PAPERS AND SHORT REPORTS

Risk of breast cancer in women with history of benign disease of the breast

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Abstract

A consecutive series of 791 women who had attended diagnostic breast clinics during 1967-70 and been found to be free of malignant disease were later traced to determine their subsequent incidence of breast cancer. Of the 770 (97%) successfully traced, 22 had developed breast cancer. Based on data from the Welsh Cancer Registry only eight cases of breast cancer had been expected, so that the excess risk for the group was 2.7. The increased risk occurred in all age groups and in women deemed "essentially normal" as well as in those who had had a pathological abnormality. The risk was increased when epithelial hyperplasia was present. No excess mortality from breast cancer was apparent, but follow up was short. More breast symptoms were experienced and more biopsies performed than expected in this group of women.

Women with a past history of benign breast disease have a slightly increased risk of breast cancer. Selective screening of these women, however, may be uneconomic and a cause of groundless anxiety.

Introduction

Much evidence suggests that women who have had a biopsy for a benign condition of the breast are at an increased risk of developing breast cancer. This has been shown by several American prospective studies based on pathology records of individual clinics or hospitals.¹⁻⁸ Some, but not all, case-control

studies of patients with breast cancer also show that women with the disease are more likely than control women to have had a breast biopsy for benign conditions.⁹⁻¹⁵ This inconsistency may be related to selection factors in the patients studied, as there is considerable variation in the frequency with which previous breast biopsy is reported (table I).

When we began our study in 1979 we discovered that little information was available for British women. Also we did not know whether this could be a problem in terms of health service resources. Although the current national study of screening for breast cancer is based on a population of normal women,¹⁶ it is often suggested that screening should be offered only to women at increased risk in order to increase efficiency and reduce costs. It is therefore important to obtain information about such risk factors in Britain, and that was the purpose of the present study.

TABLE I—Previous benign disease (proved by biopsy) in case-control studies of breast cancer; variation of prevalence

Reference	No of cases	No of controls	Prevalence (%) of previous benign disease		Relative risk
			Cases	Controls	
Duffy <i>et al</i> ⁹	236	2962	7	3	4.5
Shapiro <i>et al</i> ¹⁰	101	9914	27	11	2.5
Lubin <i>et al</i> ¹¹	577	822	15	8	2.2
Vessey <i>et al</i> ¹²	621	621	8	4	2.0
Paffenbarger <i>et al</i> ¹³	819	1523	17	12	1.5-1.6
Wynder <i>et al</i> ¹⁴	785	2231	9	9	1.0
Brinton <i>et al</i> ¹⁵	405	1156	22	19	0.8

Subjects and methods

In late 1967 the surgical unit at the University Hospital of Wales set up a diagnostic breast clinic using precoded record forms which were then computerised. Epidemiological information and clinical history were recorded together with details of clinical, mammographic, and pathological examinations. Of the 1015 women seen consecutively from December 1967 to December 1970, 224 were found to have breast cancer. The remaining 791 women form the basis of this study. The method used for tracing these women was based on the experience of Sims.¹⁷ If hospital notes provided no recent information the general practitioner and local family practitioner committee were contacted. When necessary, the NHS central register was consulted for current practitioner, cancer registration, or death. When all else

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failed, neighbourhood visits were made. Referrals for breast problems and other serious illnesses during the period of follow up were recorded as well as any history of breast or other cancer.

All the women were from the South Glamorgan area, and cancer registration figures for the area (1972-80) were obtained from the Welsh Cancer Registry. Female mortality statistics for the whole of Wales (1970-80) were obtained from Register General publications and a midpoint figure used.

Pathological review—Slides were available for 326 of the 356 women who had undergone biopsy. They were reviewed independently and without knowledge of subsequent events (RWF and SW). Classification was by a system similar to that of Page *et al*⁶ and Wellings *et al*¹⁸ but also included non-pink cell metaplasia, representing a non-eosinophilic columnar cell with secretory free surface. Lobular and ductal hyperplasia were graded as (1) benign hyperplasia, (2) and (3) mild and moderate epithelial hyperplasia, and (4) severe epithelial hyperplasia. We did not attempt to quantify the relative amounts of pathological abnormality within the biopsy specimens. Only the lesion considered to be dominant was separately classified, and no distinction was made between focal and diffuse disease.

Statistical analysis—Expected frequencies for cancer incidence and death were calculated in 10 year age groups by multiplying the age specific incidence figures by the total woman years spent in each age group. Confidence limits for risk relative to the general population were calculated using the Poisson distribution. Differences in relative risk of cancer between groups of patients classified by initial mammographic or pathological findings were tested by χ^2 tests (with expected frequencies scaled to add up to the observed frequencies) or by binomial tests when expected frequencies were low.

