Risk factors for benign breast disease: a 30-year cohort study

T. GREG HISLOP,* MD; J. MARK ELWOOD,† MD, FRCP[C]

Data on the menstrual history, family history and degree of obesity of 1374 Vancouver nursing students were collected in 1945 and from 1947 to 1956. In 1979, 768 of these women were located; 726 (94%) responded and participated in a follow-up study, providing information on their subsequent medical history and on breast-related problems. No major differences were found between the early histories of these participants and those who were not located or did not respond. Among the respondents 215 gave a history of symptoms compatible with benign breast disease; in 107 this diagnosis was confirmed by biopsy. By age 50 the cumulative risk for benign breast disease was 17% for biopsied and 31% for symptomatic disease. Biopsied benign breast disease was associated with premenstrual breast discomfort, irregular menses, a history of abortions, a family history of both benign and malignant breast disease, lack of use of oral contraceptives, a low index of obesity and small breasts, obesity and breast size being independent. Factors associated with symptomatic benign breast disease were usually associated with a greater likelihood of biopsy for symptomatic disease; hence, the relative risks for biopsied disease were generally greater than those for symptomatic disease. Although the risk factors for benign breast disease differ from those for breast cancer, the findings are consistent with the hypothesis of excessive circulating estrogen.

En 1945, puis de 1947 à 1956, on a colligé des données sur l'histoire menstruelle, les antécédents familiaux et le degré d'obésité de 1374 étudiantes infirmières de Vancouver. En 1979, 768 de ces femmes ont été repérées: 726 (94%) ont accepté de participer à une étude de contrôle destiné à accumuler de l'information sur leur histoire médicale subséquente et leurs problèmes mammaires. Aucune différence importante n'a été observée entre les antécédents initiaux de ces participantes et ceux des personnes qui n'ont pu être repérées ou qui n'ont pas répondu. Parmi les répondantes, 215 ont évoqué des symptômes compatibles avec ceux d'une mastite bénigne; chez 107 d'entre-elles, ce diagnostic a été confirmé par une biopsie. Atteint l'âge de 50 ans, le risque cumulatif de mastite bénigne était de 17% pour les cas qui furent soumis à une biopsie et de 31% pour les cas présentant des symptômes. Une association a été mesurée entre les mastites bénignes prouvées par biopsie et des douleurs mammaires prémenstruelles, des règles irrégulières, des antécédents d'avortement, des antécédents familiaux de maladie bénigne ou maligne du sein, le non usage des anovulants oraux, un faible indice d'obésité et de petits seins, l'obésité et la grosseur des seins étant des facteurs indépendants. Les facteurs reliés à une mastite bénigne étaient habituellement associés a une plus grande possibilité de biopsie pour une maladie symptomatique; en conséquence, les risques relatifs pour une mastite biopsiée étaient généralement plus considérables que pour une maladie symptomatique. Bien que les facteurs étiopathogéniques de la mastite bénigne diffèrent de ceux du cancer du sein, ces observations sont compatibles avec l'hypothèse d'un excès d'oestrogène circulant.

The study of benign breast disease is important because it is the commonest type of breast disease, it causes much psychologic stress until a biopsy confirms that the condition is benign, it frequently recurs, necessitating further biopsies, and, with some types, it is associated with an increased risk of breast cancer. Studies have reported that the risk of breast cancer is two to three times greater for women with benign breast disease than for unaffected women.[1-5] There is evidence that this risk increases sharply for patients with specific categories of benign breast disease, especially fibroadenoma, adenosis, fibrosing adenosis and intraductal papilloma,[5] and for those whose benign lesions show considerable ductular atypia.[4,5] Several case–control studies of breast disease have shown that some of the factors associated with an increased risk for breast cancer appear to be associated with a higher risk of benign breast disease as well, including nulliparity,[6-9] low parity[7-9] and becoming menopausal at a late age.[6,8-10] However, benign breast disease does not appear to be associated with age when first giving birdth,[7,8,10] age at menarche[7-10] or a family history of breast cancer[7,10] — all factors associated with an increased risk for breast cancer. Whereas breast cancer

From the division of epidemiology, Cancer Control Agency of British Columbia

*Epidemiologist
†Head, division of epidemiology

Reprint requests to: Dr. Greg Hislop, Division of epidemiology, Cancer Control Agency of British Columbia, #700–686 W Broadway, Vancouver, BC V5Z 1G1

appears to be more common in the obese, benign breast disease appears to be less common in obese women.[6,10] It has been clearly shown by both case–control and cohort studies that benign breast disease is less common in women who use oral contraceptives, whereas studies of breast cancer have shown no association, positive or negative, with the use of oral contraceptives.[7,10-19] It is possible that those who use these drugs have a decreased risk only for those types of benign breast disease that are not associated with the subsequent development of breast cancer.[20] There is some evidence that the use of oral contraceptives or other forms of estrogen therapy may increase the risk of breast cancer in women who have had benign breast disease.[10,15,21]

The case–control studies were restricted to cases of benign breast disease in which biopsies were done, and the cohort studies concentrated predominantly on examining the association of oral contraceptive use with either symptomatic or biopsied benign breast disease. In this paper we present results from a follow-up study of a cohort of nurses in Vancouver, which is the first such study of various risk factors for both symptomatic and biopsied benign breast disease. The study was originally designed by the late Dr. Ethlyn Trapp at the British Columbia Cancer Institute in the early 1940s to identify risk factors for breast cancer and other diseases.

