

Epidemiology of Breast Fluid Secretion: Association With Breast Cancer Risk Factors and Cerumen Type^{1,2,3}

Nicholas L. Petrakis, M.D.,^{4,5} Virginia L. Emster, Ph.D.,⁴ Susan T. Sacks, Ph.D.,⁴ Eileen B. King, M.D.,⁴ Robert J. Schweltzer, M.D.,⁶ Thomas K. Hunt, M.D.,⁷ and Mary-Claire King, Ph.D.^{4,8}

ABSTRACT—The epidemiology of breast fluid secretion was studied on the basis of nipple aspirates of breast fluid obtained from 3,929 nonlactating women of various racial groups. The results confirmed and extended earlier findings by our group: Variation in the proportion of secretors was related to most breast cancer risk factors, including age, race, age at menarche, age at first pregnancy, age at menopause, clinically diagnosed fibrocystic disease, menopausal estrogen use, and cerumen phenotype. Secretory activity as measured by nipple aspiration appeared to reflect hormonal and genetic effects on breast epithelium.—*JNCI* 1981; 67:277-284.

Investigations in our laboratory and by other researchers have demonstrated that the adult nonlactating female breast secretes and reabsorbs fluid within the alveolar-ductal system (1-4). The ductal fluid, readily sampled through the nipple with a simple aspiration device, can provide a clinical index of the secretory activity of the breast and an opportunity for cytologic and biochemical studies of breast fluid components.

We report on the epidemiology of breast fluid secretion on the basis of nipple aspirates obtained from 3,929 nonlactating women. We will describe the epidemiologic characteristics that distinguish women who yield fluid (secretors) when the breast nipple is aspirated from women who do not (nonsecretors).

In earlier, preliminary studies, we reported an association between the ability to aspirate breast fluid and race, age, menopausal status, and genetic type of cerumen (1). The highest proportion of breast fluid secretors was observed among white women and the lowest among Chinese women. In all ethnic groups, the proportion of secretors declined after the menopause, but the reduction was especially marked among Chinese women in whom only a small proportion yielded fluid after age 50. In contrast, over half the postmenopausal white women gave fluid, suggesting that a persistent hormonal stimulus in this group maintains breast secretory activity into older age.

We identified an apocrine genetic factor associated with breast secretion: Among Chinese (and white) women, the proportion of secretors was higher for women of the wet cerumen phenotype than for women of the dry cerumen type. It is generally accepted that whether one secretes dry- or wet-type cerumen is genetically determined. The finding of secretory activity in over half the postmenopausal Caucasian women and in only a small proportion of Chinese women and its association with cerumen type would suggest that genetic influences on breast epithelial function underlie the differences in breast cancer rates for white and Chinese women. We hypothesize that decreased secre-

tory activity—perhaps indicative of lower metabolic activity—minimizes the exposure of the breast epithelium to exogenous and endogenous carcinogens and cocarcinogens.

We now update our earlier findings based on a larger sample of women across ethnic groups. We also examine other variables of secretory status. It might be expected, on the basis of the endocrine-dependent nature of the breast, that variations in breast secretory activity would be consistent with many epidemiologic features found in women having risk factors for breast cancer. Our results support the expectation and lend further support to the hypothesis of an association between breast secretory activity and breast cancer risk and, in addition, of the role of an apocrine genetic factor in breast secretion.

MATERIALS AND METHODS

The 3,929 women were drawn from: a) various clinical departments of the University of California, San Francisco, including surgery and obstetrics and gynecology, as well as the private practices of university-affiliated physicians (31.9%) (the women, many of whom had breast concerns, were referred by physicians or were self-referred); b) the Breast Screening Center of Northern California at Merritt Hospital, Oakland, Calif., one of 29 breast cancer screening demonstration centers established throughout the country under the joint auspices of the National Cancer Institute and the American Cancer Society (the participants were self-referred women 35 yr and older) (46.3%); c) other community sources including volunteer participants in

¹ Received July 11, 1980; revised December 12, 1980; accepted January 21, 1981.

² Supported in part by Public Health Service grant P01-CA13556 from the National Cancer Institute.

³ Research procedures were in accord with the ethical standards of the Committee on Human Research, University of California, San Francisco.

⁴ Department of Epidemiology and International Health, University of California, San Francisco, Calif. 94143.