Results

Tracing—Of the original 791 women, 770 (97%) were traced, giving a total of 8470 woman years of follow up (to December 1981). Although most were relatively easy to trace, some (particularly younger women) proved difficult (table II). Interestingly, 124 women (16%) had changed health districts (though some of this change reflected the reorganisation of boundaries in 1974) and 241 (30%) had changed their family doctor during the period.

Incidence of breast symptoms—During the follow up period 188 women (24%) had been referred back to the clinic because of symptoms related to the breast, 111 of whom had then undergone biopsy. Altogether 84 women in the series (11%) had had multiple breast biopsies performed over the period.

Incidence of breast cancer—Of the 770 women who were traced, 22 were found to have developed breast cancer as compared with an expected 8.14 (95% confidence limits 1.69 and 4.09 for relative risk). This highly significant excess risk occurred at all ages (table III).

TABLE II—Methods used in tracing the 791 women

Method of tracing	No (%) traced	Mean age (years)
(1) Hospital notes	168 (21)	41
(2) Original general practitioner	323 (41)	39
(3) New general practitioner	47 (6)	36
(4) New general practitioner via family practitioner committee	51 (6)	36
(5) NHS central register (dead)	5 (1)	54
(6) New general practitioner via NHS central register	81 (10)	30
(7) Occupier/other	95 (12)	34
(8) Not traced	21* (3)	37

*Eight had gone abroad.

TABLE III—Observed and expected incidences of breast cancer according to age at initial diagnosis. Expected rates calculated from Welsh Cancer Registry data (1972-80)

Age group (years)	No of cases		Relative risk
	Observed	Expected	
15-34	0	0.26	0
35-44	5	1.86	2.69
45-54	11	3.62	3.04
55-64	4	1.54	2.60
65-74	2	0.59	3.39
≥75	0	0.27	0
Total	22	8.14	2.70

TABLE IV—Observed and expected incidences of breast cancer according to diagnosis, derived either from histopathological or combination of clinical and mammographic findings. Cysts generally proved by biopsy or aspiration

	Observed	Expected	Relative risk
Diagnosis:			
Cyst (n = 428)	17	4.79	3.55
Fibroadenoma (n = 138)	0	1.04	0
Other (n = 97)	1	1.23	0.81
Presumed normal (n = 107)	4	1.08	3.70
Previous biopsy (ever) (n = 356)	14*	3.94	3.55
No previous biopsy (n = 414)	8	4.20	1.90

*Includes 11 who underwent biopsy as a result of clinic visit, and three whose biopsy had been carried out before referral—that is, before 1967.

There was an increased risk in women who had not undergone biopsy (table IV) and even in those whose original diagnosis had been “essentially normal”—that is, they had had symptoms but no palpable or mammographic lesion.

Patients with breast cancer—Of the 22 cases of breast cancer, three had been diagnosed within two years of the original clinic visit and the other 19 between four and 11 years later. Careful review of the hospital records indicated that in the three cases that occurred within two years of the clinic visit the lesion had probably been “missed” by the clinician, radiologist, and surgeon (in two cases biopsy had been done). In one further case the tumour may have been misdiagnosed; a biopsy for suspicious microcalcification had been reported as fibrocystic disease, but the patient returned seven years later with an advanced tumour affecting the whole breast. There was no evidence in the other 18 cases that the cancers had been missed or that they had arisen at the original site of complaint. Review of the mammograms from these 18 patients showed no evidence of malignancy but, interestingly, over 80% were reported as showing Wolfe’s P2 or DY pattern.¹⁹ We are currently reviewing the frequency of these patterns in the rest of the study group (IHG). All but two of the 22 cases were considered “operable” at diagnosis and 19 patients underwent mastectomy, of whom seven had evidence of spread to axillary nodes; one woman chose breast conservation treatment.

Relation to mammographic findings—As nearly all of the women had undergone mammography the initial reports were coded and a score given for diagnosis—(1) normal, (2) benign, (3) probably benign, (4) probably malignant, (5) malignant—and for the presence of cysts, fibroadenosis, fibroadenoma, microcalcification, duct ectasia, or hypervascularity. Table V shows the numbers of cancers found among women with or without these findings, together with the relative risk as compared with the general population. Although none of the findings showed a significant relation to risk of cancer at the 5% level, there was a strong suggestion of excess risk associated with microcalcification. Those who had developed cancer did not differ significantly from the remainder in their overall diagnostic score for mammography.