Methods

The study cohort included all second-year nursing students at the Vancouver General Hospital during the years 1945 and 1947 to 1956 who volunteered to enter a study of breast disease; approximately 85% of the eligible students volunteered for the study. Their ages at entry into the study ranged from 18 to 38 years, with over 90% being between 18 and 21 years. At entry all students completed a questionnaire covering their medical history from birth, and selected physicians conducted a breast and general physical examination. The records were kept at the British Columbia Cancer Institute, now the Cancer Control Agency of British Columbia, but because of other commitments no systematic follow-up was undertaken.

In late 1978 and early 1979 we attempted to locate all the participants, using nursing registrations, telephone directories, class secretaries, fellow classmates, notices in nursing journals, and radio public service messages. Of the 1374 participants in the original study, we found reasonably current addresses for 814 (59%). These women were sent a short questionnaire on breast problems, and 768 (94%) responded. To these 768 women we sent a longer questionnaire requesting information on their medical history, with special reference to breast disease; 726 (94%) responded. We requested from the hospitals concerned a copy of the pathology report for all 147 reported breast biopsies; 110 (75%) of these were received. The response was much better for fairly recent biopsies: about 90% of the reports were received for biopsies reported at ages 30 to 50, as compared with 60% for biopsies reported at ages under 30. This probably reflects more complete records and a better recall of dates for more recent events.

To study the factors associated with biopsied benign breast disease, we compared the women reporting biopsies with those who had no history of either symptomatic benign breast disease or a biopsy for such disease. For the factors associated with symptomatic benign breast disease we compared women reporting symptoms compatible with benign disease, whether or not a biopsy was done, with those reporting no symptoms. We defined benign breast disease as comprising fibrocystic disease (such pathological diagnoses as mammary dysplasia, lobular hyperplasia with evidence of cyst formation, apocrine metaplasia or atypia, collagenosis, fibrosclerosis, interstitial fibrosis, papillomatosis, sclerosing adenosis and fibrosing adenosis), fibroadenoma and intraductal papilloma, but not such conditions as breast abscess, eczema or lipoma.

Age-specific incidence rates were obtained by comparing the number of new diagnoses in a particular age group with the total number of woman-years at risk in that age group, and cumulative probabilities of benign breast disease were calculated by actuarial methods.[22] The association of various factors with biopsied benign breast disease was assessed by comparing cumulative risks within categories of these factors, using the log–rank test to assess statistical significance.[22] This type of analysis takes into account both the occurrence and the time of occurrence of a disease and thus should be more sensitive than simply comparing the proportions of affected individuals. However, we found that the estimates of relative risk based on these actuarial methods were very similar to those based simply on the proportion of women in each category in whom benign breast disease developed, so we described the association of factors and breast disease in terms of relative risks, comparing a defined category of women with a defined reference category; for example, comparing contraceptive users with nonusers. The relative risk for biopsied disease is the ratio of the proportion of women with a biopsy in the defined category to the proportion with a biopsy in the reference category. Similarly, the relative risk for symptomatic disease is the ratio of the proportions with symptoms in the defined and reference categories. The relative biopsy ratio is the ratio of the proportion of symptomatic women with a biopsy in the defined category to the corresponding proportion in the reference category. The relative risk for biopsied disease is equal to the relative risk for symptomatic disease multiplied by the relative biopsy ratio. There were 14 women with no prior history of benign breast disease in whom breast cancer developed; they are included in the actuarial calculation only up to the date their breast cancer was diagnosed, and are excluded from further analyses.

Results

Of the 1374 entrants in the original study 726 completed both follow-up questionnaires. To check for biases resulting from this incomplete response we compared the information collected on entry into the study

from responders with that from nonresponders (Table I). This comparison showed that the two groups were very similar with respect to these initial data, which favoured the assumption that the responders were representative of the entire original study cohort. This assumption gained further support from the fact that nonresponse was mainly a result of our failure to locate subjects and not of their refusal to participate. Also, we did not expect that the subjects' status for benign breast disease would influence the likelihood of locating them.

Incidence of benign breast disease

Of the 726 respondents 215 had a history of symptomatic breast disease: 97% reported breast lumps or cysts; the remainder reported that benign breast disease had been diagnosed by aspiration biopsy or mammography. Of the 215 women 107 (50%) had had a biopsy confirming benign breast disease; breast cancer was diagnosed at a later date in 3 of these women. Breast cancer was also reported by another 14 women without a history of benign disease. Incidence rates were determined for all 107 women with a biopsy among the 215 with symptomatic benign breast disease. The remaining 497 women (68%) reported no history of breast disease. The ages at follow-up ranged from 41 to 68 years (mean 47.4 years; standard deviation 4.0 years) and were similar for those with biopsied or symptomatic benign breast disease or no breast disease. Those with breast cancer were slightly older (mean 50.5 years; standard deviation 5.2 years).

Fig. 1 shows the actuarial estimates of the probability of benign breast disease occurring among women aged 18 to 50. The probabilities that symptomatic and biopsied benign breast disease would occur were 9% and 5% respectively at age 30 years and increased to 31% and 17% by age 50.

