

Sensitivity and specificity of occult blood testing in symptomatic single duct nipple discharge to detect ductal carcinoma

Sensibilidad y especificidad de la presencia de sangre oculta en la secreción patológica del pezón para detectar cáncer ductal de seno

HEINZ HILLER¹, MARCUS GALEA²

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ABSTRACT

I*ntroduction:* Testing asymptomatic nipple discharge in women for occult hemoglobin to predict the presence of ductal carcinoma remains controversial. The purpose of this study is to describe the sensitivity and specificity of occult blood testing in patients with asymptomatic single duct nipple discharge.

Methods: Data was collected ambispectively during a 7 year period. All patients with asymptomatic single duct nipple discharge were included in this study. The results of occult blood testing were correlated with the histopathological results after microductectomy.

Results: All 63 patients were female. They underwent mammography and ultrasound examination of the discharging breast which were normal in all cases. The average follow up period was 2

1 MD MRCS Ed D Lap, Vascular Surgeon, Clínica Rosario Medellín, Colombia

2 MD FRCS, Consultant Breast Surgery, Great Western Hospital, Swindon, UK

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years (0.5 to 5 years). Occult blood was positive in 37 (58.8 %) patients and negative in 26 (41.2 %) patients. Histopathological diagnosis was ductal ectasia in 30 % (n=18), intraductal papilloma in 44 % (n=28), granuloma 2 % (n=1), normal 12 % (n=8) and ductal carcinoma in situ 12 % (n=8). The most frequent cause for positive occult blood was ductal papilloma (n=23) followed by ductal ectasia (n=13). The sensitivity of the test was 87.5 % and specificity 45.4 %, with a positive predictive value of 18.9 % and a negative predictive value of 96.1 % and an Odds ratio of 5,833.

Discussion: Positive occult blood testing can help to predict the presence of either in situ or invasive ductal carcinoma in the absence of other symptoms. We recommend, however, an approach based on clinical examination, radiological testing and risk factor analysis to decide which patients require microductectomy to exclude the presence cancer definitively.

KEY WORDS

Nipples secretion

Breast cancer

Ductal carcinoma

RESUMEN

Introducción: la utilidad de la prueba de sangre oculta en la secreción patológica por el pezón en pacientes no lactantes para detectar cáncer de seno, es motivo de gran debate en la actualidad. El propósito de este estudio fue describir la sensibilidad y especificidad de la prueba en esta población.

Materiales y métodos: estudio de cohorte ambispectivo por un periodo de siete años. Se incluyeron pacientes con secreción patológica por el pezón, a quienes se les realizó prueba de sangre oculta y se obtuvieron características operativas de una prueba diagnóstica con los

resultados histopatológicos luego de una microductectomía.

Resultados: se obtuvo información de 63 pacientes de sexo femenino. En todos los casos se realizaron mamografía y ultrasonido de mama, adicional al examen físico. El tiempo de seguimiento fue en promedio de dos años (0,5 a 5 años). La sangre oculta fue positiva en 58,8 % de las pacientes. Se obtuvo un resultado negativo (líquido claro) en 41,2 % de las pacientes. Los diagnósticos histopatológicos obtenidos fueron: ectasia ductal 30 %, papiloma intraductal 44 %, granuloma 2 %, normal 12 % y carcinoma ductal in situ 12 %. La causa más frecuente de sangre oculta positiva en la secreción fue el papiloma ductal (n=23) seguido por la ectasia ductal (n=13). La sensibilidad fue del 87,5 % y la especificidad del 45,4 %, el valor predictivo positivo fue 18,9 % y el valor predictivo negativo fue del 96,1 %, con un Odds Ratio de 5,8.

Conclusiones: detectar sangre oculta en la secreción asintomática de un solo ducto del pezón puede ayudar a predecir la presencia de cáncer en los ductos mamarios. Sin embargo, recomendamos una aproximación basada en un algoritmo de decisiones utilizando una combinación de examen físico, pruebas de laboratorio e imagenología avanzada para detectar la presencia de malignidad en el tejido ductal.

