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To cite this version:

Isacco Montroni, Donatella Santini, Giorgia Zucchini, Monica Fiacchi, Simone Zanotti, et al.. Nipple discharge: is its significance as a risk factor for breast cancer fully understood? Observational study including 915 consecutive patients who underwent selective duct excision. Breast Cancer Research and Treatment, 2010, 123 (3), pp.895-900. 10.1007/s10549-010-0815-1 . hal-00522542

HAL Id: hal-00522542

https://hal.science/hal-00522542v1

Submitted on 1 Oct 2010

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Nipple Discharge: is its significance as a risk factor for breast cancer fully understood? Observational study including 915 consecutive patients who underwent selective duct excision

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ABSTRACT

Background

Nipple discharge is a common symptom seen in breast cancer clinics. The primary aim of this study was to identify preoperative risk factors for breast cancer in patients with pathologic nipple discharge. The secondary aim was to assess the clinical and pathological effectiveness of physical examination, galactography, cytological examination of the discharge, selective duct excision and ductoscopy.

Methods

All patients operated on between 1975 and 2008 who presented with nipple discharge as their only symptom were analyzed. Discharge's characteristics, cytological data and galactography reports were recorded. The relationship between each individual finding and the risk of breast cancer was calculated. For each diagnostic tool the sensitivity, specificity and complication rates were calculated and compared.

Results

Nine-hundred-fifteen patients underwent selective duct excision. Two-hundred-nineteen patients (23.9%) were found to be affected by carcinoma. In 100/330 (30.3%) patients with bloody discharge and in 42/239 (17.6%) patients with serous secretion cancer was detected (p=0.004, p=0.013 respectively). Patients with sero-sanguinous or coloured discharge had the same risk of cancer as the population analyzed (23.9%, p=NS). Galactographic finding of irregular stenosis seemed to be associated with a higher risk of cancer (p=0.0001). Cytological findings C5 and C4 were associated with cancer (p=0.001). Selective duct excision showed highest sensitivity and specificity.

Conclusions

The well established role of bloody secretion is confirmed. The supposed benign etiology of serous, coloured or sero-sanguinous discharge is questionable. The high specificity of the cytological exam justifies routine examination of the nipple discharge. Selective duct excision can be considered as the diagnostic gold-standard.

KEYWORDS: Nipple Discharge, Breast Cancer, Selective duct excision, Risk Factors, Surgery.

INTRODUCTION

Nipple discharge (ND) is a fairly common symptom for thousands of patients referred to breast cancer clinics all over the world (4-7%) [1-3]. ND can be divided into three categories: physiological, para-physiological and pathologic. Physiological secretion obviously occurs during lactation for new mothers after delivery. Para-physiological ND can be related to hypothyroidism, pituitary adenomas, ectopic production of Prolactin (broncogenic carcinoma) and hypothalamic disorders. It can also occur as a result of side effects from certain medications (anti-psychotics, H2 inhibitors, anti-hypertensive and anti-emetic drugs) or it can be idiopathic. Physiological and para-physiological discharge usually occur from both breasts and from a number of ducts [4-6]. On the other hand, pathologic discharge is usually produced by a single duct unilaterally. Both pathologic and para-physiological ND can be spontaneous or non-spontaneous.

Pathologic ND can be secondary to the presence of a benign pathology (single or multiple papillomas, ductal hyperplasia, ductal ectasia) or of a breast carcinoma (ductal in situ or invasive).

Breast cancer is the most frequently diagnosed carcinoma among American and European women and is the most common cause of death from cancer [7]. Many authors have studied the relationship between breast carcinoma and ND, observing that malignancy occurs in from 9.3% to 21% of women with a pathologic discharge [8,9].

In addition, it is essential to note that as many as 20% of breast cancers are not palpable during physical examination and are mammographically occult [10].

