

DETECTION BIAS AND RELATION OF BENIGN BREAST DISEASE TO BREAST CANCER

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Summary The relation between benign breast disease and breast cancer was investigated in a case-control study of postmenopausal patients selected either by diagnostic procedure sampling (mammography 150 cases and controls, breast biopsy 107 cases and controls) or by conventional sampling procedures (257 controls to match total number of cases). For mammography patients, the odds ratio for association between benign breast disease and breast cancer was 0.9; for biopsy patients the odds ratio was 0.8; but by use of conventional methods, the odds ratio was elevated to a "causal" and statistically significant 2.6. When patients were classified according to cancer stage, benign breast disease was present in 56/147 patients with localised cancer compared with 24/107 patients with non-localised cancer (odds ratio 2.3). Evidence that benign breast disease is a risk factor for breast cancer may therefore be misleading if choice of control groups makes no provision for bias produced by inequalities in detection of disease.

Introduction

IT is widely believed that benign breast disease is an established risk factor for breast carcinoma;^{1,2} numerous epidemiological studies published over the past twenty years have suggested that patients with benign breast disease have a two to five fold increased risk of breast cancer.³⁻⁵ As a result, women with benign breast disease often have increased breast examinations, as well as mammography, cyst aspirations, and biopsies. Patients with benign disease who are followed-up closely have a higher frequency of breast cancer—eg, patients who have had biopsies, by comparison with those who have not, have a two-fold risk of carcinoma being diagnosed.⁶

Some workers, however, have argued that benign disease is simply a physiological variant which does not require special clinical management;^{7,8} a study of women who had had breast biopsies showed an increased breast cancer risk only for patients with proliferative lesions.⁹ Nevertheless, no new evidence has emerged as to whether women with a history of benign disease of the breast (established by clinical examination without biopsy confirmation) also have an increased breast cancer risk. After reviewing the published studies, we suspected that the postulated causal association was misleading, and may have occurred because women with benign disease were more likely than women without benign disease to have had frequent breast examinations that led to the detection of early-stage breast cancer. We therefore designed a case-control study with two methods of assembling patients. To equalise disease detection efforts between cases and controls, we selected breast cancer patients and controls by a diagnostic procedure method (the two procedures were breast biopsy and mammography); a second control group without comparable diagnostic surveillance was chosen by conventional selection methods from women admitted to hospital on the medical or surgical wards.

Patients and Methods

Selection of Cases

Eligible patients were postmenopausal women, aged 45 or older, who were evaluated at Yale-New Haven Hospital between July 1, 1976 and June 30, 1979. We identified 353 potentially eligible patients with newly diagnosed and histologically confirmed breast cancer; of these patients, we excluded 56 who were premenopausal and 25 who had a history of a previous gynaecological cancer. Of the remaining 272 patients, we eliminated a further 15 because a control patient without breast cancer was unavailable for matching, leaving 257 patients who comprised the total case-group. In 150 of the cases, breast cancer was diagnosed first by mammography, and in 107 by breast biopsy.

Selection of Controls

Two distinct series of case and control groups were assembled in which patients were identified according to the results of mammography or biopsy; a third series was assembled by conventional methods. One series matched the 150 breast cancer patients with initial diagnosis by mammography to 150 controls with mammographically normal breasts (matching criteria included age, ± 4 years; race; and date of procedure). The second series included 107 breast cancer patients initially diagnosed by breast biopsy and the same number of controls with histologically benign disease; these women were matched according to the same criteria used in the first series. (No patient in the biopsy group had normal breasts.)

For the conventional sampling, controls were selected from the hospital discharge roster of general medical or surgical wards. This series contained all 257 patients with breast cancer and the same number of control patients who were matched to each case by means of the criteria noted above. These controls differed from those in the diagnostic procedure group in that they had not necessarily received a systematic clinical examination to identify either breast cancer or benign disease.

Data Collection and Analysis

Details of each patient's medical history and antecedent benign breast disease were obtained from hospital records and from doctors' personal records. Data collectors were unaware of our research hypothesis. Since we were interested in a patient's reported history of benign breast disease, we did not require surgical confirmation of the diagnosis. Benign disease was classified as *present* if there was a specific notation that a physician had diagnosed benign breast disease at least six months before the date of the diagnostic procedure or hospital admission; as *absent* if there was a specific notation that benign breast disease had not been diagnosed; and as *unspecified* if there was no mention of benign disease. The rest of the medical history included details of the breast disease, gynaecological history, reason for hospital admission, previous illnesses, and indication for the diagnostic procedure.