PALABRAS CLAVE

Cáncer de mama

Líquido aspirado del pezón

Carcinoma ductal

INTRODUCTION

Nipple discharge in a non-lactating patient can be troubling and lead to misinterpretation of

clinical findings by the treating physician. It is a common finding and is seldom associated to ductal cancer. In one of the first reports in 1982, Chaudary et al., found an incidence of cancer of 5.9 % in a total of 270 patients with this clinical presentation (1). All cancer cases had positive occult blood on testing nipple discharge. When this occurs, further investigations should be sought out, like performing a mammogram, ultrasound and a ductal biopsy (microductectomy).

The incidence of finding cancer increases when nipple discharge is associated with other clinical findings such as palpable mass and positive radiological findings (2). The most common cause for positive occult blood testing is, however, a ductal papilloma.

Physiological causes of nipple discharge include galactorrhea, antihypertensive, oral contraceptives, hypothyroidism, pituitary adenoma, excessive nipple stimulation and hyperprolactinemia, and are usually bilateral, green colored and provoked by stimulus. Pathological causes usually produce a clear, bloodstained, spontaneous and unilateral discharge most frequently caused by ductal ectasia or papilloma (3).

There are numerous studies that have attempted to establish if there is a correlation between the type and color of the nipple discharge and the incidence of ductal cancer, and to date, no study has shown that discharge characteristics has a strong association with the presence of cancer (4,5).

At present, the only pre-surgical test that has shown reliable results with excellent sensitivity and specificity is a galactography associated to traditional radiological imaging (6). This test is slightly cumbersome as it requires the sometimes painful cannulation of the secreting duct, injection of contrast material and subsequent radiological imaging with conventional X-ray or magnetic resonance imaging.

The purpose of this study is to establish the sensitivity and specificity of occult blood testing in patients with pathological nipple discharge with normal radiological and clinical tests.

MATERIALS AND METHODS

We conducted an ambispective cohort study including patients from the Great Western Hospital in Swindon, UK, all which attended the Breast Unit during the period between January 2000 and December 2007. For this study we included a subgroup of patients with asymptomatic, single duct nipple discharge that had a normal clinical examination, normal mammogram and normal ultrasound examination. All demographic data including age at diagnosis, gender, type of discharge were collected. Follow up was recorded for all patients, including radiological and clinical examinations.

Occult blood testing was performed using spontaneous discharge from the affected nipple with minimal manipulation, the sample was analyzed using a multireagent strip (Uristix)[®] to detect the presence of blood. The independent variable was a positive test result, and the dependent variable was the histopathological result of the microductectomy (gold standard).

All results from mammography, ultrasonography and clinical examination were collected. Patients with pathological nipple discharge who had a positive finding on either clinical examination or radiological examination were excluded from the study, as well as patients with physiological causes for nipple discharge.

All data was collected in an encrypted Excel database. Descriptive statistics such as frequencies and median ranges for all categorical variables were obtained, as well as values for the test such as specificity, sensitivity, positive and

negative predictive values and the odds ratio for the 2x2 table. All analysis was calculated using the EpiMax Health Decision Strategies®, LLC, Princeton New Jersey, USA (www.healthstrategy.com) online software.

All patients gave their informed consent to use the data from their respective clinical charts. The data collected for this study had no influence on the decision making process for treatment of the patients as the departmental policy to operate all non-physiologic nipple secretions was well established before this study.

RESULTS

A total of 63 patients were included in this study, all with pathological, asymptomatic nipple dis-

charge. All patients were female, the median age was 52 years (range 24 to 94), and all underwent a physical examination which was normal in all cases, as well as all mammographies and ultrasound examinations. Mean time of follow up was 2 years (0.5 to 5 years). All cases underwent a microductectomy and compared to the result of the occult blood testing.