⁵ Address reprint requests to Dr. Petrakis, c/o Editor, Department of Epidemiology and International Health, 1699 HSW, University of California, San Francisco.

⁶ Department of Surgery, University of California, San Francisco.

⁷ Breast Screening Center of Northern California, Merritt Hospital, Oakland, Calif. 94609.

⁸ We thank Lynn Mason, Dixie Tilley, Rose Lee, and Mary Edith Dupuy for their valuable assistance in these studies.

local health fairs, screening programs, and patient self-help groups (21.8%).

Fibrocystic disease status was based on physical examination by physicians and trained nurses employing standard criteria such as those described by Haagen- sen (5), Leis (6), and Cutler (7). While some differences would be expected among examiners, it is likely that most would agree on the presence of gross fibrocystic disease. Gross fibrocystic disease is common among white American women, but specimens for biopsy are drawn from only a small proportion of women with the disease.

The age and racial distributions of the study population are shown in table 1. All women completed a questionnaire that included items relating to demographic, marital, reproductive, and other clinical characteristics of potential relevance to benign or malignant breast disease. All women received a clinical breast examination by trained nurses and underwent nipple aspiration for breast fluid. The technique previously described was used (1). The nipple was carefully cleansed with a detergent (Ceruminex) before the duct fluid was aspirated. In our earlier study the aspiration technique was performed under a rigidly standardized method by withdrawing the plunger of the syringe to the 10-mm³ mark (≈ 300 -mm Hg-negative pressure) for 15 seconds. For the results presented here, fluid was collected by several individuals, usually nurses specially trained in breast examination, who were instructed to pull the syringe to at least 5-6 mm³ (≈ 150 -mm Hg-negative pressure) for 10-15 seconds, this degree of negative pressure being necessary to overcome the closed nipple ducts in most women. If fluid did not appear at the nipple surface within 10-15 seconds, the plunger was withdrawn to the full 10-mm³ mark and held 10-15 seconds longer. During aspiration the women compressed the breast with both hands to achieve gentle but firm uniform pressure. Breast fluids were collected and stored in capillary tubes for cytologic and biochemical tests. Women were designated as "secretors" if a drop or more of breast fluid, collectable by capillary tube, appeared at the surface of one or both nipples following application of the breast pump as described above.

Cerumen type was determined by otoscope employing the criteria described previously (8).

RESULTS

Age, race, and income.—The distribution of the study population ($n=3,929$) by age, race, and percentage of women in each racial group who yielded breast fluid is shown in table 1. We will confine our remarks mostly to white, black, and Chinese women, the 3 ethnic groups for whom we had adequate numbers across age groups and who are of particular interest owing to their markedly differing breast cancer rates in their respective general populations.

Text-figure 1 shows the pattern of breast secretion by age (data from table 1) for white, black, Chinese, and Japanese women. In all racial groups, there was a clear upward trend in the proportion of secretors through ages 40-49 followed by a steady decline. For most age groups, the highest proportion of secretors was among white women followed closely by black women; at every age, the proportion of secretors was lowest among Chinese women. For Japanese, our data were confined to women aged 30 and older and in that age range paralleled the data for Chinese. At the peak of secretory activity, between 40 and 49 years, white and black women had nearly identical proportions of secretors, 70.9 and 72.8%, respectively, compared to 42.6% for Chinese and 24.1% for Japanese women. Among Japanese women, the peak activity was in the 30- to 39-year group but the numbers were small. The differential continued to hold through age 70 and older, when approximately 30% of white and black women yielded fluid compared to 5% of Chinese. Across race- and age-specific groups, educational level (elementary school, high school, and college educated) was not related to secretor status. However, family income was directly associated with secretor status. This relationship is shown in text-figure 2 for white women under and over age 50. A progressive and significantly higher proportion of secretors was associated with increasing family income.