However, controversy remains concerning the criteria of the definition of any pathologic ND and, above all, concerning the physical characteristics of the discharge (colour and type of onset) and cytological examination correlating with the incidence of malignancy. Some reports have found no association with cancer in patients with serous, sero-sanguinous or coloured secretion [11]; others have found a higher malignancy rate with bloody ND while still others have reported no such findings [12,13].

While physiological and para-physiological ND do not require breast surgery, the treatment of choice for a pathologic secretion is selective duct excision (galactophorectomy) [14,15]. If malignancy is detected after the final pathological examination of the specimen, surgery for radicalization may be required in the majority of cases.

For those reasons, during the last decade, various preoperative diagnostic tools have, more or less successfully, indcated that the presence of malignancy is a primary cause of ND. Thus, ductoscopy [9], MRI and MR ductography [16] were added to galactography, and the physical and cytological examinations as part of the preoperative algorithm for unilateral-single-duct ND.

The primary aim of our study was to clarify the role of any unusual preoperative physical, instrumental, and laboratory findings. Our goal was to identify which of these could be considered a risk factor for possible malignancy in patients with unilateral-single duct ND not associated with lumps in the breast or a mammographic suspicion of malignancy.

The second aim was to recognize the most effective diagnostic tools from the panel of tests carried out in our surgical unit (physical and cytological examination, galactography) or described in the literature (ductoscopy).

PATIENTS AND METHODS

Data from our Breast Database were retrospectively analysed from 1975 to 2008. Only patients who underwent a selective duct excision for unilateral single-duct ND admitted to the study. Every patient enrolled underwent a mammogram and a physical exam prior to surgery confirming the absence of any evidences of lumps in the breast or pathologic microcalcifications.

Data regarding the type of secretion (colour, spontaneous, non-spontaneous), preoperative tests (cytological exam, galactography), type of surgery and complications from the preoperative and postoperative procedures (diagnostic and therapeutic) were examined as well.

The ND was divided into four categories according to its colour: Serous (SS), Sero-Sanguinous (SSS), Hematic (HS) or Coloured (CS) Secretion. Coloured discharge was defined as milky or greenish. Spontaneous or non-spontaneous onset was also recorded. Cytological examination was carried out and the following criteria were reported: C1-non-diagnostic, C2-benign pathology without atypia, C3-presence of atypical features, C4-suspected malignancy and C5-clear malignant disease [17]. The galactographic report was standardized into five categories following the radiological findings: Duct Ectasia (DE), Singular Filling Defect (SFD), Multiple Filling Defect (MFD), Suspected Carcinoma (SC) and No Pathological Finding (NPF). A finding of SC was confirmed when the presence of irregular stenosis or chaotic distribution of the ducts was detected.

Selective duct excision was routinely performed after injection into the single secreting duct of 0.5-1 ml of Methylene Blue through a specifically designed probe immediately before surgery. After that, a 40% periareolar incision of the skin was carried out; the injected duct was isolated and resected from the nipple to the proximity of the muscular fascia with preservation of the surrounding ducts. After the excision, surgical reconstruction of the mammary gland was performed.

Galactography images make the procedure much easier for the surgeon to locate the pathologic ducts on the breast gland.

The relationship between each individual result and the risk of cancer was statistically calculated.

Since the secondary aim of the study was to evaluate which diagnostic tool would be considered the most accurate, the sensitivity and specificity of each methodology were calculated.

Due to the fact that ductoscopy is not practised in our hospital, we decided to consider the sensitivity and specificity for detecting malignancy as reported in the international literature using PubMed. A search was performed with the following terms: ductoscopy, sensitivity, specificity, nipple discharge and malignancy. Seventy-six papers were found and specifically analysed to identify the accuracy of ductoscopy in predicting malignant breast disease; only articles in English were evaluated.

We also decided to add the results of all the selective galactophorectomies performed in our surgical unit to these diagnostic procedures considering the opportunity to redefine the role of this tool.