All samples were analyzed histopathologically (gold standard) and the presence or absence of ductal carcinoma was sought out. We then compared the results of this with the clinical findings previously.

A positive occult blood test was found in 37 (58.8 %) patients. In the patients with negative results, 38 % had clear fluid and two had either cream colored and green discharge respectively (3.18 %) (table 1).

Table 1. Demographic data

Demographic characteristics	Patients (n=63)	Complementary tests
Female	n=63	Mammography R2 n=63
Age (Median)	52 (Range 24-94 years)	Ultrasound U2 n=63
Occult blood test +	37	Physical Examination P2 n=63
Occult blood test -	26	
Pathological Diagnosis		
Ductal papilloma	28 (44 %)	
Ductal ectasia	18 (30 %)	
Normal	8 (12 %)	
Granuloma	1 (2 %)	
Ductal carcinoma in situ	8 (12 %)	

Diagnosis obtained after histopathological analysis was ductal ectasia in 30 %, intraductal papilloma 44 %, granuloma 2 %, normal in 12 % and ductal carcinoma in situ 12 %. Ages of patients with ductal carcinoma ranged from 37 to 80 years. The most common cause for a positive occult blood test was a ductal papilloma

(n=23, 36.5 %) followed by ductal ectasia (n=13, 20.63 %). In all cases who presented normal histopathological results or patients with granulomas the occult blood test was negative. In the cases with ductal carcinoma 7 tested positive to occult blood preoperatively (table 2).



Table 2. Results of sensitivity and specificity analysis

	Cancer	No Cancer	Totals	Predictive value
Positive Test	7	30	37	18.0 %
Negative Test	1	25	26	96.1 %
Totals	8 (12 %)	55 (88 %)	63 (100 %)	
	Sensitivity: 87.5 %	Specificity: 45.4 %		

During follow up, two patients presented with ipsilateral malignant lesions de novo. In both cases ductal carcinoma in situ was the initial presentation. Unfortunately in one case the disease progressed and she required a total mastectomy and chemo-radiotherapy follow by her death after 5 years of treatment. The interesting finding in these cases is that the initial occult blood test was positive and an initial diagnosis of ductal ectasia was made.

According to these results preoperative occult blood testing had a sensitivity of 87.5 % and a specificity of 45.4 % with a positive predictive value of 18.9 % and a negative predictive value of 96.1 % (Odds ratio: 5,83, and 95 % confidence interval: 0.636-137.16). The likelihood ratios (LR) were as follows: positive LR of 1.604 and a negative LR of 0.275. No complications were recorded that were directly caused by the microductectomy.

DISCUSSION

Additional diagnostic tools during clinical examination of a patient with pathological nipple discharge have improved in recent years. At present it is imperative to use mammography and ultrasound to examine suspicious lesions or manifestations of breast disease. In our subgroup of patients, the situation is more complex, as none of them have positive findings with the accepted modes of diagnosis such as mammography, ultrasound and clinical examination and

additional diagnostic tools are thus necessary. Several other ways of analyzing nipple discharge have been proposed such as cytology of the discharge and occult blood testing of the secretion (7-9).

In 1990, Welch *et al.* published a study in which a group of 162 patients with pathological nipple discharge and no mammography were tested for occult blood. The results of this study showed an incidence of ductal carcinoma in situ (DCIS) of 10 % (n=16) in which the test was positive in 14 patients. In two patients the test was negative and the color was clear. The initial recommendation was to perform a microductectomy based on clinical findings rather than on the result of the test (7,8).

These results are comparable with our findings, in such that our incidence of ductal carcinoma was 12 % and that one patient had a negative occult blood test on examination. Later, several groups have attempted to shed a better light on the matter, Wong *et al.*, and Richards *et al.*, published in 2000 and 2007 respectively, two retrospective studies comparing the color of the discharge with the presence of cancer.