The incidence rates at different ages for symptomatic and biopsied benign breast disease (Fig. 2)

Table I—Comparison of information on breast disease obtained prospectively from responders and nonresponders

Variable	% of women	
	Responders (n = 726)	Nonresponders (n = 648)
Birth weight (g)		
< 3000	23.1	25.0
3000–3499	34.3	31.3
3500–3999	23.0	21.9
⩾ 4000	12.1	9.9
Unknown	7.4	11.9
Menses as a young adult		
Regular	86.0	88.0
Irregular	11.4	9.1
Unknown	2.6	2.9
Premenstrual breast engorgement as a young adult		
No	89.7	86.1
Yes	9.0	10.9
Unknown	1.4	2.9
Premenstrual breast pain or tenderness as a young adult		
No	71.4	69.3
Yes	27.3	27.8
Unknown	1.4	2.9
Breast pain in mother		
No	96.6	95.1
Yes	1.7	1.7
Unknown	1.8	3.2
Breast cancer in mother		
No	95.7	95.4
Yes	1.8	1.4
Unknown	2.5	3.2
Degree of obesity as a young adult (Quetelet's index*)		
< 21	30.9	30.2
21–22	36.8	31.8
⩾ 23	31.0	36.4
Unknown	1.4	1.5
Breast size as a young adult		
Small	35.3	37.0
Medium	54.5	52.8
Large	9.5	8.2
Unknown	0.7	2.0

*Weight (kg)/height (cm)^2 × 10 000.

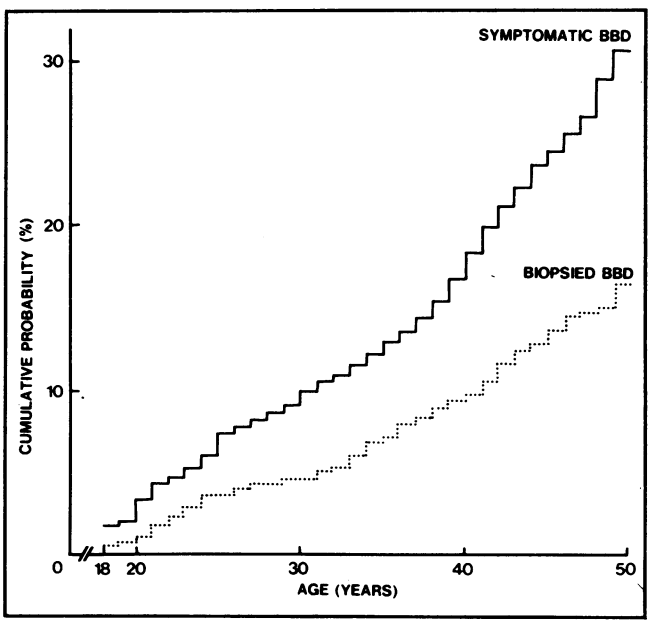

FIG. 1—Cumulative probability of symptomatic and biopsied benign breast disease (BBD) in nurses, by age.

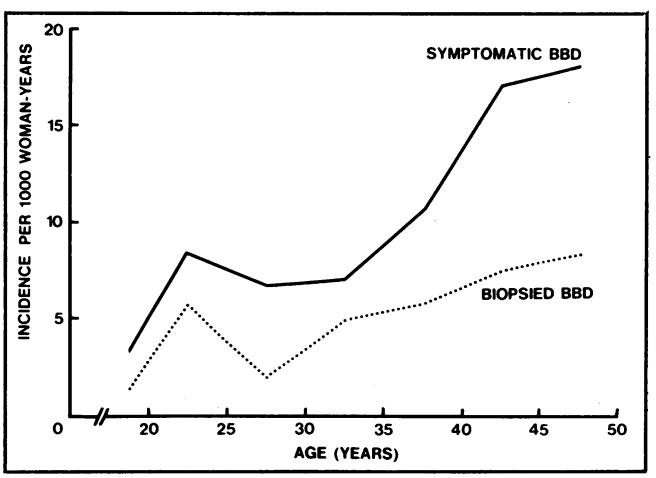

FIG. 2—Incidence of symptomatic and biopsied benign breast disease per 1000 woman-years in nurses, by age.

peaked between the ages of 20 and 24 years, decreased briefly, then rose between age 30 and ages 45 to 49. This bimodal pattern suggests two different types of benign disease. A review of the pathology reports showed that among cases of benign disease diagnosed in women under the age of 30 fibrocystic disease and fibroadenoma were approximately equally represented, each accounting for 35% of the total, whereas among lesions diagnosed after the age of 30 fibrocystic disease was more common (frequency 76%) and fibroadenoma relatively less common (frequency 10%). As well, diagnoses reflecting the fibrosis component of fibrocystic disease, such as collagenosis, fibrosis and fibrosclerosis, were not reported before the age of 30 but were commonly reported (frequency 20%) after 30. This may reflect changing trends in the diagnosis of fibrocystic disease over time, the natural history of this disease or, possibly, the existence of several distinct disease entities. To investigate this further would require a review of all pathological specimens.

Since most participants entered the study cohort at about the age of 20 years and few in follow-up were beyond the age of 50, the overall incidence rate was calculated only for ages 20 to 49 years, and was 10.4 per 1000 woman-years for symptomatic benign breast disease and 5.4 per 1000 woman-years for biopsied benign breast disease.

Factors associated with biopsy-proven benign breast disease

We assessed the association of the factors studied with biopsied benign breast disease by actuarial meth-

Table II—Cumulative risks for biopsied benign breast disease by various factors and age