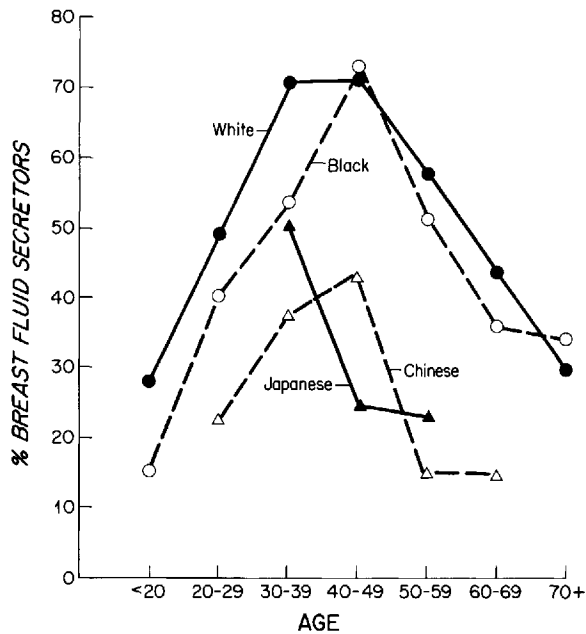
Menstrual history.—We examined age at menarche,

TABLE 1.—Distribution of study population and proportion of breast fluid secretors by age and race

Age, yr	White		Black		Chinese		Japanese		Latin American		Filipino	
	No./total ^a	Percent secretors	No./total ^a	Percent secretors	No./total ^a	Percent secretors ^b	No./total ^a	Percent secretors	No./total ^a	Percent secretors	No./total ^a	Percent secretors ^b
<20	9/32	28.1	2/13	15.4	1/1	—	0	—	1/1	—	1/1	—
20-29	208/424	49.1	25/62	40.3	11/48	22.9	5/5	—	7/13	53.8	2/10	20.0
30-39	428/607	70.5	55/102	53.9	29/78	37.2	7/14	50.0	32/45	71.1	10/17	58.8
40-49	580/819	70.9	83/114	72.8	40/94	42.6	7/29	24.1	35/56	62.5	8/18	44.4
50-59	361/628	57.6	50/98	51.0	7/47	14.9	7/31	22.6	18/30	60.0	3/8	—
60-69	119/272	43.8	15/42	35.7	6/41	14.6	1/7	—	2/7	—	1/1	—
≥ 70	19/65	29.2	8/24	33.3	1/20	5.0	1/1	—	1/2	—	2/2	—
Total	1,724/2,847	60.5	238/455	58.7	95/329	28.5	28/87	32.2	96/154	61.6	27/57	47.4

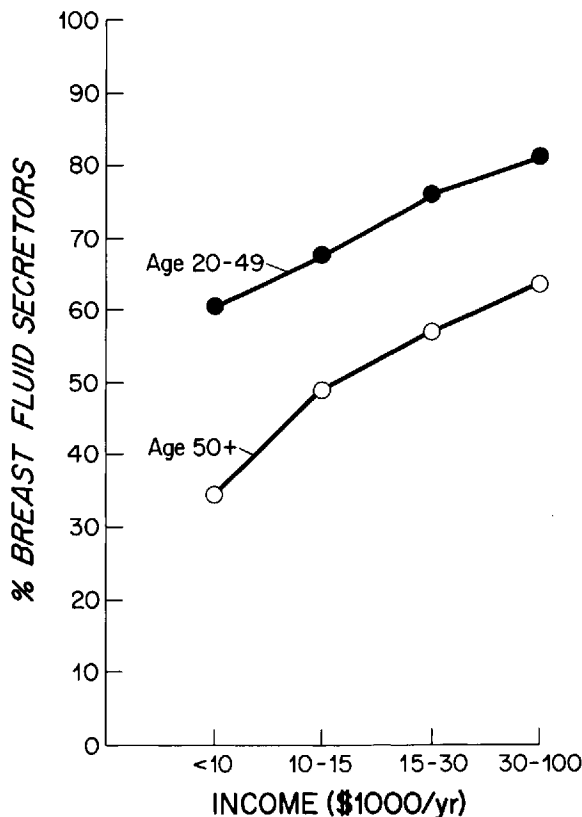
^a No. of secretors/total No. of women studied.

^b —=proportion of secretors was not calculated when total No. of women in any cell was <10.



TEXT-FIGURE 1.—Breast fluid secretors by age in white, black, and Asian women.

stage in menstrual cycle, and menopause in relation to secretor status. Among white and Chinese women, menarche before age 15 is associated with a higher proportion of secretors compared to menarche at age 15



TEXT-FIGURE 2.—Breast fluid secretors by family income in premenopausal and postmenopausal white women.

or older. These findings (table 2) were statistically significant for white women between 20 and 49 years of age ($P < 0.025$), but not for Chinese women. We found no relationship between age at first menstruation and secretor status in black women.

