DCIS") [2]. The prevalence of cancer and high-risk lesions in the population can inform the development of screening and prevention strategies. The total population prevalence can be thought of as the prevalence of detectable lesions identified in routine medical care plus the prevalence of occult lesions in the population.

Studies from breast screening cohorts have shown an estimated detectable carcinoma incidence ranging from 0.1 to 0.7% proportional to age [3–11], and the Breast Cancer Surveillance Consortium (BCSC) reported that 0.4% of all screened women were diagnosed with ADH [3] and less than 0.01% of women were diagnosed with LCIS [3]. As these lesions were identified in patients with abnormal mammograms or other clinical findings, they represent the rate of identifiable breast disease, but provide no information on the rate of occult high-risk lesions or cancer.

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One way to identify the rate of occult lesions in a normal population is to evaluate pathology findings in autopsy series. Thomas et al. reported a meta-analysis of 13 studies that included 2363 autopsies [12]. The median rate of occult breast carcinoma and ADH/ALH was 1.1% and 3.4%, respectively [12]. However, one potential bias in trying to estimate the rate of occult lesions using autopsy series is the older populations included in these studies (ages ranged between 39 and 79).

As autopsy series are limited, an alternative approach is to review reduction mammoplasty series, which are essentially random biopsies of women without signs or symptoms of BC. Breast reduction or mammoplasty surgery is one of the most common plastic surgery procedures. In 2016, over 100,000 procedures were performed in the U.S. alone [13, 14]. These procedures, if performed in patients without prior history of BC, can be treated as bilateral random biopsies in otherwise healthy women with no indication of breast disease. In other words, mammoplasty tissue can be regarded as the best representation of the normal state [15].

It should be noted that some mammoplasty studies include patients with prior BC while others do not. Mammoplasty studies excluding cancer patients have shown that the incidence of incidental cancer or high-risk lesions ranges from 1.5 to 8.9% [16–22], while those including prior BC patients show incidence rates ranging from 4 to 14% [23–28]. As expected, patients with a BC history have higher rates of occult cancer and high-risk lesions, which may skew the results when estimating the number of occult lesions.

In the largest published mammoplasty study of patients without prior cancer, Desouki et al. reported an incidence rate of 4.3%, with 2 cases of invasive carcinoma (0.08%) and 4 cases of DCIS (0.16%) in their cohort of 2498 patients.

In our study, utilizing the largest cohort of reduction mammoplasties reported to date, we try to determine the incidence of high-risk and malignant lesions in patients without prior BC. This allows us to obtain a minimum approximation of the incidence of these lesions in healthy women.

Methods

Patients

With Institutional Review Board (IRB) approval, we reviewed pathology reports from patients undergoing bilateral mammoplasty procedures for macromastia from five Partners network institutions (Brigham and Women's Hospital, Massachusetts General Hospital, Faulkner Hospital, North Shore Medical Center, and Newton-Wellesley Hospital) dating back to the period when electronic pathology reports first became available, which ranged from 1990 (depending on the institution) to 2017. We extracted data from pathology reports using a Natural Language Processing (NLP) algorithm and by manual review. In order to exclude patients with previous history of BC or high-risk lesions, all pathologic reports for mammoplasties and for reports dated before the mammoplasty procedure were retrieved.

Pathology

No central review of pathologic specimens was performed. The presence of high-risk lesions (LCIS, severe ADH, ADH, and ALH) and carcinomas (both invasive and DCIS) was determined from the pathology reports. In the event of a synchronous lesion in either the ipsilateral or contralateral breast, we considered the lesion with the worst prognosis (invasive carcinoma over DCIS and other high-risk lesions) or the highest-risk (Severe ADH over LCIS; LCIS over ALH; and ALH over ADH was the estimated trumping order.) [29].

Natural language processing and machine learning

We used NLP and machine learning to identify and extract structured data from the pathology reports. The methods and details are reported elsewhere [30]. In short, all reports of bilateral breast cases were split into two reports and parsed into two records in the database (one for each side). Training the NLP machine learning required an annotated dataset which was created by our team. The algorithm extracted 20 separate categories of information (including ADH, ALH, severe ADH, LCIS, DCIS, and invasive cancer). All mammoplasty cases and the associated diagnoses were confirmed manually by reviewing the pathology reports. The following cases were excluded: (1) unilateral mammoplasties, (2) patients who had a previous history of BC (either DCIS or invasive carcinoma), and (3) patients with a previous biopsy of any high-risk lesion.