Relation to pathological findings—Of the 326 patients who had undergone biopsy as a result of their initial clinic visit and for whom slides were available, 11 had subsequently developed breast cancer as compared with 3.57 expected on the basis of Welsh Cancer Registry figures (relative risk 3.08). Table VI shows the numbers of cancers observed in the different pathological subgroups. No statistically significant relations were detected between the incidence of breast cancer and presence of fibroadenoma, lipoma, non-pink cell metaplasia, periductal fibrosis, or normal breast tissue. Conversely, lobular hyperplasia and pink cell metaplasia were significantly related to excess risk. The numbers of cases in each category were, however, small and it is difficult to draw firm conclusions from these data.

Mortality—Altogether 34 of the 770 traced women had died. Only

TABLE V—Incidence of cancer among patients classified according to initial mammographic findings. Numbers in parentheses show estimated relative risk compared with general population, calculated as ratio of observed numbers to those expected from Welsh Cancer Registry figures

Mammographic finding	Absent	Present
Cystic disease	8 (1.90)	14 (3.55)
Fibroadenosis	19 (2.71)	3 (2.65)
Fibroadenoma	18 (2.67)	4 (2.86)
Microcalcification	19 (2.43)	3 (9.38)*
Duct ectasia	21 (2.70)	1 (2.70)
Hypervascularity	21 (2.75)	1 (1.96)

*p = 0.053.

TABLE VI—Incidence of cancer among patients classified according to pathological review of initial biopsy. Numbers in parentheses show estimated relative risk compared with general population, calculated as ratio of observed numbers to those expected from Welsh Cancer Registry figures

	Absent	Present	Dominant
Cysts	3 (1.61)	4 (7.02)	4 (3.47)
Sclerosing adenosis	8 (2.67)	1 (2.27)	2 (15.38)
	Absent	Grade 1	Grade 2 +
Non-pink cell metaplasia	10 (3.07)	0	1 (7.14)
Pink cell metaplasia	4 (1.87)	1 (1.79)	6 (6.90)*
Ductal hyperplasia	7 (2.48)	1 (2.63)	3 (7.31)
Lobular hyperplasia	4 (2.35)	2 (1.83)	5 (6.41)*

*p=0.03.

TABLE VII—Observed and expected deaths due to cancer and other causes

Age group (years)	Breast cancer		Other cancer		Non-cancer	
	Observed	Expected	Observed	Expected	Observed	Expected
15-34		0.11		0.26		1.08
35-44		0.67	3	0.87	3	1.39
45-54	2	1.46	6	3.37	5	6.34
55-64	1	0.74	2	2.65	2	6.52
65-74		0.33		1.38	2	5.86
≥75		0.12	3	1.03	5	9.44
Total	3	3.43*	14	9.56*	17	30.63†

*Not significant.

†p<0.05.

three of the deaths were due to breast cancer, and 14 from other types of cancer. Observed deaths from cancer did not differ significantly from expected (age specific mortality figures, Wales, 1975) and there were no excess deaths from breast cancer (table VII). Deaths due to causes other than cancer were significantly fewer than expected and thus the proportion of all deaths due to cancer was higher than expected ($p<0.01$). No patient with breast cancer died of other causes.

Discussion

We have shown that with persistence an excellent long term follow up of patients may be obtained through the primary care system and the NHS Central Register in Britain. Hence we can say with confidence that our series of women with symptomatic breast disease had a twofold to threefold greater risk of developing breast cancer over 10 to 13 years of follow up when compared with the normal population. We, however, must also consider the adequacy of the cancer registration data used to calculate the expected incidence of breast cancer. We therefore compared our observed findings with the expected breast cancer rate calculated from both the south west of England and the Birmingham Cancer Registry figures, as well as from the Welsh Cancer Registry data. A similar increase in risk was found for our series of women whichever cancer registry was used. In addition, we found that 19 of the 22 cases of breast cancer identified were already known to the Welsh Registry Office, indicating that its system of registration is reasonably adequate. This supports a recent report of the Advisory Committee on Cancer Registration.²⁰

The diagnostic accuracy of the breast clinic was high, the three cases in which the tumour had apparently been missed representing a misdiagnosis of only 1.3% of all cases of breast cancer referred to the clinic. Even if we exclude these three from our calculations, there is still a significant increase in risk for this group of women.