Among premenopausal women we found no discernible differences in the proportion of secretors by stage in menstrual cycle defined in terms of weeks since last menstrual period.

We examined the effect of menopausal status on breast secretion in white women between 40 and 54 years. In each of the three 5-year age groups, premenopausal women were more likely secretors than were women who had already experienced natural or surgical menopause. No statistically significant differences in the proportion of secretors were found between women having natural or surgical menopause. The differences between premenopausal and postmenopausal women were statistically significant for the 3 combined groups (table 3).

Reproductive history.—Several characteristics of pregnancy history were examined in relation to secretor status (i.e., nulliparity, age at first pregnancy, age at last pregnancy, number of children born, and lactation). In contrast to our earlier report, on the basis of a much larger study population, we now find a significantly higher proportion of secretors among parous than among nonparous women. This effect was confined to white and black women in the age group 20-49 (table 4). Although the proportion of secretors among nonparous Chinese women aged 20-49 was also lower than that among parous ones, the difference was slight and statistically not significant. Among white women aged 50-59, parous and nonparous groups contained similar proportions of secretors, but among women 60 years or older, the proportion of secretors among parous women was lower than that among nonparous women (text-fig. 3). These findings for white women may be related to estrogen use, which we will discuss below. Among parous and nonparous black women aged 50 or older, we found no consistent differences in secretor status.

Among parous women aged 40-49 whose first pregnancy occurred before age 20, the secretors comprised 72.9%, whereas among those whose first pregnancy occurred at age 30 or later, the secretors comprised 86.5%. This finding was reversed in women aged 50-59 in whom first pregnancy before age 20 is associated with a higher frequency of secretors than in women

TABLE 2.—Secretors by age at menarche in whites and Chinese, 20-49 yr old

Age at menarche, yr	White		Chinese	
	No./total ^a	Percent secretors	No./total ^a	Percent secretors
<13	545/808	67.5	22/45	48.9
13-14	526/797	66.0	24/73	32.9
≥15	79/140	56.4	29/92	31.5

^a No. of secretors/total No. of women studied.

TABLE 3.—Secretors among white women 40–54 yr old by menopausal status

Menopausal status	Age group, yr							
	40–44		45–49		50–54		Combined 40–54	
	No./total ^a	Percent secretors	No./total ^a	Percent secretors	No./total ^a	Percent secretors	No./total ^a	Percent secretors
(a) Menstruating	256/339	75.5	151/205	73.5	40/70	68.6	455/614	74.1
(b) Natural menopause	4/10	40.0	40/63	63.5	107/172	62.2	151/245	61.6
(c) Surgical menopause	37/62	59.7	81/122	66.4	86/141	61.0	204/325	62.7
	(a) vs. (b) $P<0.01$ (a) vs. (c) $P<0.01$		PNS ^b		PNS ^b		(a) vs. (b) $P<0.001$ (a) vs. (c) $P<0.001$	

^a No. of secretors/total No. of women studied.^b NS=not significant.

whose first pregnancy occurred after age 30 (i.e., 66.7% vs. 44.0%, respectively). These differences, shown in text-figure 4, were statistically significant. No marked differences were apparent among women under 40 years nor in those 60 years and older. However, the variables, age at last pregnancy and number of children born, showed no consistent relation to secretor status.

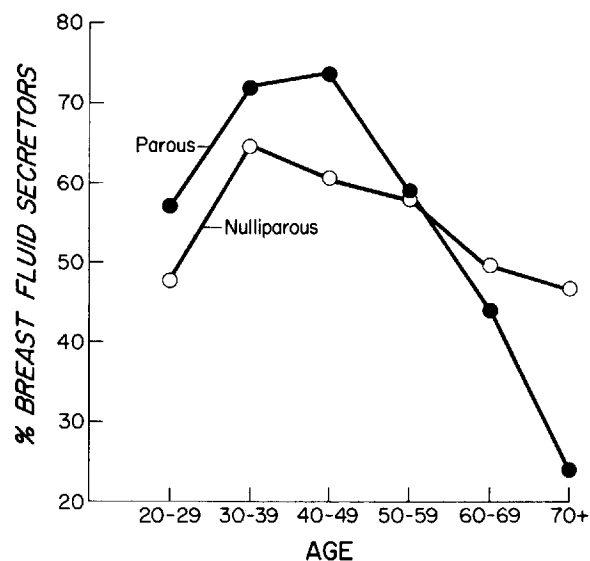
Among parous women two variables concerning breast-feeding were examined in relation to secretor status: Women who had ever breast-fed their children were compared with those who had never done so and the influence of duration of lactation was studied. Among parous white women aged 20–49, a higher proportion of secretors was found for women who had breast-fed (72.6% of 738) compared to those who had never done so (65% of 664). Similar relative differences were observed for black and Chinese women, but these findings were not statistically significant. But the difference was statistically significant for white women only. Among women over 50 years, no such trend was apparent. When the number of months nursed was examined in relation to secretor status, there appeared to be no consistent differences among women who had nursed less than 3 months, 3–12 months, or a year and longer across the 3 racial groups. No relationship was found between secretor status and either age at first birth or breast-feeding, except for postmenopausal