Statistical analyses

To analyze whether younger patients presented with a different prevalence than older ones, we divided the patients into two age groups: (1) ≤ 40 years, and (2) ≥ 40 years. Age 40 was chosen as the cutoff value as this was the age at which screening mammography was recommended most of the years of this study. Chi square was used to calculate the difference between these two groups. We further looked at patients in 5-year subgroups to obtain a more granular estimate of the effect of age.

Wilcoxon test was used to compare age medians. Significant difference was considered when the p value was < 0.05. The statistical software used for this study was XLSTAT v.19.4.

Results

Using NLP followed by manual validation, we identified 4804 patients who underwent bilateral reduction mammoplasty without a history of BC. Of these, 29 patients had a previous personal history of high-risk lesion and were excluded from the analysis. After excluding these patients, the study population consisted of 4775 patients and 9550 reports (two reports per patient). Four hundred forty-four reports (4.65%) had at least one incidental finding identified, with a total of 549 lesions. A total of 107 (2.2%) patients presented with bilateral abnormal findings. Considering the maximum lesion identified in each patient as described in "Methods" section, we found that 337 (7.06%) patients were diagnosed with an incidental finding.

The median age of all mammoplasty patients was 40 years (range 13–86). The median age of those with an incidental finding was 52 years, which was significantly different from that of patients with a normal pathologic report (39 years, $p < 0.0001$).

Among the 337 patients with incidental findings, there were 15 patients with invasive carcinomas (0.31%), 23 DCIS (0.48%), 14 severe ADH (0.29%), 55 LCIS (1.15%), 139 ALH (2.91%), and 91 ADH (1.91%) (Table 1). Thus, 38 (0.79%) of women had an occult malignancy and 299 (6.26%) had a high-risk occult lesion.

The rate of finding any lesion increased with age (Table 2; Fig. 1). There was a significant difference between patients categorized in the under 40 group (2455) and those over 40 (2320) in terms of prevalence of both cancer (0.16% vs. 1.47%, respectively; $p < 0.0001$) and high-risk lesions (1.63% vs. 11.16%, respectively; $p < 0.0001$). There was a trend toward increasing incidence with age that was robust into the early 6th decade, although small numbers at older ages weakened our ability to show this connection beyond that age group.

Table 1 Distribution of maximum pathologic findings by patients in our cohort (All patients with pathologic lesions ($n = 336$) among 4774 mammoplasty procedures)

Pathologic lesion	Number of patients affected	% (of total)
Cancer invasive	15	0.31
Ductal carcinoma in situ	23	0.48
Severe atypical ductal hyperplasia	14	0.29
Lobular carcinoma in situ	55	1.15
Atypical lobular hyperplasia	139	2.91
Atypical ductal hyperplasia	91	1.91

Discussion

In this study, the rate of occult cancer and high-risk lesions in patients undergoing mammoplasty was 7.06%. This is likely an estimate of the minimum prevalence, as mammoplasty removes only a random sample of the breast tissue.

Reduction mammoplasties can be treated as bilateral random biopsies in otherwise healthy women with no indication of breast disease. On the assumption that all patients had recent appropriate screening (i.e., mammography for those

Table 2 Rate of pathologic findings by age

Age	N (total)	All pathologic lesions	%	HRL*	%	Cancer**	%
11–15	8	0	0.00	0	0.00	0	0.00
16–20	356	2	0.56	2	0.56	0	0.00
21–25	551	4	0.73	4	0.73	0	0.00
26–30	493	5	1.01	4	0.81	1	0.20
31–35	497	10	2.01	9	1.81	1	0.20
36–40	550	23	4.18	21	3.82	2	0.36
41–45	615	47	7.64	43	6.99	4	0.65
46–50	525	57	10.86	52	9.90	5	0.95
51–55	472	61	12.92	54	11.44	7	1.48
56–60	388	77	19.85	68	17.53	9	2.32
61–65	194	34	17.53	27	13.92	7	3.61
66–70	81	11	13.58	9	11.11	2	2.47
71–75	36	6	16.67	6	16.67	0	0.00
76–80	6	0	0.00	0	0.00	0	0.00
81–86	3	0	0.00	0	0.00	0	0.00