For analysis, data were assembled in the form of two-by-two tables in which the presence or absence of benign disease was related to the patient's status as a breast cancer or a control patient. The measure of association of antecedent benign disease of the breast to the risk of breast cancer is the odds ratio, calculated as the cross-product of this table. Since control patients were chosen by a matching procedure, each set of results could be analysed with either a matched or unmatched form of analysis. We used the matched odds ratio and 95% confidence intervals as the preferred form of analysis, but have presented the results of the unmatched format which is easier to understand. For comparison, unmatched odds ratios are also shown. When calculating the odds ratio, we excluded patients (cases and controls) whose benign disease status was unspecified, since we were unable to distinguish those who were truly free of the disorder from those who were simply not examined. We have previously shown the bias that may result from including such patients in the analysis.¹⁰ 95% confidence intervals were calculated according to standard techniques.¹¹

Results

Table I compares case and control groups according to selected clinical and demographic features. All subgroups were similar for age at diagnosis and menopause. Among the two case and three control groups, approximately similar proportions of patients were nulliparous, had a natural (rather than a surgical) menopause, and had hypertension or diabetes.

Table II shows the relation of antecedent benign disease to risk of breast cancer by use of two sets of diagnostic-procedure controls. Calculated odds ratio is 0.9 for mammography, and 0.8 for biopsy patients; in both instances the 95% confidence interval includes 1, indicating that the relation is not statistically significant.

In table III, all 257 breast cancer patients and 257 controls are classified according to antecedent history of benign breast disease. Calculated odds ratio for this relation is 2.6, and the 95% confidence interval excludes 1, indicating a statistically significant association. (As in table II, odds ratio was calculated excluding patients whose benign disease status was unspecified. Even inclusion of these patients in the analysis does not change the result, however—the odds ratio becomes 2.5 and remains statistically significant.) Thus, using hospital controls we detected a significantly increased risk for breast cancer among patients with benign disease that was not present when using diagnostic-procedure controls.

TABLE I—CLINICAL CHARACTERISTICS

Clinical feature	Cases		Controls		
	Mammography n=150	Biopsy n=107	Mammography n=150	Biopsy n=107	Hospital n=257
Age (±SD)					
At diagnosis	63±10	62±10	63±10	63±10	63±9
At menopause	48±9	49±9	48±10	49±9	48±5
Nulliparous (%)	17	24	21	23	16
Natural menopause (%)	78	81	76	82	77
Hypertension (%)	45	38	43	35	49
Diabetes (%)	13	7	9	10	18

TABLE II—RELATION OF ANTECEDENT BENIGN DISEASE TO RISK OF BREAST CANCER BY USE OF DIAGNOSTIC PROCEDURE CONTROLS

Antecedent benign disease	Mammography		Biopsy	
	Cases	Controls	Cases	Controls
Present	51	52	13	48
Absent	58	53	45	52
Unspecified	41	45	31	7
	OR* = 0.9 95% CI = 0.5-1.7 Matched OR = 0.7 95% CI = 0.4-1.4		OR* = 0.8 95% CI = 0.4-1.4 Matched OR = 0.6 95% CI = 0.3-1.2	

*OR calculated excluding unspecified category.
OR = odds ratio; CI = confidence interval.

TABLE III—RELATION OF ANTECEDENT BENIGN DISEASE TO RISK OF BREAST CANCER BY USE OF HOSPITAL CONTROLS

Antecedent benign disease	Hospital cases	Hospital controls
Present	82	40
Absent	103	131
Unspecified	72	86
	OR* = 2.6 95% CI = 1.7-4.1 Matched OR = 4.1 95% CI = 1.8-8.5	

*OR calculated excluding unspecified category.

If the higher odds ratio calculated by use of hospital controls occurs because of detection bias, there should be an equally strong association between antecedent benign disease and presence of early-stage breast cancer. Table IV shows the data for 254 patients for whom the Yale-New Haven Hospital Tumor Registry had recorded breast cancer stage at initial diagnosis. Patients were considered to have localised cancer if the tumour was restricted to the breast, and non-localised if there was regional extension, or lymph node or distant metastases. Odds ratio for the association of benign disease to risk of localised breast cancer can be calculated by comparing the status of antecedent benign breast disease in localised cancer cases with non-localised cancer cases. Antecedent benign disease was present for 56 of 147 localised cases but for only 24 of the 107 non-localised cases. Odds ratio for this comparison is 2.3 and is statistically significant (inclusion of unspecified patients results in only a slight change to 2.1); this value resembles the ratio of 2.6 calculated in table III for hospital controls.

The results in table IV can also be used to examine the direct effects of breast cancer stage on the association between breast disease and risk of breast cancer. For patients with localised cancer, the risk associated with an antecedent history of benign disease is 4.0, and is statistically significant. In contrast, for patients with non-localised cancer, the odds ratio is only 1.4 and is not statistically significant.

Discussion

The results of this study support our hypothesis that the association between benign breast disease and subsequent breast cancer may be attributable, in part, to detection bias. Thus, the risk of breast cancer was not increased in patients with benign disease when controls were chosen by the diagnostic procedure method, but it was increased (elevated odds ratio) when hospital controls were used. The role of detection bias in creating this elevated odds ratio was shown by two important and related types of evidence: the similar odds ratio between benign disease and non-localised early-stage breast cancer; and the elevated odds ratio between benign disease and early-stage breast cancer that was not present for advanced (non-localised) disease. We conclude that a diagnosis of benign disease of the breast leads to frequent examinations and earlier detection of localised breast cancer.