			Risk (%) and associated significance level*							
			Up to age 30			Age 30–50			Total to age 50	
Factor	Category	No. of subjects	Cumulative risk	Relative risk†	P value	Cumulative risk	Relative risk†	P value	Cumulative risk	P value
Menstrual history										
Premenstrual breast engorgement as a young adult‡	Never/ occasionally	691	4	1.0		13	1.0		16	
	Every period	24	25	6.4	≪ 0.001	9	0.8	0.90	32	0.006
Premenstrual breast pain or tenderness as a young adult‡	Never	517	4	1.0		12	1.0		15	
	Occasionally/ every period	198	7	1.7	0.13	15	1.5	0.08	21	0.02
Menses as a young adult‡	Regular	623	4	1.0		13	1.0		16	
	Irregular	83	12	3.4	< 0.001	10	0.8	0.69	21	0.10
Reproductive history										
Number of term pregnancies (among those ever married)	0	46	7	1.0		15	1.0		20	
	1–2	202	5	0.7		9	0.5		13	
	3+	423	5	0.7	0.78	13	0.8	0.13	17	0.13
Number of abortions (among those ever married)	0	401	4	1.0		10	1.0		13	
	1	180	7	1.8		14	2.0		20	
	2+	89	6	1.5	0.14	17	2.1	0.003	21	0.001
Oral contraceptive use	Nonusers	339	6	1.0		16	1.0		20	
	Users	379	3	0.6	0.16	10	0.6	0.07	13	0.02
Family history of breast disease										
Breast cancer in mother	No	664	5	1.0		13	1.0		17	
	Yes	61	0	–	0.08	11	0.8	0.60	11	0.16
Breast cancer in sister(s) (among those with sisters)	No	440	5	1.0		13	1.0		17	
	Yes	14	14	3.1	0.10	36	2.9	0.005	45	0.001
Benign breast disease in mother	No	687	5	1.0		12	1.0		16	
	Yes	38	5	1.2	0.85	32	2.5	0.002	36	0.009
Benign breast disease in sister(s) (among those with sisters)	No	394	5	1.0		12	1.0		16	
	Yes	60	3	0.7	0.56	22	2.2	0.008	25	0.07
Degree of obesity (Quetelet's index)										
As a young adult‡	< 21	224	5	1.0		19	1.0		23	
	21–22	266	4	0.8		11	0.6		15	
	⩾ 23	229	4	0.8	0.65	8	0.4	0.001	12	0.004
Maximum lifetime	< 23	245	4	1.0		19	1.0		22	
	23–24	202	5	1.3		12	0.5		17	
	⩾ 25	262	5	1.1	0.90	8	0.5	0.003	13	0.02
Current	< 21	196	5	1.0		20	1.0		24	
	21–22	220	5	1.0		12	0.6		16	
	⩾ 23	294	4	0.9	0.83	9	0.5	0.008	13	0.02
Breast size										
As a young adult‡	Small	255	6	1.0		15	1.0		20	
	Medium	396	5	0.8		12	0.8		16	
	Large	69	1	0.3	0.25	10	0.7	0.21	11	0.08
Current brassière size	Cup A or B	521	5	1.0		14	1.0		18	
	Cup C or D	189	2	0.3	0.04	10	0.8	0.24	11	0.03

*Based on log-rank statistic, a test for trend in relative risk if there are more than two categories of risk factor.
†Relative risk: ratio of risk for women in the designated category relative to risk for women in the reference category (1.0).
‡Data obtained at study entry.

ods, considering disease before and after age 30 separately because of the age-related differences in incidence. Table II shows the cumulative risks and the corresponding relative risks for biopsied disease by age.

Menstrual symptoms in early adulthood were assessed on the basis of the information collected while the subjects were nursing students. Those who reported frequent premenstrual breast engorgement had a significantly higher risk of biopsied benign breast disease up to age 30, but a risk similar to that of the other subjects at later ages. Those who reported premenstrual breast pain or tenderness had a greater risk of biopsied benign breast disease up to 50 years; however, this association was weaker and not statistically significant ($P = 0.08$) after adjustment for breast engorgement. Irregular menstruation in early adulthood was associated with significantly higher rates of biopsied benign breast disease below the age of 30, but the age at menarche and at menopause, the type of menopause and a history of dysmenorrhea were not associated with biopsied benign breast disease.

There was a higher risk of biopsied benign breast disease among nulliparous women, women who had one or more abortions (probably spontaneous) and those who did not use oral contraceptives; though apparent at all ages, these associations became statistically significant only after age 30. They persisted when other factors were controlled by stratified analysis, and the increased risk for nulliparous women, which was not statistically significant when assessed alone, became significant ($P = 0.05$) when controlled for other factors related to reproductive history. Marital status, age when first giving birth, lactation history and the use of noncontraceptive estrogen therapy were not associated with biopsied benign breast disease.

A family history of breast problems in either mothers or sisters was associated with a higher risk of biopsied benign breast disease. Women whose mother or sister(s) had benign breast disease had a significantly increased risk for biopsied benign breast disease only after the age of 30. Those who had sisters with breast cancer had a higher risk for biopsied benign breast disease at all ages, although the increase was statistically significant only for those over 30. Women whose mothers had a history of breast cancer had no increased risk for biopsied benign breast disease.

Obesity was estimated from the measures of weight and height obtained from the physical examinations of the student nurses to derive the index of obesity as a young adult, and from the follow-up questionnaire to derive the current and maximum indices of obesity. For each of these factors there was little association with the risk of benign breast disease up to the age of 30, but beyond that age obese women had significantly lower risks. Breast size, which may be associated with the degree of obesity, was also assessed during the initial physical examination and through the later questionnaire. Subjects with larger breasts had a lower risk of benign breast disease, an association that was stronger for current breast size, perhaps reflecting greater accuracy of the current classification, based on brassière size, compared with the undefined categories used by the earlier examiners. The effects of the degree of obesity and breast size were independent, each remaining despite adjustments to control the other (Table III), and different, in that obesity was more strongly associated with benign breast disease after the age of 30, whereas breast size had a greater influence on disease diagnosed before the age of 30.

Factors found not to be associated with biopsied benign breast disease included the woman's ethnic origin, the age of her parents at the time of her birth, her socioeconomic status and a history of other conditions, such as diabetes, hypertension, arthritis, thyroid and gallbladder problems, and benign uterine disease. The lack of association with ethnic origin and socioeconomic status was expected, as the study group was relatively homogeneous.