women who had their first pregnancy after age 30 (table 5).

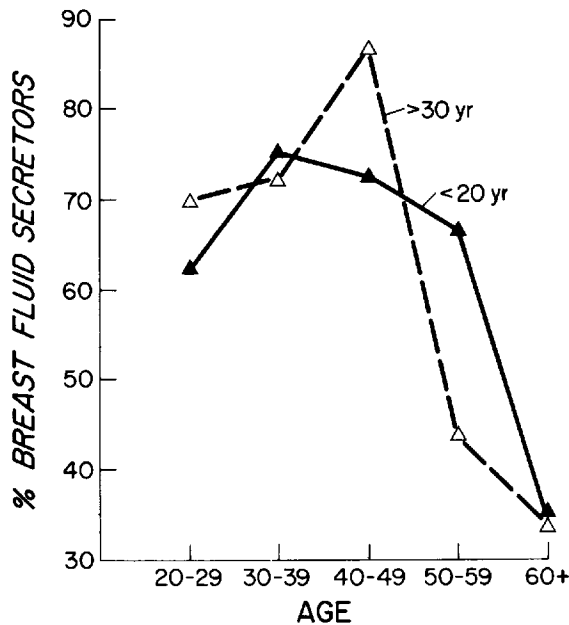
Replacement estrogen use.—The relationship between breast secretion, age, and use of replacement estrogens among white women is shown in table 6. Compared to nonusers, white women between 40 and 49 years who took estrogens had a statistically significant lower frequency of secretors (69.3% vs. 76.9%, respectively). In contrast, postmenopausal women aged 60 and older who took estrogens had a statistically significant higher frequency of secretors than had nonusers (41.4% vs. 23.7%, respectively), which suggests that postmenopausal estrogen use maintains breast secretory activity at a higher level. The relationship between use of menopausal estrogen replacement and breast fluid secretion was compared in women who had a natural and in women who had undergone surgical menopause. In both groups, a higher rate of secretors was found among women taking estrogens

TABLE 4.—Secretors 20–49 yr old by age, race, and parity status

Parity status	White		Black		Chinese	
	No./total ^a	Percent secretors	No./total ^a	Percent secretors	No./total ^a	Percent secretors
Nulliparous	250/470	53.2	18/55	32.7	10/29	34.5
Parous	853/1,199	71.1	136/209	65.1	67/171	39.2
	$P<0.001$		$P<0.001$		NS ^b	

^a No. of secretors/total No. of women studied.^b Not significant.

TEXT-FIGURE 3.—Breast fluid secretors by age according to parity status.



TEXT-FIGURE 4.—Breast fluid secretors by age according to age at first pregnancy (>30 yr of age vs. <20 yr of age).

compared to nonusers. However, possibly because of the low numbers in the sample, the differences were not statistically significant.

Estrogen use among parous and nonparous women showed similar frequencies. Present users had a lower proportion of secretors premenopausally and a higher proportion postmenopausally, but the differences were not statistically significant. We had no data on duration of estrogen use.

Family history of breast cancer; oral contraceptive and tranquilizer use; smoking and acne.—We compared women who had a history of breast cancer in the immediate family, on the maternal or paternal side, with women who had no such history and found no differences in the proportion of secretors in either group.

