Long term follow-up and risk of breast cancer after a radial scar or complex sclerosing lesion has been identified in a benign open breast biopsy

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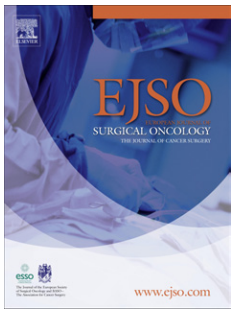

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Abstract

Aims

Radial scars (RS)/complex sclerosing lesions (CSL) are rare, benign breast lesions of unknown aetiology. Associations with breast cancer have been suggested particularly with larger lesions. This study aims to identify the risk of developing subsequent breast cancer after excision of a benign RS/CSL with respect to lesion size and compared to expected rates in the normal UK population.

Methods

A prospective cohort analysis was performed on patients diagnosed with RS/CSL in benign, open breast biopsy specimens over a 20-year period. The rate of subsequent breast cancer development was compared to expected rates in the normal UK population. Subjects were divided into two groups according to lesion size and the rates of subsequent breast cancer compared.

Results

149 women without proliferative breast disease were followed for an average of 68 months. Five women developed subsequent cancer, equating to a rate of 0.84% per year. This compares to 0.32% per year in the normal population (RR 2.6, 95% CI 0.86 – 6.0). There were two subsequent cancers in the RS group and three subsequent cancers in the CSL group, *P*= 0.64.

Conclusions

The study finds no evidence to suggest that lesions greater than 10mm (CSL) have any greater risk of developing cancer after excision than those below 10mm (RS). Women treated for RS/CSL do not need any additional follow up beyond routine mammographic breast screening. Additional surveillance

should only be performed if there is associated pathology indicating an increased risk of subsequent malignancy.

Keywords: breast neoplasms; precancerous conditions

Introduction

Background

Radial scars/complex sclerosing lesions (RS/CSL) are rare, benign breast lesions of unknown aetiology. Larger lesions may be associated with typical mammographic appearances although many smaller lesions are incidental microscopic findings on benign breast biopsies or therapeutic excision specimens for breast cancer. The characteristic microscopic appearance is that of a stellate abnormality with slender, radially arranged bands containing ductal structures surrounding a central fibroelastotic core. Mammographic features include an asymmetric density or distortion with spicules radiating from a central lucency. Typically, appearances differ depending on the radiological projection. Radial scars and complex sclerosing lesions are seen as the same clinical entity [1] with the latter term used for lesions 10mm or greater in diameter [2].

Clinical Significance

The main clinical significance of radial scars is their possible association with the development of breast cancer. Several observations have led to this suggestion including similar mammographic and histological appearances [3-7]; the finding of carcinomas in radial scars [1, 5, 8-16]; and the association with other forms of benign proliferative disease known to predispose to the development of breast cancer [17-20].

Various studies have investigated the possible association between radial scars and breast cancer, with conflicting results. There is a trend towards the presence of radial scars being an independent risk factor for the development of breast cancer, but only a minority of studies have reached significance [21]. Whilst it is becoming clear that the presence of a RS/CSL is associated with an increased risk of

development of carcinoma, it is not clear whether these lesions act simply as a marker of increased risk, whether they independently increase the risk or whether they are themselves premalignant.

Size of RS/CSL

The effect of lesion size has not yet been fully evaluated. A number of reports suggest that larger RS/CSLs are more often associated with cancers [15, 22]. It has been proposed that lesions of greater than 6-7mm [22] and in particular more than 10mm [15] are the most likely to be associated with carcinomas. Other studies have also shown a trend towards larger RS/CSLs having a greater risk of developing breast cancer [17, 21, 23] but none have reached statistical significance. Whilst there are some data published on the associations of smaller radial scars (median 4.0mm [17, 21], majority <5.0mm [23]) there is little information available on the long term follow-up of larger radial scars in studies of significant size.

Aims

This study investigates the long term outcome in a cohort of women with a history of RS/CSL in a benign excision biopsy specimen. It aims to analyse the rate of development of subsequent breast cancer with respect to lesion size and to compare to the rate of breast cancer development to that expected in an age matched UK population.