Table III—Cumulative risks and standard errors for biopsied and symptomatic benign breast disease to age 50, by obesity as a young adult and breast size

Category of benign breast disease and current brassière size	Obesity (Quetelet's index) and risk (%)		
	< 21	21–22	⩾ 23
Biopsied			
Cup A or B	21.1 ± 3.0	13.8 ± 2.5	13.0 ± 2.9
Cup C or D	12.1 ± 5.7	12.7 ± 4.2	8.2 ± 3.0
Symptomatic			
Cup A or B	35.6 ± 3.6	30.6 ± 3.3	28.2 ± 3.9
Cup C or D	24.2 ± 7.5	27.0 ± 5.6	23.5 ± 4.6

Symptomatic disease and biopsy rates

The rate of biopsied benign breast disease depends both on the frequency of the woman's symptoms of breast disease and on the probability that she will have a biopsy because of these symptoms. As the members of our study group were all nurses, the information they gave as to when they first recognized the symptoms of breast disease was likely to be consistent. Therefore, we assessed the relation between the age when a breast lump was detected and the amount of time that passed before a biopsy was done (Table IV), and found most biopsies were done within 2 years after the lump was first detected. Although it was not statistically significant, there was a consistent trend for this delay to decrease as the woman's age at the time of detection increased.

We then assessed the association of the factors studied with the occurrence of symptomatic disease

Table IV—Cumulative probability of having a biopsy for a breast lump, by interval from onset of symptoms to biopsy and age at onset of symptoms

Age (yr)	No. of patients	Interval (yr) and cumulative probability (%)*				
		1	2	3	5	10
⩽ 29	60	30.0	36.7	40.2	41.9	45.5
30–39	52	21.2	46.2	50.1	54.1	–
⩾ 40	66	32.3	50.0	50.0	–	–

*– = insufficient information: less than 20 patients at risk of biopsy.

and with the probability of having a biopsy, expressing each as rates relative to those in the reference category (Table V). For breast engorgement, breast pain and menstrual history factors the associations with symptomatic and with biopsied disease were similar, as were the biopsy rates for each subcategory of women.

The associations with parity, a history of abortions and the use of oral contraceptives showed that the differences in risk seen with biopsied benign breast disease were due to similar trends in both the risk of symptomatic benign breast disease and the biopsy rate: low parity, previous abortions and the lack of use of oral contraceptives were associated with both an increased risk of symptomatic benign breast disease and an increased biopsy rate. A history of breast cancer or benign breast disease in sisters, or of benign breast disease in mothers, was associated with increased rates of symptomatic breast disease and breast biopsy. Women with a maternal history of breast cancer had rates of symptomatic breast disease similar to those of other women, but they had a much lower rate of breast biopsy; thus the risk of biopsied benign breast disease was reduced.

Both obesity and large breasts were associated with a reduced risk of symptomatic benign breast disease and a reduced biopsy rate, thus markedly reducing the risk of biopsied benign breast disease. As with biopsied disease, analysis of symptomatic disease showed that the associations with degree of obesity and breast size appeared to be independent (Table III).

Table V—Relative risks for biopsied and symptomatic benign breast disease, and relative biopsy rates, by various factors

Factor	Category	Relative risk*		Relative biopsy ratio†
		Biopsied disease	Symptomatic disease	
Menstrual history				
Premenstrual breast engorgement as a young adult	Never/occasionally	1.0	1.0	1.0
	Every period	2.3	2.1	1.1
Premenstrual breast pain or tenderness as a young adult	Never	1.0	1.0	1.0
	Occasionally/every period	1.6	1.5	1.1
Menses as a young adult	Regular	1.0	1.0	1.0
	Irregular	1.4	1.4	1.0
Reproductive history				
Number of term pregnancies (among those ever married)	0	1.0	1.0	1.0
	1–2	0.6	1.0	0.6
	3+	0.8	0.9	0.9
Number of abortions (among those ever married)	0	1.0	1.0	1.0
	1	1.7	1.4	1.3
	2+	1.8	1.3	1.4
Oral contraceptive use	Nonusers	1.0	1.0	1.0
	Users	0.6	0.9	0.7
Family history of breast disease				
Breast cancer in mother	No	1.0	1.0	1.0
	Yes	0.5	1.0	0.5
Breast cancer in sister(s) (among those with sisters)	No	1.0	1.0	1.0
	Yes	2.9	1.5	1.9
Benign breast disease in mother	No	1.0	1.0	1.0
	Yes	2.0	1.4	1.4
Benign breast disease in sister(s) (among those with sisters)	No	1.0	1.0	1.0
	Yes	1.7	1.3	1.3
Degree of obesity (Quetelet's index)				
As a young adult	< 21	1.0	1.0	1.0
	21–22	0.6	0.9	0.8
	⩾ 23	0.5	0.8	0.7
Maximum lifetime	< 23	1.0	1.0	1.0
	23–24	0.7	0.8	0.9
	⩾ 25	0.7	0.8	0.8
Current	< 21	1.0	1.0	1.0
	21–22	0.8	1.0	0.7
	⩾ 23	0.7	0.9	0.8
Breast size				
As a young adult	Small	1.0	1.0	1.0
	Medium	0.8	1.0	0.8
	Large	0.6	0.7	0.8
Current brassière size	Cup A or B	1.0	1.0	1.0
	Cup C or D	0.6	0.8	0.8
Screening methods used				
Breast self-examination	Never/occasionally	1.0	1.0	1.0
	Regularly	1.2	1.1	1.1
Breast examination by a physician	Never/occasionally	1.0	1.0	1.0
	Regularly	1.4	1.5	0.9
Cervical smear	Never/occasionally	1.0	1.0	1.0
	Regularly	1.1	1.2	0.9

*Ratio of risk for women in the designated category to risk for women in the reference category (1.0).
†Ratio of proportions of symptomatic subjects having a biopsy in the designated and reference categories.