Three groups of women, those who had never used oral contraceptives, those who currently use them, and those who had used them in the past, showed no differences in their secretor status. White women aged 50 and older and black women of all ages who reported

TABLE 6.—Secretors by estrogen use and age among white women

Estrogen use	Age, yr, of women studied					
	40-49		50-59		≥60	
	No./total ^a	Percent secretors	No./total ^a	Percent secretors	No./total ^a	Percent secretors
User	260/375	69.3	275/477	57.7	99/239	41.1
Nonuser	273/355	76.9	63/106	59.4	14/59	23.7
	$P<0.05$		NS ^b		$P<0.05-0.02$	

^a No. of secretors/total No. of women studied.

^b Not significant.

regular or frequent use of tranquilizers had a slightly higher proportion of secretors than had nonusers (premenopausal: 66.4 vs. 64.7%; postmenopausal: 58.1 vs. 49.5%), but the differences were not statistically significant. The number of Chinese and Japanese women of all ages reporting tranquilizer use was too small for analysis.

Finally, we compared separately past and present smokers with women who had never smoked, with women who had a history of acne, and with those who had not. We discerned no pattern of differences in secretory activity among these groups.

Fibrocystic disease.—We compared secretor status of women who had clinically palpable fibrocystic disease with that of women judged not to have clinically palpable fibrocystic disease. White women of every age group had a higher proportion of secretors among those found to have fibrocystic disease (table 7). Among white women aged 20-49, the proportion of secretors in the fibrocystic group was 73.7%; in those reported not to have the disease, it was 63.2% ($P<0.001$); in women 50 years and older, the proportions were 58.9 and 50.1% ($P<0.05$), respectively. The few black women with fibrocystic findings in most age groups prevented age-specific comparisons, except in the 30-59 age range where 80.0% of black women with fibrocystic findings secreted fluid compared to 55.6% who had no such findings ($P<0.001$). Among Chinese women, fibrocystic disease is rare; but it is of interest that 6 of the 10 women (in the 30-59 age range clinically judged to have fibrocystic disease) were secretors and that of 209

TABLE 5.—Proportion of secretors by age at first pregnancy and nursing

Age at first pregnancy, yr	Women 20-49 yr old				Women >50 yr old			
	Never nursed		Ever nursed		Never nursed		Ever nursed	
	No./total ^a	Percent secretors	No./total ^a	Percent secretors	No./total ^a	Percent secretors	No./total ^a	Percent secretors
<20	66/95	69.5	64/83	77.1	15/27	55.6	44/81	54.3
21-30	180/272	66.2	317/433	73.3	121/226	53.5	200/389	51.4
>30	23/26	88.5	23/30	76.6	11/39	28.2 ^b	26/50	52.0

^a No. of secretors/total No. of women studied.

^b Significantly different from >30 ever nursed; $P<0.01$.

TABLE 7.—Proportion of secretors by age, race, and presence or absence of clinically palpable fibrocystic disease^a

Age, yr	White				Black				Chinese			
	Present		Absent		Present		Absent		Present		Absent	
	No./total ^b	Percent secretors	No./total ^b	Percent secretors	No./total ^b	Percent secretors	No./total ^b	Percent secretors	No./total ^b	Percent secretors	No./total ^b	Percent secretors
20-29	41/61	67.2	167/363	46.0								
30-39	120/154	77.9	308/453	68.0	11/12	91.7	44/90	48.9	2/4		27/74	36.5
40-49	172/237	72.6	409/582	70.3	22/28	78.6	61/86	70.9	4/5	60.0	36/89	40.4
50-59	84/134	62.7	278/494	56.3	11/15	73.3	39/83	47.0	0/1		7/46	15.2
60-69	23/47	48.9	96/225	42.7								
≥70	6/11	54.5	13/54	24.1								

^a Difference between women with and without clinically palpable fibrocystic disease is statistically significant at $P < 0.05$ for white women age 20-49 yr old and ≥ 50 yr old, black women 30-59 yr old, and Chinese women 30-59 yr old.