Patients and Methods

Patients

Data were collected from women with a histological diagnosis of RS/CSL at a single institution over a 20-year period, 1989 to 2009. Patients with a simultaneous breast malignancy were excluded from the study leaving 164 subjects.

Methods

For the purpose of this study, breast cancer was defined as any invasive carcinoma or carcinoma-in-situ, an established practice in similar reports. Data were recorded on the patients' age at diagnosis, past history of breast disease and any previous breast imaging. Details of the procedures performed, size and number of RS/CSLs and presence of any other associated pathology such as atypical hyperplasia were noted. The database was updated with details of follow-up events and any subsequent mammogram results. The total length of follow up was then recorded in months from initial diagnosis to the most recent episode.

From the initial cohort of 164 patients, those with atypical ductal hyperplasia (ADH) or lobular carcinoma-in-situ (LCIS) at the time of diagnosis were excluded.

The rate of developing subsequent cancer was calculated and compared to nationally available data for expected rates of breast cancer in women of comparable age.

Groups

Subjects were divided into two groups depending on whether the lesion was < 10mm (RS) or ≥ 10mm (CSL). Groups were compared for age at diagnosis, length of follow up, number of RS/CSL and proportion of patients developing subsequent cancer.

Statistical Methods

SPSS 14.0 for Windows was used for Chi-squared, Fisher's exact, t-tests and Mann-Whitney tests as appropriate.

Results

Patients

The series of patients diagnosed with RS/CSL in a benign biopsy from 1989 to 2009 comprised 164 women. 110 patients were identified through the NHS Breast Screening Programme. Of the remaining 54, 36 had symptoms such as a breast lump, thickening or pain, the others having mammograms for other reasons.

Of the total 164 patients with RS/CSL, 15 patients had associated atypical ductal hyperplasia (ADH) or lobular carcinoma-in-situ (LCIS) at the time of their initial diagnosis and were excluded from further analysis. Two patients from the excluded group developed subsequent breast cancers.

149 patients who had no atypia went on to further analysis. Mean age was 52.4 years (range 21-73). 110 had long term follow up data available with a range of 9-216 months (median 68 months).

Rate of subsequent cancer

Five patients developed subsequent carcinoma giving an incidence of breast cancer development of 0.84% per year (95% confidence interval 0.28% - 1.92%). The equivalent risk in the UK population of a comparable age is 0.32% [24] giving a relative risk of 2.63 (95% confidence interval 0.86 – 6.0). Of the 5 patients developing subsequent cancer, three were in the ipsilateral breast and two were in the contralateral breast.

Groups

After exclusion of three patients whose size of lesion was unknown, the study population was divided into RS (n=45) and CSL (n=101) groups according to the size of the lesion. The mean ages in the groups

were 54.0 (range 38-72) years and 51.5 (range 21-73) years respectively (P=0.06). Median follow up length in both groups was similar; 66 months (range 12-216) and 68 months (range 9-192), respectively, *P*=0.53. A single lesion was found in all cases except for one subject in each group, having two lesions each.

Rate of subsequent cancer by group

There were two subsequent cancers in the RS group and three subsequent cancers in the CSL group, *P*= 0.64. Two cancers affected the contralateral breast and three were in the ipsilateral breast.

Within the RS group, one patient with subsequent cancer presented with a lump and one was identified through routine screening mammography. Cancers were of invasive ductal and tubular types. Mastectomy was performed for the invasive ductal carcinoma, whereas the tubular carcinoma was treated with a wide local excision and radiotherapy.

In the CSL group, one patient presented with a symptomatic lump, one through a routine follow up appointment and one was identified through routine screening mammography. Two were invasive ductal carcinomas and one a tubular carcinoma. The ductal carcinomas were treated by mastectomy and the tubular carcinoma by wide local excision. All received radiotherapy.