In both studies the incidence of DCIS was 5 % and 2.3 % respectively, and in both positive occult blood testing was better correlated with the presence of ductal papilloma and ductal ectasia (10-12). The conclusion of both studies was that the color or presence of positive occult blood does not correlate or predict the occurrence of

DCIS. They suggested using a decision making algorithm based on patient characteristics and risk factors.

In the largest series reviewed, Florio *et al.* published in 2003 their personal experience with 2818 cases during a 21 year period. The results showed that nipple discharge was clear, dark, blood stained or watery. These findings were, however, more common in patients with ductal papillomas and other ductal inflammatory conditions. The possibility of detecting DCIS was increased when clinical findings were complemented with mammography, cytology and galactography, especially in patients older than 50 years (13).

All results a very similar to those obtained in our study. The association between the presence of positive occult blood and DCIS was not strong, with a sensitivity of 87.5 % and a specificity of 45.5 % ,showing that a positive test has to interpreted with caution, especially to make a decision whether to perform a microductectomy or not. However, the negative predictive value of 96.1 % might help the clinician to make a more informed decision in this subgroup of patients wether to perform a microductectomy or not.

Based on optimized breast cancer diagnostic and treatment models, two studies by Nelson RL *et al.* (2006) and Sauter (2006) suggest that patients should be stratified according to risk factors and clinical presentation, discharge color helped to increase the likelihood of finding DCIS, however, they recommended to perform a microductectomy in all patients with pathological nipple discharge (14,15). The same recommendation was followed in this study.

One common observation of this and other studies is that no single diagnostic test is useful to predict the occurrence of DCIS. It is a combination of clinical history, examination and radiological tests that offer the best possibility for detecting early stages of cancer (16-18).

The role of cytology in detecting DCIS has been the target of multiple studies, the largest one offered by Gupta RK *et al.*, in 2004, who proved that cytology had a high sensitivity to detect DCIS but a low specificity. Additionally, 20 % of samples where inadequate for interpretation for which a microductectomy was necessary (19).

Differentiation of cells in a cytology specimen can be difficult due to the low volume of the sample and can be the cause for disagreement between pathologists. Because of this and the conflicting results of other studies (20,21), the cytological analysis of nipple discharge was not included in the present study.

Novel modalities such as ductoscopy and galactography promise to allow better preoperative testing for the presence of DCIS, especially when associated to traditional radiological tests. Reimer *et al.* in Rostock, Germany, published a study in which all patients with pathological nipple discharge underwent a galactography and compared to histopathological results. The results showed an incidence of DCIS of 9.3 % in premenopausal and of 12.5 % in post-menopausal women. Most interesting is the fact that correlation was 94.1 % between both methods and no additional clinical tests were used such as cytological or occult blood testing (22).

Finally, newer, less invasive methods are being developed such as biological markers in the discharge fluid. In a recent study by Sauter *et al.*, a significant correlation was found between the levels of basic fibroblast growth factor (bFGF) and the Fase S fraction (SPF) with the presence of DCIS (23). Still, the problem remains as these tests are not widely available and are too expensive to be cost effective. Newer modalities such as magnetic resonance ductography and ultrasound gactography are in its evaluation phases and promise more specific ways of predicting carcinoma in mammary ducts (24, 25).

The limitations of this study are the small number of patients to make a more powerful calcu-

lation of the true value of occult blood testing in this scenario. But as other comparative studies suggest, the occurrence of patients within this subgroup is small, and other types of presentation of ductal carcinoma is far more common.

CONCLUSIONS

The results show that with a positive occult blood test a physician can detect 1 in 5 DCIS and only a 1 in 26 chance of missing a potential cancer in situ. This can aid the treating specialist in whether or not to perform a microductectomy, especially in places where more advanced diagnostic tools are not available. We recommend however an approach based on clinical examination, radiological testing and risk factor analysis to decide which patients require microductectomy to exclude the presence of cancer definitively. Future research of newer biological markers may prove to be more accurate as initial screening tools.

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