The rate of biopsy was not associated with the frequency of breast examination, either by the woman or by her physician, or of cervical smears.

Discussion

This study was unique in that records were obtained on the medical history, the symptoms and the results of physical examination of a group of women in early adulthood, who were then studied prospectively. As the study subjects were all nurses, it is likely that the information from the questionnaires was reliable and consistent, an important consideration when symptomatic disease is being studied. Though many of the original study cohort did not participate in the follow-up, our results suggest that those who did were similar in all recorded characteristics to those who did not. For those who were contacted for the follow-up study the response rate was extremely high, reducing the potential error from voluntary noncooperation. A comparison of their responses on the follow-up questionnaire to those on the early questionnaire, completed when they were students, showed close agreement: information on year of birth, ethnic origin of parents, history of breast lumps or injuries, and family history of cancer was compatible in 99% of the subjects; age at menarche was consistent to within 1 year in 95% and to within 2 years in 99% of the subjects.

The incidence of benign breast disease from 20 to 49 years of age was 10.4 per 1000 woman-years for symptomatic disease and 5.4 per 1000 woman-years for biopsied disease. These rates are similar to those found in other studies: 2.8 per 1000 woman-years for biopsied benign breast disease in Boston women aged 20 to 49 years when age was standardized for comparison with our study population;[6] 4.7 per 1000 woman-years for breast disease clinically diagnosed as benign in white, married British women of reproductive age;[23] and 8.5, 11.4 and 10.6 per 1000 woman-years for breast disease clinically diagnosed as benign in married British women of reproductive age who were current users, ex-users or nonusers of oral contraceptives, respectively.[19]

The age–incidence pattern for benign disease in our subjects, with peaks at 20 to 25 years and 40 to 49 years, was similar to that seen in Boston,[6] where fibroadenoma occurred mainly during the first peak and fibrocystic disease during the second. In our study, however, a considerable number of cases of fibrocystic disease occurred before the age of 30.

The age–incidence pattern and the difference in risk factors associated with benign breast disease before the age of 30 and after that age suggest that at least two distinct types of disease exist, though the pathological reports did not clearly delineate these subtypes. A comparison of risk ratios for biopsied benign breast disease for these two age periods shows that premenstrual breast engorgement, irregular menses and small breasts were associated primarily with early disease, while a family history of benign breast disease in the mother or sisters and obesity were associated primarily with later disease. Premenstrual breast pain, nulliparity, a history of abortions, the nonuse of oral contraceptives and a history of breast cancer in sisters were associated with both early and later benign breast disease (Table II). Neither age group showed a matrix of risk factors for benign disease that corresponded to recognized risk factors for breast cancer.

The higher risk of biopsied benign breast disease in those who had premenstrual breast discomfort as young adults probably reflects the natural history of fibrocystic disease. Painful, tender premenstrual swelling in the late teens and early 20s has been described as an early stage of fibrocystic disease.[24]

The findings on variables related to reproductive history were in general agreement with those in the literature. Nulliparity[6-9] and the nonuse of oral contraceptives[7,10-19] have been associated with higher risks of biopsied benign breast disease, whereas age at menarche,[7-10] age at the time of first giving birth,[7,8,10] lactation history[7,8] and type of menopause[8] have not shown any association with such disease. The higher risk of biopsied disease in those who had an abortion has not been found in other studies.[6,9] Though information was not obtained on the type of abortion, it is probable that most were spontaneous, considering both the time when abortions became more available and the age distribution of the study population.

We had insufficient information to determine whether pregnancies, abortions or the use of oral contraceptives necessarily preceded the development of benign breast disease. It is conceivable that spontaneous abortions are more common in women who have had benign breast disease and that oral contraceptives would be less frequently prescribed following the occurrence of this disease. In one study of women living in New York State it was found that a significantly greater proportion of those with benign breast disease than of those without reported discontinuing oral contraceptives on their physician's advice. Of the New York State physicians interviewed, 47% considered the occurrence of a benign breast tumour a contraindiction for the continued use of oral contraceptives.[25] On the other hand, some physicians treat benign breast disease with oral contraceptives.[26] To examine the direction of the relation between the use of oral contraceptives and the occurrence of benign breast disease we would have to consider the age at which the disease was first diagnosed rather than the age at which the first biopsy was performed, because many women with symptoms of breast disease are followed clinically for a long time before having a biopsy. In our study the consistency of the relative risk in the two age groups suggests that a history of benign breast disease did not appreciably alter the likelihood that a woman would use oral contraceptives. Also, our estimates of the relative risk associated with the use of oral contraceptives are similar to those reported from case–control studies looking only at the use of these drugs before breast disease occurs.[17]

These findings support the hypothesis that benign breast disease is associated with an endocrine imbalance. We know that estrogen stimulates the proliferation of epithelial cells and ductal growth in the

breast, while progesterone promotes the development of acini and moderates the effects of estrogen. Thus, an imbalance in the secretion of these two hormones, involving a relative excess of estrogen, possibly resulting from inadequate corpus luteum function, could produce lobular hyperplasia of the breast and subsequently benign breast disease. In addition, estrogen promotes interlobular edema of the breast, resulting in breast discomfort: women who suffer premenstrual breast discomfort have been found to have excessive amounts of estradiol in the plasma.[27,28]

The association of benign breast disease with nulliparity and a history of abortions that were probably spontaneous could also result from endocrine dysfunction. Inadequate corpus luteum function is a common cause of hypofertility;[24] a subcritical level of progesterone permits implantation but will not promote the necessary placental growth, resulting in spontaneous abortion.[29] Again there is a hormonal imbalance with a relative excess of estrogen. The lack of association of benign breast disease with age at menarche or age at the time of first giving birth suggests that the amount of estrogen present in a woman's system may be more important than the length of time she is exposed to the estrogen.