Discussion

Background

A RS/CSL may be an incidental finding at biopsy in asymptomatic patients. The lesions are also increasingly identified through population based mammographic screening programmes and confirmed

histologically when excised. RS/CSLs have been associated with cancer at the time of diagnosis and an increased risk of subsequent development of breast cancer. Whilst some studies have suggested it may be safe in selected patients to manage these lesions conservatively following satisfactory core biopsies [25-28], most authors advise excising all lesions in order to exclude any coexisting carcinoma [1, 5, 8, 9, 15, 29-32]. Recently the Royal College of Radiologists have revised their guidelines for assessment in the screening programme. The have indicated that where available, vacuum biopsy excision is an acceptable alternative to surgical excision in cases with no atypia, though this practice is not yet widespread in the UK.

Association with cancer

It is not currently known whether RS/CSLs only represent a marker for cancer or are in themselves premalignant. It is difficult to study the natural history of RS/CSLs given that they are quite rare and usually excised. The finding of cancers in association with these lesions has prompted the theory that they represent a premalignant condition [5, 8-15]. In contrast, autopsy studies have commonly identified radial scars but they report no difference in the frequency of radial scars identified between women with and without breast malignancy [33, 34].

Following excision, RS/CSLs have been associated with an increased risk of developing cancer [17, 21, 23]. This has also been described in other forms of benign proliferative disease [18, 19]. RS/CSLs are also known to be more common in the presence of benign proliferative disease and therefore, the question has been raised whether it is the associated disease which gives rise to a greater risk of cancer or the RS/CSLs themselves.

Jacobs *et al* stated that radial scars are an independent risk factor for the development of breast cancer [21]. In contrast to this, Berg *et al* concluded that these lesions were not independent risk factors and

that any increased risk was attributable to associated proliferative disease such as atypical hyperplasia [23].

When RS/CSLs have been stated to increase the risk of cancer development, contralateral and ipsilateral sides have been affected equally [21]. This suggests that any predisposition to breast cancer may be a generalised phenomenon affecting all breast tissue rather than a localised consequence of the RS/CSL.

Our study suggests a trend toward higher rates of cancer than in the age-matched UK population even when atypical proliferative diseases are excluded. As with similar studies [17, 23], this does not reach statistical significance. This study therefore gives no evidence to support the idea that RS/CSLs are independent risk factors. It is possible that the study population is not large enough to demonstrate this statistically, a commonly identified problem in previous similar studies. Large patient numbers are required to increase the power of future studies. Our study excludes RS/CSL associated with ADH/LCIS, but it may be that ADH/LCIS association is part of the natural history by which RS/CSL increase the likelihood of malignancy, thus our study would underestimate the risk of carcinoma. In addition, longer follow up lengths are required as RS/CSLs are frequently identified through the incident mammographic screening round soon after the age of 50 years whereas the incidence of breast cancers continues to increase with increasing age, possibly representing a significant time lag.

Size of RS/CSL

It has also been suggested that the size of RS/CSL may be important, with larger lesions more likely to have malignant potential [15, 22]. There are few data available in significant numbers on lesions greater than 10mm in diameter.

Manfrin *et al* analysed follow up in 117 cases of RS/CSL with a mean diameter of 10.1mm [15]. They identified a heterogenous group of patients including those with carcinoma in association with radial

scars. Follow up was available in 62 per cent of patients with mean durations of 100, 86 and 75 months in their groups of pure radial scar, radial scar with atypia and radial scar with carcinoma respectively. Only one patient developed a cancer following excision of a radial scar. In comparison, we identified 7 carcinomas out of 164 patients following RS/CSL excision and 5 carcinomas out of 149 when subjects with ADH/LCIS were excluded with follow up data available in 74 per cent. The greater number of cancers observed may be due to the larger sample size or greater proportion of follow-up data available. Manfrin et al found that patients with coincident cancer generally had larger RS/CSL and suggest that radial scars and complex sclerosing lesions represent a natural model of carcinogenesis from proliferative disease, through atypia to insitu and invasive carcinoma. However, the patients in the cancer/atypical hyperplasia groups were older than those in the group without cancer. It is known that both RS/CSLs [17, 23] and breast cancer are more common with increasing age, therefore, the association of breast cancer and larger RS/CSLs may simply reflect age related changes.