The women in our study had a lower overall mortality than expected, implying that they were "healthier" than women in the general population. This is not unexpected in women attending special clinics.²¹ It seems likely that few women with chronic disease, for example, would be referred to a breast clinic, and there was also a possible (but not proved) bias towards attendance by women of higher social class. It is also relevant that these women were studied because they did not have breast cancer initially.

The number of deaths due to breast cancer was slightly less than expected, despite the increase in incidence of this disease in our study group. This may change with longer follow up, and the records of all 770 women are now flagged at the NHS Central Register for future studies. Nevertheless, it might imply that women who have had breast problems in the past are more self aware and may present earlier than the average patient. Interestingly, only two of the cases (9%) were inoperable when first diagnosed compared with the usual 30% or more.²²

Only long term follow up will show whether the excess risk persists and whether mortality from breast cancer is increased in these women.

Our findings of excess risk in cystic disease and in epithelial hyperplasia are in broad agreement with other studies. We also, however, report a new finding: women who attended a breast clinic because of symptoms but who did not have a definite abnormality were also at increased risk of subsequent breast cancer. This is surprising in view of reports that only women with histological evidence of epithelial hyperplasia are at increased risk.^{5,6} We cannot explain our finding, but clearly there may be an element of self selection in women who attend a breast clinic. "Problems" related to the breast, however, are evidently also common in women who are not referred to hospital, as decision about referral is not always clear cut. It is also true that the decision to carry out biopsy may not always be straightforward and depends on the individual surgeon.

Over the period of follow up most of the women were found to have no further abnormality but there was a high level of referral back to the breast clinic and a number of breast biopsies were performed. The biopsy rate was about five times that expected²³ (M P Vessey, personal communication, 1982), although its predictive value was only 20%. This is further evidence that these women may have a high level of self awareness, or possibly an increased level of anxiety about their breasts. If all these women had been kept under regular surveillance rather than discharged back to the care of the general practitioner at least 8000 visits would have been made to hospital over the 10 years. This would have entailed high cost radiological and medical time, as well as costs to the women, yet only 22 cases of breast cancer would have occurred. Such a policy might bring further benefits in that earlier diagnosis may be achieved but, on the other hand, the level of anxiety for many women may be increased. Plainly any policy that entails continued surveillance of women with breast disease will increase rapidly with time. In view of the slight increase in risk we believe that a special case cannot be made for the selective screening of women who have had previous benign disease, unless they so wish, or if they have severe epithelial hyperplasia. This policy, however, demands high diagnostic accuracy at the initial visit by both a radiologist and cytologist as well as by the surgeon. This may be achieved in the setting of a specialist breast clinic such as the one we describe. The woman may then be given appropriate reassurance and should not be told that she has "disease" for which there is no evidence—indeed, some believe that the concept of benign breast "disease" is a myth.²⁴

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References

- 1 Davies HH, Simons M, Davies JB. Cystic disease of the breast: relationship to carcinoma. *Cancer* 1964;17:957-78.
- 2 Veronesi U, Pizzocaro G. Breast cancer in women subsequent to cystic disease of the breast. *Surg Gynecol Obstet* 1968;126:529-32.