The inverse association of biopsied benign breast disease with obesity has been reported elsewhere;[6,10] in our subjects it persisted when controlled for breast size but was stronger in women with smaller breasts (Table III). The age groups associated with biopsied disease differed as to degree of obesity and breast size: this further supported the independence of the effects of these two factors. The degree of obesity may influence the risk that benign breast disease will occur, whereas breast size may influence the likelihood that a lump will be detected. Possibly the association with obesity is not as apparent in those with large breasts because the disease is not so easily detected.

Another hypothesis that could explain some of our study's findings is that breast lumps are very common but only people more sensitive to certain internal and external stimuli notice them. These individuals may be more likely to experience premenstrual breast engorgement and psychogenic amenorrhea and to have a biopsy performed because they noticed a breast lump. Since the central nervous system can affect corpus luteum function through gonadotropin secretion, it is possible to integrate these observations into the endocrine imbalance hypothesis. Animal studies,[30,31] clinical trials with progesterone[27] and tamoxifen citrate,[32] and the discovery of estrogen receptors in benign breast lesions[27] all support this hypothesis.

In our subjects there was a consistent trend for the lapse between the time breast symptoms were detected and a biopsy was performed to be shortened with advancing age, most biopsies being done within 2 years of symptom detection. Also, in spite of the limited number of older women available for follow-up, it appeared that a breast lump was more likely to be biopsied in these women. This is appropriate in view of the increasing risk that a lump will be malignant with increasing age. The higher biopsy rates for those who were nulliparous, whose sisters had a history of breast cancer and possibly whose sisters and mother had benign breast disease were also in accord with the risk of breast cancer. However, the lower biopsy rates for those who were obese and had large breasts was not as appropriate because obesity is associated with an increased risk of breast cancer, and lumps in large breasts are difficult to assess clinically. The lower biopsy rate for those with a history of maternal breast cancer was unexpected, and may have been the result, in part, of the small numbers with such a history; since this lower rate was largely restricted to respondents who had had benign breast disease before the age of 30, some breast cancers in the mothers may not yet have been diagnosed and hence would not have influenced the physician's decision to request a biopsy.

Distinguishing between physiologic and pathologic breast changes on clinical grounds alone is difficult, and the histologic confirmation of organic disease depends on biopsy practices that vary with the symptoms and the risk factors. Hence, we advise caution in making generalizations about benign breast disease based only on cases in which biopsies have been done, especially when assessing risk factors that might influence the decision about whether to do a biopsy of a suspicious lesion. Our results show that women having the characteristics associated with a higher risk of symptomatic breast disease are more likely to have a biopsy, so that stronger associations are seen with biopsied than with symptomatic disease; alternatively, the relation of these factors to severe or progressive disease that leads to biopsy may be stronger than the relation of factors associated with less severe disease that does not lead to biopsy. Clearly, more work is needed on the natural history and classification of benign breast disease, for there may be differing relations with breast cancer. The epidemiologic data on incidence rates and risk factors indicate that there are two subtypes of benign breast disease. It seems likely that these subtypes differ in their pathological features, yet the descriptive terms in general use do not adequately distinguish them. Further work, perhaps along the lines suggested by Black and coworkers[4] and LiVolsi and colleagues,[20] may provide a pathological classification that more closely distinguishes benign breast disease in terms of both its epidemiologic features and its relation to subsequent breast cancer. Our study has shown that the frequency of this disease is very high, yet severely underestimated when only cases in which a biopsy has been done are considered.

We thank Dr. D.A. Boyes and other members of the staff at the Cancer Control Agency of British Columbia for their interest and participation in this study over the years, Dr. A. Worth for helpful comments, Mr. R. Sizto for aid in programming and Ms. K. Anderson for typing the manuscript.

This study was supported by the Canadian Cancer Society, and in part by a national health fellowship to Dr. Hislop from the national health research and development program of the Department of National Health and Welfare.