Our series contains a significant proportion of larger lesions with follow up lengths up to 18 years in subjects without previous cancer. There were no differences between the RS and CSL groups in terms of age, length of follow up or number of radial scars per subject. RS and CSL groups did not differ in the proportion of patients developing subsequent cancer giving no support to the theory that lesions greater than 10mm in diameter (CSL) are associated with a greater risk of developing cancer compared with lesions below 10mm (RS).

Conclusion

Given the rate of subsequent malignancy in women who have a RS/CSL excised, no additional follow up beyond routine mammographic breast screening is required. Additional surveillance should only be performed if there is associated pathology indicating an increased risk of subsequent malignancy.

Conflict of interest statement

There are no conflicts of interest

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References

1. Patterson JA, Scott M, Anderson N, Kirk SJ. Radial scar, complex sclerosing lesion and risk of breast cancer. Analysis of 175 cases in Northern Ireland. Eur J Surg Oncol 2004; 30: 1065-8.

2. Page DL, Anderson TJ. Radial scars and complex sclerosing lesions. In: Page DL, Anderson TJ, eds. Diagnostic histopathology of the breast. Edinburgh: Churchill Livingstone, 1987: 89-103.

3. Eusebi V, Grassigli A, Grosso F. Breast sclero-elastotic focal lesions simulating Infiltrating carcinoma. Pathologica 1976; 68(985–986):507–18.

4. Adler DD, Helvie MA, Oberman HA, Ikeda DM, Bhan AO. Radial sclerosing lesions of the breast: mammographic features. Radiology 1990; 176: 737-40.

5. Alleva DQ, Smetherman DH, Farr GH Jr, Cederbom GJ. Radial scar of the breast: radiologic-pathologic correlation in 22 cases. Radiographics 1999 Oct; 19 Spec No: S27-35; discussion S36-7. 1997 Nov; 17(5):353-62.

6. Oprić D, Fajdić J, Hrgović Z, Granić M, Milosević Z, Gugić D, Oprić S, Babić D, Fassbender WJ. Radial scar of the breast--a confusing lesion. Adv Med Sci 2007; 52:257-61.

7. Mokbel K, Price RK, Carpenter R, Connoly JL, Schnitt SJ. N Engl J Med 1999; Jul 15;341(3):210. Comment on 'Radial scars and breast cancer'. N Engl J Med 1999; 340: 430-6.

8. Fasih T, Jain M, Shrimankar J, Staunton M, Hubbard J, Griffith CD.

All radial scars/complex sclerosing lesions seen on breast screening mammograms should be excised.

Eur J Surg Oncol 2005; 31:1125-8. Epub 2005 Jul 15.

9. Vega A, Garijo F. Radial scar and tubular carcinoma. Mammographic and sonographic findings. Acta Radiol 1993; 34:43-7.

10. Tükel S, Koçak S, Aydintuğ S, Erekul S, Akyar G. Radial scar and tubular carcinoma of the breast. Australas Radiol 1997 May; 41:190-2.

11. Bonzanini M, Gilioli E, Brancato B, Pellegrini M, Mauri MF, Dalla Palma P. Cytologic features of 22 radial scar/complex sclerosing lesions of the breast, three of which associated with carcinoma: clinical, mammographic, and histologic correlation. Diagn Cytopathol 1997; 17:353-62.

12. Inoue S, Inoue M, Kawasaki T, Takahashi H, Inoue A, Maruyama T, Matsuda K, Kunitomo K, Murata S, Fujii H. Six cases showing radial scar/complex sclerosing lesions of the breast detected by breast cancer screening. Breast Cancer 2008; 15:247-51. Epub 2008 Mar 1.

13. Douglas-Jones AG, Pace DP. Pathology of R4 spiculated lesions in the breast screening programme. Histopathology 1997; 30: 214-20.

14. Denley H, Pinder SE, Tan PH, Sim CS, Brown R, Barker T, Gearty J, Elston CW, Ellis IO. Metaplastic carcinoma of the breast arising within complex sclerosing lesion: a report of five cases. Histopathology 2000; 36: 203-9.

15. Manfrin E, Remo A, Falsirollo F, Reghellin D, Bonetti F. Risk of neoplastic transformation in asymptomatic radial scar. Analysis of 117 cases. Breast Cancer Res Treat 2008; 107: 371-7.