A list of potential complications was defined for each individual diagnostic methodology and is reported in Table 1. Each diagnostic tool was evaluated for its sensitivity and specificity as was the complication rate in order to define the most accurate procedure.

Statistical analysis

The Binomial Test procedure was run to compare the frequencies observed in the two categories (malignancy and non-malignancy) and the dichotomous variables in each individual category of data (SS, SSS, HE, CS, Spontaneous, non-spontaneous, C1, C2, C3, C4, C5, DE, SFD, MFD, SC, NPF). The parameters obtained were statistically compared to the frequency of breast cancer in the entire study population. The statisticaxl software used was the Statistical Package for the Social Sciences version 11 for Windows® (SPSS® Chicago, Il).

The results were considered statistically significant for p values <0.05.

RESULTS

Nine hundred and fifteen patients in our surgical unit underwent selective galactophorectomy for pathological ND from 1975 to 2008. All the procedures were performed by five different surgeons specifically trained in breast pathology. Two hundred and nineteen patients who underwent galactophorectomy were diagnosed with breast carcinoma at the final pathology exam, 23.9% of the entire study population.

Galactography was routinely performed and recorded on 792 patients prior to surgery. It was possible to identify the galactographic report only for those patients operated on after 1985 (818/915 patients). Galactography was not performed in 26 cases because, having been attempted, the discharging duct was deemed impossible to be cannulised. In six-hundred and thirty-four cases, a cytological exam of the ND was executed. The analysis of the physical characteristics of the discharge, the results of the galactographic reports, cytological examination of the discharge and final pathology reports are reported in Table 2. The colour of the ND was not reported in 22 patients.

The different types of secretion (SS, SSS, HS, CS), galactographic findings (DE, SFD, MFD, SC, NPF) and cytological exams (C1-C5) were all considered as separate potential risk factors. The statistical relationship between each individual risk factor and the discovery of breast cancer was calculated and is reported in Table 3. According to our analysis, only the presence of HS was statistically strongly related to an increased risk of breast cancer (p=0.004) in our study population. From our data, patients with SS and non-spontaneous secretion are statistically less frequently affected by cancer than was our study population (p=0.013 and 0.005 respectively). For SSS, CS and spontaneous discharge, the risk of cancer was the same as the entire study population, 23.9%.

The discovery of irregular stenosis or chaotic distribution of the ducts (SC) is statistically related to an increased risk of breast cancer (p=0.0001). All other findings (DE, SFD, MFD, NPF) reported at galactography are less frequently associated with cancer as compared to the general risk of the study population.

The cytological tests gave an unequivocal indication of cancer when C4 or C5 result is reported (p=0.0001) while C3-C2-C1 are all less frequently related to any presence of malignancy.

Sensitivity and specificity were calculated for each methodology (physical characteristics of the ND, galactography, cytological exams and galactophorectomy) and are reported in Table 4.

The results of research found in the international scientific literature regarding the opportunity of performing a mammary ductoscopy for pathologic ND failed to identify any clear evidence of satisfactory sensitivity and specificity in detecting breast cancer [18,19].

The list of complications reported in our surgical unit during this 33 year period is reported in Table1.

Selective duct excision clearly represents the optimal combination of elevated sensitivity and specificity with absolutely acceptable complications (2.2%, with only 3 major complications, 0.3%). Therefore, it can be considered the best diagnostic (and therapeutic, for benign disease) procedure for patients with pathologic ND.

DISCUSSION

Over the last two decades numerous studies have been published regarding the clinical strategy for pathologic ND and the preoperative clues for a correct diagnosis of breast cancer before surgery but documented evidence is lacking [20].

In particular, the lack of data on the identification of preoperative risk factors could be secondary to both unclear indications for surgery and the exiguity of the population analysed in the different scientific papers.