- ³ Monson RR, Yen S, MacMahon B. Chronic mastitis and carcinoma of the breast. *Lancet* 1976;ii:224-6.
- ⁴ Kodlin D, Winger EE, Morgenstern NL, Chen U. Chronic mastopathy and breast cancer. *Cancer* 1977;39:2603-7.
- ⁵ Page DL, Vander Zwaag R, Rogers NW, et al. Relation between component parts of fibrocystic disease complex and breast cancer. *Journal of the National Cancer Institute* 1978;61:1055-64.
- ⁶ Hutchinson WB, Thomas DB, Hablin WB, et al. Risk of breast cancer in women with benign breast disease. *Journal of the National Cancer Institute* 1980;65:13-20.
- ⁷ Coombs LJ, Lilienfeld AM. A prospective study of the relationship between benign breast diseases and breast carcinoma. *Prev Med* 1979;8:40-52.
- ⁸ Haagenson CD, Bodian C, Haagenson DE. *Breast carcinoma risk and detection*. Philadelphia: WB Saunders Co, 1981:70-4.
- ⁹ Duffy SW, Roberts MM, Elton RA. Risk factors for breast cancer: relevance to screening. *J Epidemiol Community Health* 1983;37:127-31.
- ¹⁰ Shapiro S, Strax P, Venet L, Fink R. The search for risk factors in breast cancer. *Am J Public Health* 1968;58:820-35.
- ¹¹ Lubin JH, Burns PE, Blot WJ, et al. Risk factors for breast cancer in women in Northern Alberta, Canada, as related to age at diagnosis. *Journal of the National Cancer Institute* 1982;68:211-7.
- ¹² Vessey MP, Doll R, Jones K, McPherson K, Yeates D. An epidemiological study of oral contraceptives and breast cancer. *Br Med J* 1979;i:1755-8.
- ¹³ Paffenbarger RS, Kampert JB, Chang HG. Characteristics that predict risk of breast cancer before and after the menopause. *Am J Epidemiol* 1980;112:258-68.
- ¹⁴ Wynder EL, MacCormack FA, Stellman SD. The epidemiology of breast cancer in 785 US Caucasian women. *Cancer* 1978;41:2341-54.
- ¹⁵ Brinton LA, Williams RR, Hoover RN, et al. Breast cancer risk factors among screening programme participants. *Journal of the National Cancer Institute* 1979;62:37-44.
- ¹⁶ Chamberlain J. Trial of early detection of breast cancer. *Br J Cancer* 1981;44:618-27.
- ¹⁷ Sims ACP. Importance of a high tracing rate in long-term medical follow-up studies. *Lancet* 1973;ii:433-5.
- ¹⁸ Wellings SR, Jensen HM, Marcum RG. An atlas of subgross pathology of the human breast with special reference to possible precancerous lesions. *Journal of the National Cancer Institute* 1975;55:231-73.
- ¹⁹ Wolfe J. Risk for breast cancer development determined by mammographic parenchymal patterns. *Cancer* 1976;37:2486-92.
- ²⁰ Office of Population Censuses and Surveys. *Report of the Advisory Committee on Cancer Registration, England and Wales*. London: OPCS, 1980:18-22.
- ²¹ Vessey MP, McPherson K, Johnson B. Mortality among women participating in the Oxford/Family Planning Association contraceptive study. *Lancet* 1977;ii:731-3.
- ²² Langlands AO, Kerr GR, Shaw S. The management of locally advanced breast cancer by x ray therapy. *Clin Oncol* 1976;2:365-71.
- ²³ Cole P, Elwood JM, Kaplan SD. Incidence rates and risk factors of benign breast neoplasms. *Am J Epidemiol* 1978;108:112-20.
- ²⁴ Love SM, Gelman RS, Silen W. Fibrocystic "disease" of the breast—non-disease? *N Engl J Med* 1982;307:1010-4.

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Infection after abdominal surgery: five year prospective study

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Abstract

A total of 1504 consecutive abdominal operations were studied prospectively over a five year period. The incidence of wound (2.8%) and intraperitoneal (0.8%) infections was low compared with contemporary reports. It is difficult to justify modifying existing practice on the basis of small controlled clinical trials when information from accurate audit discloses results superior to those of experimental studies.

Introduction

The large amount of recent work that has gone into attempts to reduce septic complications after abdominal surgery has concentrated on choice of dose regimen for the appropriate agents and with few exceptions has not taken other technical factors into account. Antibiotics and antiseptics have had variable but always positive effects in reducing wound infection. In some instances, however, particularly in colonic surgery and perforated appendicitis, though the reduction has been real, a troublesome incidence of both wound and residual intra-abdominal abscess persists. During the past 10 years we have

used a consistent combination of surgical techniques to minimise contamination supplemented in its presence by tetracycline lavage of the wound and peritoneal cavity. The volume of lavage fluid used has varied with the degree of operative contamination from 0.5 to 7.0 litres; the measures taken to minimise operative contamination are detailed elsewhere.¹ This paper presents a prospective audit of wound and peritoneal infection during a consecutive five year period.

Present study

DEFINITIONS

Wound infection refers to the discharge of pus or of a serous or sanguineous discharge that grew a pathogenic organism. All patients who at follow up reported a discharge from their wound were considered to have had an infected wound. Wound healing was assessed by several different observers during the five years. It was usual for two people (not necessarily those performing the original operation) to determine the presence or absence of wound infection.

Intraperitoneal abscess was recorded when pus was drained, aspirated, or discharged from the peritoneal cavity or there was radiological, ultrasonic, or necropsy evidence of an intraperitoneal collection.

Operative contamination was classified as follows, based on the American National Research Council criteria²: *clean*—no infection encountered, no hollow abdominal viscus opened; *clean/contaminated*—hollow abdominal viscus opened with minimal spillage of contents; *contaminated*—inflammation without pus formation, viscus opened with gross spillage of contents; *dirty*—pus encountered or perforated viscus found.

PATIENTS AND METHOD OF DATA COLLECTION

From January 1977 to December 1981 all patients under the care of NAM and undergoing an abdominal operation were included.

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