**HRL* high-risk lesions

**"Cancer" includes invasive carcinoma and DCIS

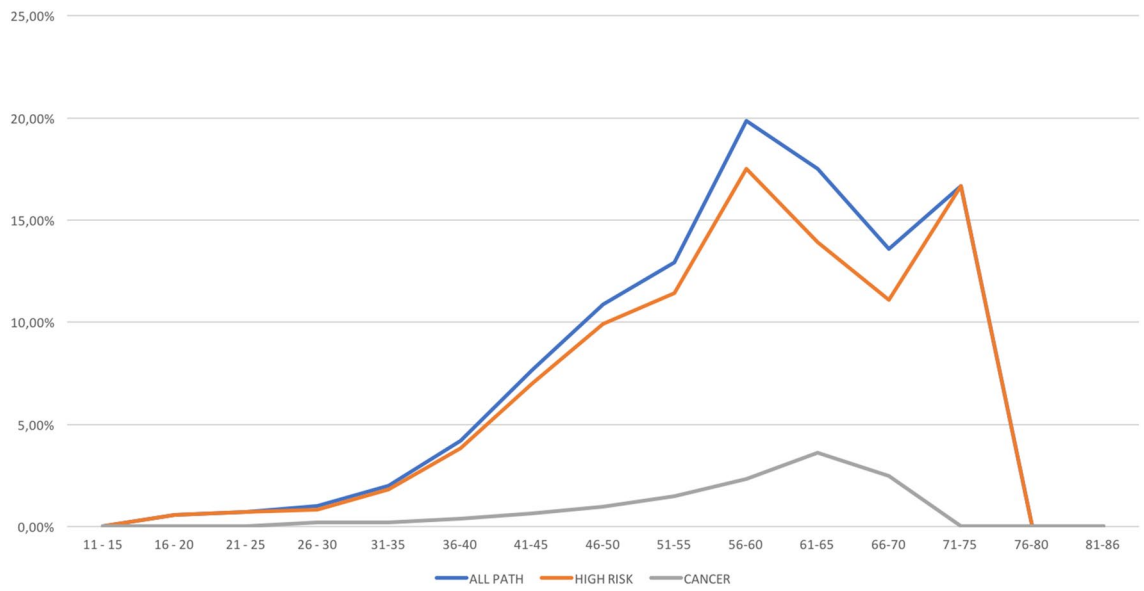

Fig. 1 Age distribution of any incidental finding (blue line), high-risk lesion (orange line), or cancer (gray line)

40 and above), the findings represent a reservoir of disease in asymptomatic women. According to previous studies utilizing mammoplasty specimens, in patients without a history of cancer, the probability of finding an abnormal lesion ranges from 1.5 to 9% with a cancer rate of approximately 1% (Table 3) [16–22].

We found that the prevalence of carcinoma and high-risk lesions in mammoplasty procedures is 0.77% and 6.26%, respectively. In the two largest mammoplasty studies published prior to our series, Desouky et al. and Pitanguy et al. reported a carcinoma prevalence of 0.2% and 0.4%, respectively [16, 17]. Desouki et al. further reported a high-risk lesion prevalence of 4.3% [16]. Our higher numbers may reflect a different age group (mean age in our study was 39.9 years old vs. 35.9 in the study written by Pitanguy et al.), a different population (Pitanguy's work involved a Brazilian population where cancer risk has been reported to be lower compared to the United States) [31], or more thorough pathological examination and/or reporting.