16. Mokbel K, Price RK, Mostafa A, Williams N, Wells CA, Perry N, Carpenter R. Radial scar and carcinoma of the breast: microscopic findings in 32 cases. Breast 1999; 8: 339-42.

17. Sanders ME, Page DL, Simpson JF, Schuyler PA, Dale Plummer W, Dupont WD. Interdependence of radial scar and proliferative disease with respect to invasive breast carcinoma risk in patients with benign breast biopsies. Cancer 2006; 106: 1453-61.

18. Dupont WD, Parl FF, Hartmann WH et al. Breast cancer risk associated with proliferative disease and atypical hyperplasia. Cancer 1993; 71: 1258-65.

19. Page DL, Dupont WD, Rogers LW, Rados MS. Atypical hyperplastic lesions of the female breast. A long-term follow up study. Cancer 1985; 55: 2698-708.

20. Miltenburg DM, Speights VO Jr. Benign breast disease. Obstet Gynecol Clin North Am. 2008 Jun; 35(2):285-300.

21. Jacobs TW, Byrne C, Colditz G, Connoly JL, Schnitt SJ. Radial scars in benign breast-biopsy specimens and the risk of breast cancer. N Engl J Med 1999; 340: 430-6.

22. Sloane JP, Mayers MM. Carcinoma and atypical hyperplasia in radial scars and complex sclerosing lesions: importance of lesion size and patient age. Histopathology 1993; 23: 225-31.

23. Berg JC, Visscher DW, Vierkant RA, *et al*. Breast cancer risk in women with radial scars in benign breast biopsies. Breast Cancer Res Treat 2008; 108:167-74. Epub 2007 May 22.

24. Cancer Research UK statistics.http://info.cancerresearchuk.org/cancerstats/types/breast/incidence

25. Kennedy M, Masterson AV, Kerin M, Flanagan F. Pathology and clinical relevance of radial scars: a review. J Clin Pathol 2003; 56: 721-24.

26. King TA, Scharfenberg JC, Smetherman DH, Farkas EA, Bolton JS, Fuhrman GM. A better understanding of the term radial scar. Am J Surg 2000; 180:428-32; discussion 432-3.

27. Brenner RJ, Jackman RJ, Parker SH, Evans WP, Philpotts L, Deutsch BM, Lehrer D, Sylvan P, Hunt R, Adler SJ, Forcier N. Percutaneous core needle biopsy of radial scars of the breast: when is excision necessary? Am J Roentgenol 2003; 181: 1179-84.

28. Cawson JN, Malara F, Kavanagh A, Hill P, Balasubramanium G, Henderson M. Fourteen-gauge needle core biopsy of mammographically evident radial scars: is excision necessary? Cancer 2003; 97: 345-351.

29. Doyle EM, Banville N, Quinn CM, Flanagan F, O'Doherty A, Hill AD, Kerin MJ, Fitzpatrick P, Kennedy M. Radial scars/complex sclerosing lesions and malignancy in a screening programme: incidence and histological features revisited. Histopathology 2007; 50: 607-14.

30. Ung OA, Lee WB, Greenberg ML, Bilous M. Complex sclerosing lesion: the lesion is complex, the management is straightforward. ANZ J Surg 2001; 71: 35-40.

31. Douglas-Jones AG, Denson JL, Cox AC, Harries IB, Stevens G. Radial scar lesions of the breast: analysis of cases containing occult malignancy. J Clin Pathol 2007; 60: 295-8.

32. Pediconi F, Occhiato R, Venditti F, Fraioli F, Napoli A, Votta V, Laghi A, Catalano C, Passeriello R. Radial scars of the breast: contrast enhanced magnetic resonance mammography appearance. Breast J 2005; 11: 23-8.

33. Nielsen M, Christensen L, Andersen J. Radial scars in women with breast cancer. Cancer 1987; 59:1019-25.

34. Nielsen M, Jensen J, Andersen JA. An autopsy study of radial scar in the female breast. Histopathology 1985; 9: 287-95.