References

1. MONSON RR, YEN S, MACMAHON B: Chronic mastitis and carcinoma of the breast. *Lancet* 1976; 2: 224–226
2. DONNELLY PK, BAKER KW, CARNEY JA, O'FALLON WM: Benign breast lesions and subsequent breast carcinoma in Rochester, Minnesota. *Mayo Clin Proc* 1975; 50: 650–656
3. HAAGENSEN CD: The relationship of gross cystic disease of the breast and carcinoma (E). *Ann Surg* 1977; 185: 375–376
4. BLACK MM, BARCLAY THC, CUTLER SJ, HANKEY BF, ASIRE AJ: Association of atypical characteristics of benign breast lesions with subsequent risk of breast cancer. *Cancer* 1972; 29: 338–343
5. KODLIN D, WINGER EE, MORGENSTERN NL, CHEN U: Chronic mastopathy and breast cancer. A follow-up study. *Cancer* 1977; 39: 2603–2607
6. COLE P, ELWOOD JM, KAPLAN SD: Incidence rates and risk factors of benign breast neoplasms. *Am J Epidemiol* 1978; 108: 112–120
7. KELSEY JL, LINDFORS KK, WHITE C: A case–control study of the epidemiology of benign breast diseases with reference to oral contraceptive use. *Int J Epidemiol* 1974; 3: 333–340
8. NOMURA A, COMSTOCK GW, TONASCIA JA: Epidemiologic characteristics of benign breast disease. *Am J Epidemiol* 1977; 105: 505–512
9. SARTWELL PE, ARTHES FG, TONASCIA JA: Benign and malignant breast tumours: epidemiological similarities. *Int J Epidemiol* 1978; 7: 217–221
10. FASAL E, PAFFENBARGER RS JR: Oral contraceptives as related to cancer and benign lesions of the breast. *J Natl Cancer Inst* 1975; 55: 767–773
11. RAVNIHAR B, SEIGEL DG, LINDTNER J: An epidemiologic study of breast cancer and benign breast neoplasias in relation to the oral contraceptive and estrogen use. *Eur J Cancer* 1979; 15: 395–405
12. VESSEY MP, DOLL R, SUTTON PM: Oral contraceptives and breast neoplasia: a retrospective study. *Br Med J* 1972; 3: 719–724
13. PAFFENBARGER RS JR, FASAL E, SIMMONS ME, KAMPERT JB: Cancer risk as related to use of oral contraceptives during fertile years. *Cancer* 1977; 39(4) (suppl): 1887–1891
14. Report from the Boston Collaborative Drug Surveillance Programme: Oral contraceptives and venous thromboembolic disease, surgically confirmed gallbladder disease, and breast tumours. *Lancet* 1973; 1: 1399–1404
15. LEES AW, BURNS PE, GRACE M: Oral contraceptives and breast disease in premenopausal Northern Albertan woman. *Int J Cancer* 1978; 22: 700–707
16. SARTWELL PE, ARTHES FG, TONASCIA JA: Epidemiology of benign breast lesions: lack of association with oral contraceptive use. *N Engl J Med* 1973; 288: 551–554
17. COLE PT: Oral contraceptives and breast neoplasia. *Cancer* 1977; 39(4) (suppl): 1906–1908
18. ORY H, COLE P, MACMAHON B, HOOVER R: Oral contraceptives and reduced risk of benign breast diseases. *N Engl J Med* 1976; 294: 419–422
19. Royal College of General Practitioners: *Oral Contraceptives and Health*, Pitman, New York, 1974
20. LIVOLSI VA, STADEL BV, KELSEY JL, HOLFORD TR, WHITE C: Fibrocystic breast disease in oral-contraceptive users. A histopathological evaluation of epithelial atypia. *N Engl J Med* 1978; 299: 381–385
21. ROSS RK, PAGANINI-HILL A, GERKINS VR, MACK TM, PFEFFER R, ARTHUR M, HENDERSON BE: A case–control study of menopausal estrogen therapy and breast cancer. *JAMA* 1980; 243: 1635–1639
22. COLDMAN AJ, ELWOOD JM: Examining survival data. *Can Med Assoc J* 1979; 121: 1065–1071
23. VESSEY M, DOLL R, PETO R, JOHNSON B, WIGGIN P: A long-term follow-up study of women using different methods of contraception — an interim report. *J Biosoc Sci* 1976; 8: 373–427
24. PILNIK S, LEIS HP JR: Clinical diagnosis of breast lesions. In GALLAGER HS, LEIS HP JR, SNYDERMAN RK, URBAN JA (eds): *The Breast*, Mosby, St Louis, 1978: 77
25. JANERICH DT, GLEBATIS DM, DUGAN JM: Benign breast disease and oral contraceptive use. *JAMA* 1977; 237: 2199–2201
26. HATCHER RA: Oral contraceptives and breast lesions (C). *J Natl Cancer Inst* 1977; 58: 12
27. MAUVAIS-JARVIS P, SITRUK-WARE R, KUTTENN F, STERKERS N: Luteal phase insufficiency: a common pathophysiologic factor in development of benign and malignant breast diseases. In TAYLOR DJ, BULBROOK RD (eds): *Commentaries on Research in Breast Disease*, vol 1, AR Liss, New York, 1979: 25–59
28. BÄCKSTRÖM T, CARSTENSEN H: Estrogen and progesterone in plasma in relation to premenstrual tension. *J Steroid Biochem* 1974; 5: 257–260
29. PAUERSTEIN CJ: Pathology of abortion (in uterus, placenta, appendages, and ovofetus). In NOVAK ER, WOODRUFF JD (eds): *Novak's Gynecologic and Obstetric Pathology, with Clinical and Endocrine Relations*, 8th ed, Saunders, Philadelphia, 1979: 635
30. BÄSSLER R: The morphology of hormone induced structural changes in the female breast. *Curr Top Pathol* 1970; 53: 1–89
31. COWIE AT, FOLLEY SJ, MALPRESS FH, RICHARDSON KC: Studies on the hormonal induction of mammary growth and lactation in the goat. *J Endocrinol* 1952; 8: 64–88
32. RICCIARDI I, IANNIRUBERTO A: Tamoxifen-induced regression of benign breast lesions. *Obstet Gynecol* 1979; 54: 80–84

Notes on nursing

Taking care of such an unhappy patient, with so little prospect of any success, is one of the heaviest loads one can lay on a human being, which only women can carry for any length of time with never-ending patience.

—Theodor Billroth (1829–1894)

"I think," said Mr. Dooley, "that if th' Christyan Scientists had some science an' th' doctors more Christianity, it wudden't make anny diff'rence which ye called in — if ye had a good nurse."

—Finley Peter Dunne ("Mr Dooley") (1867–1936)