Since age is a well-established risk factor for the development of BC, it is not surprising that the prevalence of cancer and atypia increased with age [1]. In our study, women over 40 had a prevalence of cancer of 1.42%, which was significantly higher than the 40 and under population (0.16%). As shown in Fig. 1, this prevalence reached a peak of 3.61% in patients aged 61–65. This value then plummeted after age 70, probably due to the smaller population undergoing a mammoplasty at this age (the study cohort included only 45 patients over 70 years old). These findings have also been reported by Pitanguy el al. who found a higher rate of carcinoma in patients over 40 years as compared to younger patients (1.49% vs. 0.16%) [17]. Desouki et al. did not report any case of cancer in patients either under 40 or over 60 years old [16].

Table 3 Summary of mammoplasty studies where cancer patients were excluded

First author	Year	Data	Country	N	Cancer (%)	High risk (%)	Total (%)
This study	–	1990–2017	USA	4775	0.8	6.3	7.1
Desouki	2013	2006–2012	USA	2498	0.2	4.3	4.5
Pitanguy	2004	1957–2002	Brazil	2488	0.4	–	–
Huysmans	2016	2005–2014	Belgium	1045	0.38	1.18	1.56
Serrano	2017	2008–2014	Brazil	783	1.0	4.1	5.1
Dotto	2008	1990–2005	USA	516	0.4	5.4	5.8
Kakagia	2004	1996–2001	Greece	314	0.9	8.0	8.9
Viana	2005	1987–2002	Brazil	274	0.6	0.9	1.5
Bondeson	1985	1979–1982	Sweden	200	0	5	5
Sofianos	2015	2009–2014	South Africa	200	2	0.5	2.5

Regarding high-risk lesions, we found that 11.2% of patients over the age of 40 were diagnosed with either LCIS or atypia, whereas this was a very rare event in patients 40 and younger (1.6%). This value peaked in the 6th decade, rising to almost 14%, but thereafter our numbers lacked sufficient power to verify a true prevalence. Desouki et al. found that in 220 patients over the age of 60, 9.1% were diagnosed with a high-risk lesion [16].

An alternative method for evaluating the rate of occult disease is to analyze autopsy findings; however, the numbers are mixed and these are usually older studies with an older patient population. In the largest study published to date, Bartow et al. reported a carcinoma rate of 1.16% [32]. In another study, Giarelli et al. reported a cancer prevalence of 1.51% in 463 patients [33]. A recent meta-analysis, including 13 studies and 2,363 autopsies, found that the mean prevalence of incidental invasive cancer was 1.1% [12]. Autopsy values are slightly higher than what mammoplasty series have reported, probably because mammoplasty procedures analyze random breast tissue instead of all breast tissue, a factor which can underestimate the true prevalence. Also, mammoplasty studies represent a younger population than that represented in autopsy studies. While the median age in our study was 40 years old, the median age in the autopsy meta-analysis was 51 years [12].

The rates for high-risk lesions vary greatly in autopsy and reduction mammoplasty series. Bartow et al. found an atypical hyperplasia rate of 0.96% [12], while Nielsen et al. described a prevalence of 7% [34]. In the meta-analysis mentioned above, the median rate was 3.4% [12]. Since this meta-analysis grouped both LCIS and DCIS in one category, we cannot provide definite conclusions about the prevalence of LCIS on its own. Bartow et al. reported only one case of LCIS in their cohort (0.19%) [12]. On the other hand, Nielsen et al. described one of the highest rates of LCIS, with a prevalence of 4.54% [34]. Our data reported an atypical hyperplasia and LCIS rate of 4.82% and 1.15%, respectively. However, since there is great heterogeneity among autopsy studies, it is difficult to make a comparison.

Most of our understanding of the prevalence and incidence of atypia and cancer comes from screening studies which only identify symptomatic lesions. The BCSC evaluated 3,557,318 screening mammograms in 1,288,886 women to find 8505 (0.24%) invasive carcinomas and 2526 (0.07%) cases of DCIS [3]. Randomized clinical trials have shown prevalence and incidence values ranging from 0.3 to 0.7% at first screen and from 0.1 to 0.4% (per year), respectively, with the largest numbers presented in older populations [4–9, 11].