For these reasons, we decided to retrospectively investigate all patients who underwent galactophorectomy for unilateral single-duct nipple discharge without any signs or radiological findings of breast cancer. In the last 33 years, 915 patients were operated on using selective excision of the discharging duct (galactophorectomy) and, of this group, 23.9% (219/915) were diagnosed with breast cancer. The different physical characteristics of ND have been widely considered as a key factor in the prediction of malignancy. Our study confirms the unfavourable predictive value of HS, but, in contrast with the majority of the literature, CS or SSS are related to a non-negligible risk of cancer (23.9%, the same as the entire study population) [21]. SS can be considered as relatively less related to cancer even if we have to remember that 42 out of 239 patients operated on for pathologic ND (17.6%) were found to be affected by breast cancer.

The role of these specific types of discharge should be reconsidered in order to reduce the risk of undiagnosed breast malignancy.

The overall sensitivity and specificity (58.97% and 82.83%, respectively) of these physical findings are not sufficiently accurate to consider this diagnostic method as the most precise preoperative tool.

Interesting findings were also detected regarding the role of galactography which was executed before surgery in 792 cases. In this population, only the presence of irregular stenosis or the chaotic distribution of the ducts was confirmed as a risk factor for cancer. All other results (DE, SFD, MFD, NPF) could not be considered as statistically demonstrated risk factors. On the other hand the unpredictably elevated number of false negatives (158/792) and the consequent low sensitivity (54.2%) means that this test is inadequate when being considered as an accurate diagnostic tool for breast malignancy.

Cytological examination is experiencing an increasing role in the diagnostic algorithm of pathologic ND [22], even if some authors debate its strategic role [23]. From our case series, we can affirm the fact that preoperative cytological evaluation has a key role in the preoperative setting. C4 and C5 results have direct relationship to the occurrence of cancer with a sensitivity (almost 70%) and specificity (92%) which make this methodology a milestone in the preoperative algorithm. Many questions have been raised by our study concerning the role of

C3 (moderate atypia) since we found no statistical differences from any benign pathology, even if, in 46 cases out of 226 (20%), a malignancy was detected at the final pathological exam.

Finally, our study demonstrated that only a surgical selective duct excision can give a significantly higher level of diagnostic accuracy (sensitivity and specificity close to 100%) with almost irrelevant operative complications (6 patients/ 915 operations). From this evidence we can draw the same conclusions that Dr Adepoju et al. reached in 2005 [12] reporting that all patients with pathologic ND should be offered duct excision not only for potential therapeutic purposes but for the necessity of an accurate diagnosis.

Conclusion

The indication for surgery (selective galactophorectomy) for ND is the presence of prolonged and recurrent unilateral single duct secretion. In the case of hematic secretion, we found it to be clearly related to an increased risk of cancer in our population when compared to non-hematic discharge.

On the other hand, both coloured and sero-sanguinous secretions were related to cancer in 23.4% of cases. Serous secretion was less frequently related to malignancy but, in 17.6% of the patients, final pathology reported the presence of breast cancer.

Irregular stenosis with chaotic distribution of the ducts at galactography and C4 or C5 cytological findings is unequivocally related to an increased risk. All these well-defined conditions should be taken into account as risk factors for patients with pathological ND who are placed on any surgical waiting list.

Selective ductal excision is not only a potential therapeutic procedure but the most accurate diagnostic tool and should be proposed to every patient with pathological nipple discharge.

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TABLE 1 Complications of galactography, ductoscopy and duct excision.

Diagnostic technique	Reported Complications in Literature	Observed (N)
Galactography	Duct perforation during injection with extravasations of iodinated contrast Mastitis Hypersensitivity to iodinated contrast material	5 3 1
Ductoscopy	Pain Mammary duct rupture	0* 0
Duct Excision	Duct perforation during injection with extravasations of Methylene Blue Hematoma (postoperative loss of >2g Hb) Nipple necrosis Methylene Blue Allergy Mammary duct fistula Seroma (> 50ml) Surgical wound infection	16 3 0 0 1 0 2

*Ductoscopy is not practiced in our Hospital

TABLE 2 Clinical characteristics, preoperative diagnostic methods and Final pathological report.