Our study cannot be compared with investigations that have classified a patient's history of benign disease according to results of a breast biopsy. For example, Black and

TABLE IV—RELATION OF ANTECEDENT BENIGN DISEASE TO RISK OF BREAST CANCER, ACCORDING TO CANCER STAGE*†

Antecedent benign disease	Localised cancer		Non-localised cancer	
	Cases	Controls	Cases	Controls
Present	56	20	24	19
Absent	51	73	51	58
Unspecified	40	54	32	30
Total	147	147	107	107

*n = 254.

†OR calculated excluding unspecified category.

OR for benign disease to anatomical stage of breast cancer = 2.3 (95% CI = 1.2-4.2).

OR for benign disease to breast cancer, stratified by cancer state, = 4.0 (95% CI 2.2-7.4) for localised cancer and 1.4 (95% CI 0.7-2.9) for non-localised cancer.

colleagues have proposed a system for grading cellular atypia in benign lesions⁴ and Kodlin et al³ have suggested that breast cancer risk increases as the atypia worsens. Women with proliferative disease documented by breast biopsy were also noted to have a risk of breast cancer that was approximately twice that of women with biopsies that did not show proliferative disease. Despite the importance of these studies, they cannot provide an estimate of breast cancer risk for the many patients with a clinical or mammographic diagnosis of benign disease who have never had a surgical biopsy.

In designing our study, we chose controls by the diagnostic procedure method to overcome two important sources of detection bias: pre-hospital diagnostic surveillance bias and diagnostic examination bias. Pre-hospital surveillance bias would occur in any case-control study of this topic because breast cancer may have a long symptom-free period, and because rates of diagnostic surveillance for breast cancer are higher in women with benign breast disease who are more often examined by mammography and breast biopsy. As a result, benign breast disease may lead to an increased detection of the cancer but need not be a causal factor. Diagnostic examination bias is a more subtle issue in case-control studies of this topic, and has received little direct attention. Breast cancer in women has a cumulative lifetime incidence of nearly 11%. Consequently, equal diagnostic examination is needed in both cases and controls to check for concurrent existence of breast cancer. Most previous epidemiological studies have not specifically examined the breasts of control patients to exclude breast cancer. In our study, choice of cases and controls by the diagnostic procedure method ensures that all patients have been examined equally. Our results clearly emphasise the role of detection bias in creating an elevated odds ratio, and the importance of choosing cases and controls by the diagnostic procedure method to provide a less biased estimate of the true association.

We acknowledge that the merits of any case-control study often rest on the choice of control group, and that this is seldom perfect. We considered the possibility that mammography controls would over-represent women with a previous history of benign disease of the breast but believe this is unlikely, however, since mammography was ordered to evaluate specific clinical complaints and not as a general screening procedure. Nevertheless, to minimise any doubts about this sampling strategy, we did not use women who had mammographic evidence of benign disease, and who were especially likely to be examined because of a previous history of benign breast disease. Instead, we selected a mammography group with radiographically normal breasts. We were able to carry out this comparison because we used a diagnostic procedure which ensured that all patients (including controls) had their breasts examined.

We also recognised the limitations of the biopsy procedure control group, since this group includes many patients whose breast procedure may have been related to antecedent history of benign disease. However, we believe the data from this comparison are useful in several respects. Firstly, when patients whose antecedent history is unspecified are excluded from calculation of the odds ratio, the value is similar to the comparably calculated odds ratio with mammography controls. Secondly, the odds ratio drops to 0.5 when unspecified responses are included in the analysis, indicating that any over-adjustment is most probably related to difficulties in documenting an antecedent history of benign disease, rather than in selection of the group itself. Finally,

since women with concurrent benign disease are part of the spectrum of controls without breast cancer, presentation of their data provides a more comprehensive picture of the overall association between an antecedent history of benign disease and risk of breast cancer.

What about patients in whom the history of benign disease was unspecified? When patients so classified were reclassified as not having antecedent benign disease, the odds ratios remained virtually unchanged (except for the biopsy control comparison), and our conclusions remained unaltered. We believe that our strategy for handling unspecified responses is better than strategies in other case-control studies in which no mention is made of how the investigators coped with this important issue; it is essential to distinguish clearly between patients in whom an antecedent history of benign disease has been firmly established from those in whom the data are insufficient to make a certain judgment.

We conclude that a clinical history of benign breast disease (without surgical confirmation) is not associated with an increased risk of subsequent breast cancer in postmenopausal women. We further believe that all women over 40, irrespective of their history of benign breast disease, should be evaluated for breast cancer according to American Cancer Society guidelines.¹² Specifically, we do not believe that a history of benign breast disease should be used to make selective decisions about whether to carry out mammography. Recent studies have continued to support the usefulness of mammography in evaluating women for breast cancer.¹³ Although several reports have suggested that breast lesions with a high atypia score carry a significant risk for subsequent breast cancer, it is unclear whether such patients could be adequately identified by mammography or if most women with high-risk lesions will have biopsies because of symptoms. What is clear is that these patients represent a special category who need to be better defined by future studies.

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