In the case of atypical hyperplasia (ADH and ALH), this type of lesion is usually found on screening mammograms or incidentally in a biopsy for another indication. In the BCSC study, 1473 cases of ADH were diagnosed in their cohort, which corresponds to 0.04% of all screening mammograms [3]. Picouleau et al. also analyzed screening mammogram data describing a biopsy rate of 1.2%, of which 3% contained high-risk lesions (0.19% of all mammograms performed) [35].

In the case of LCIS, the BCSC study reported a prevalence rate of less than 0.01% among screening mammograms [3]. In another study, using the SEER registry, Li et al. estimated that LCIS incidence rates rose from 0.0009% per person-year between 1978 and 1980 to 0.0032% per person-year between 1996 and 1998, with the highest incidence in patients aged 50–59 (0.11% per person-year) [36]. The high-risk lesion numbers obtained in mammogram screening studies are much lower than the values reported in our study. One can understand why these numbers may be underestimated by considering the fact that there is a known poor mammographic–histologic correlation when studying LCIS, which is also observed in ALH [37, 38].

To summarize, it appears that the rate of identifiable cancer, atypical hyperplasia, and LCIS in women undergoing screening mammography is 0.5%, 0.04%, and 0.01%, respectively, and that the minimum reservoir of these diseases in the population as identified by our mammoplasty study is 0.75%, 4.82%, and 1.15%, respectively. Assuming that the majority of the identifiable cancer is in women over 40 years old, we might consider only the reservoir in this population, which is 1.42%, 8.93%, and 2.24%, respectively.

The excess rate of cancers is likely real and probably represents cancer that would have become identifiable over time if left in place. While some proportion might never become clinically significant (so-called "overdiagnosis" [39]), we assume the majority, if not all, are real cancers that would eventually become significant.

Our study has several limitations. Because of the retrospective nature of our study using multiple institutions over many years, we cannot be sure how histopathological sampling was done and therefore must assume it was inconsistent in its completeness. As such, we assume that the numbers we report represent the minimum prevalence of these lesions in the tissue removed. It is known that a thorough review of the mammoplasty specimens would yield a higher rate of incidental findings, especially in older patients [27]. In one of the autopsy studies, the odds of encountering an incidental finding were significantly higher in studies where at least 20 sections were examined compared to those where fewer sections were analyzed [12]. Thus, while our results are at least twice the value obtained by the two other largest studies mentioned above, we cannot be sure that every cancer and atypia was identified, as our pathologic review may have been incomplete.

In addition, mammoplasty, by design, leaves behind a significant amount of breast tissue. We cannot know the prevalence of these lesions in tissue that was not removed;

hence the numbers shown here represent a minimum of the population prevalence.

Also, we cannot confirm that all women underwent the suggested imaging before mammoplasty; hence some of these lesions may not have been occult. Although we lack these data, we assume that all women over age 40 had a negative mammography within a year before the surgery as recommended by the screening guidelines in effect when most patients had their operation.

Another limitation, which is also an inevitable bias in most mammoplasty studies, is that this group of patients may not be a representative sample of the population. For example, one can argue that these patients may present with a greater risk of developing BC since they often have a higher BMI. However, while high BMI increases BC risk in postmenopausal women it decreases risk in premenopausal women. As most of our patients were under age 50, this would suggest we should see lower cancer and atypia rates than in thinner women. Also, patients undergoing mammoplasty likely represent a population of higher economic status, a group known to present with a higher incidence of BC [40].

Several questions remain. The rate of high-risk lesions presented in our study represents the minimum reservoir of occult conditions in asymptomatic patients. Does this type of patient present with the same risk of developing BC as patients diagnosed because of an abnormal finding? Or are we overdiagnosing lesions in these cases with the consequent risk of doing more harm than good to our patients? Although we do not yet know the answer to these questions, we do expect to shed some light on them in the near future.

Conclusion

The results of this study provide information about the minimum prevalence of occult invasive carcinoma, DCIS, and high-risk lesions in the general population. Our findings indicate a much higher rate of occult lesions than might be expected based on current estimates, and may help elucidate cancer risk in the general population.

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Compliance with ethical standards

Conflict of interest All the authors declare that he/she has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the IRB.

Informed consent As this was a database/medical record study, the need for informed consent was waived by the IRB.

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