Demographic Data	
Number of Patients	**915**
ND Colour	**915**
Hematic	330
Sero-hematic	296
Colored	28
Serous	239
Not reported	22
Spontaneus	675
Non spontaneus	240
Galactography	**792**
Duct ectasia	31
Singular Filling Defect	270
Multiple Filling Defect	436
Suspected Carcinoma	39
No Pathological Finding	16
Cytology exam	**634**
C1	134
C2	175
C3	226
C4	67
C5	32
Breast cancer	**219**
DCIS	114
LCIS*	25
Ductal micro-invasive	16
(Ductal-Papillary-Mucinous)	(13-2-1)
Invasive	64
(Ductal-Mucinous-Papillary-Paget**-Lobular)	(48-5-8-2-1)

*Occasional histological finding
**Sub-clinical preoperative Paget Disease

TABLE 3 Statistical analysis. The frequency of breast cancer was calculated for every single risk factor sub-group and statistically compared to the frequency of breast cancer in the entire study population.

Type of ND	N	SG/SP*	P value	Type of ND	N	SG/SP*	P value
SS	Cancer 42 Noncancer 197 Tot 239	**17.6** /23.9	**0.013**	***Spont***	Cancer179 Noncancer496 Tot 675	26.5 /23.9	0.061
SHS	Cancer 65 Noncancer 231 Tot 296	22 /23.9	0.237	***Non-spont***	Cancer 40 Noncancer200 Tot 240	**16.7** /23.9	**0.005**
HS	Cancer100 Noncancer 230 Tot 330	**30.3**/23.9	**0.004**	***C1***	Cancer 19 Noncancer115 Tot 134	**14.2** /23.9	**0.002**
CS	Cancer 6 Noncancer 22 Tot 28	21.4 /23.9	0.466	***C2***	Cancer 35 Noncancer140 Tot 175	20.0 /23.9	0.054
DE	Cancer 10 Noncancer 21 Tot 31	32.3 /23.9	0.189	***C3***	Cancer 46 Noncancer180 Tot 226	**20.4** /23.9	**0.042**
SFD	Cancer 28 Noncancer 242 Tot 270	**10.4** /23.9	**0.0001**	***C4***	Cancer 35 Noncancer 32 Tot 67	**52.2** /23.9	**0.0001**
MFD	Cancer 114 Noncancer 322 Tot 436	26.1 /23.9	0.148	***C5***	Cancer 27 Noncancer 5 Tot 32	**84.4** /23.9	**0.0001**
SC	Cancer 29 Noncancer 10 Tot 39	**74.4** /23.9	**0.0001**				
NPF	Cancer 6 Noncancer 10 Tot 16	37.5 /23.9	0.162				

SS serous secretion
SC suspected carcinoma
SHS sero-hematic secr
NPF no pathological finding
HS hematic secr
CS coloured secr
DE duct ectasia
SFD singular filling defect
MFD multiple filling defect

*SG/SP is the cancer incidence for a specific sub-group of patients / cancer incidence in the study population

TABLE 4 Sensitivity, Specificity and complication rate of physical examination, pre-operative diagnostic methodologies and duct excision.

METHODOLOGY	NUMBER OF CASES	SENSITIVITY (%)	SPECIFICITY (%)	COMPLICATION (NUMBER/%)
Physical exam	915	58.97	82.83	0
Galactograpy	792	54.2	98.34	9/1.1%
Cytological exam*	634	69.83	92.16	0
Ductoscopy**	/	Non reported	Non reported	0.5%
Duct excision***	915	100	100	22/2.4%

*C4-C5 report were calculated as a positive expected result (for cancer)
** Not practiced in our hospital (Medline search)
** *HS was calculated as a positive (for cancer) expected result