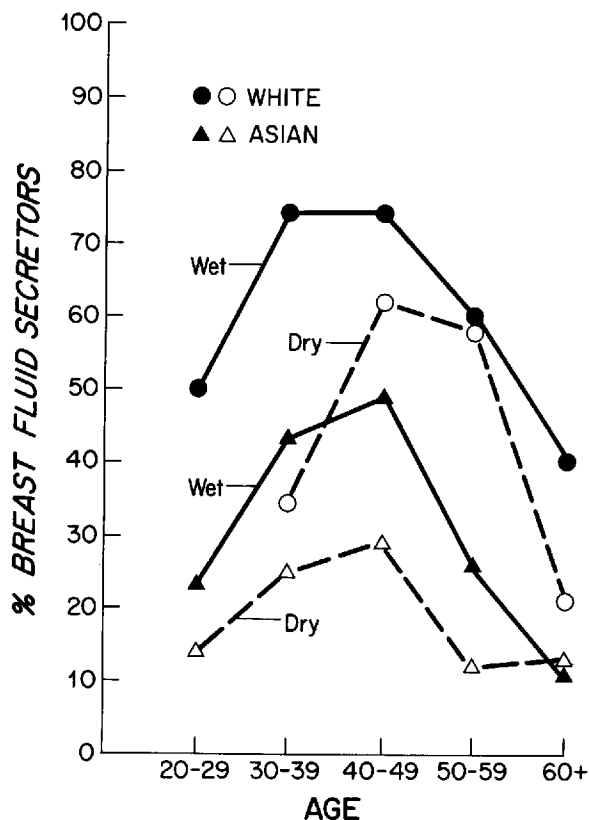
^b No. of secretors/total No. of women studied.

women found not to have the disease 70 (33.5%) ($P < 0.10$) were secretors.

Cerumen type.—We identified 1,781 white, 191 black, 300 Chinese, and 74 Japanese women 20 years and older by cerumen (wet or dry earwax) phenotype. Wet cerumen was found in 92.4% of white women, 96.9% of black women, 46.0% of Chinese women, and 17.5% of Japanese women. We examined differences in breast secretion patterns in white, Chinese, and Japanese women. The number of black women of the dry

cerumen phenotype was too small for analysis. Of 1,781 white women, 136 (7.6%) had dry cerumen, which yielded an estimated dry gene frequency (q) of 0.276. As expected, women of the wet phenotype were more likely to secrete fluid than were women of the dry phenotype (text-fig. 5). But the finding was statistically significant only in women under 50 years. The association of cerumen phenotype and secretor status that we previously reported for Chinese and Japanese was replicated here for white women. The relative racial differences in the proportion of secretors within groups of the wet and dry cerumen phenotype were maintained.

Given these findings, we wanted to know whether the amount of secreted fluid would be greater from women of the wet than from women of the dry cerumen phenotype. Unfortunately, the quantity of fluid obtained was not routinely recorded for all secretors. However, all fluid samples were initially submitted for cytologic preparation and examination; where more than one capillary tube of fluid had been collected per woman, the excess fluid was forwarded to our biochemical laboratory and quantified in microliters. We therefore had a crude measure of the magnitude of fluid for that subset of women who secreted in excess of one capillary tube, and we examined these data for white women. We grouped excess fluid specimens into < 28 and ≥ 28 μ l because 28 μ l was the average quantity that we collected per capillary tube. As expected, the proportion of women in the > 28 - μ l category was greater among women of the wet (23.2%) than among women of the dry (9.2%) cerumen phenotype (table 8).



TEXT-FIGURE 5.—Breast fluid secretors by age and cerumen type in white and Asian women.

TABLE 8.—White women who secreted excess fluid (> 28 μ l) by cerumen type^a

Cerumen type	Secretors of quantity of fluid > 28 μ l
Wet	197/849 ^b (23.2%)
Dry	5/54 ^b (9.2%)

^a $P < 0.05$.

^b No. of secretors of > 28 μ l/total No. of women studied.

DISCUSSION

In our earlier study of a preliminary smaller sample of women, we found breast secretory activity to be related to a few recognized risk factors for breast cancer. In the present study, employing a large sample, the earlier results are generally confirmed, though the absolute proportion of secretors in relation to each of the variables has been altered. We have also investigated a number of previously unexamined factors that appear to be associated with breast secretory activity. In general, secretion appears to reflect ovarian activity and is altered in relation to reproductive history. We have found a striking direct relationship between breast secretory activity and family income, which we hypothesize results from improved nutrition and possibly extensive use of estrogens among the more affluent women. We are hard pressed to explain the discrepancy between education and income in secretor status. Possibly, in this geographic area and population group, educational level and income status are not related. A dissociation between education and income was recently reported for breast cancer in black women by Devesa and Diamond (9).

Among white women, breast cancer risk increases with age, but the rate of increase slows after age 50 (10). We observed a gradual increase with age in the frequency of secretors in all racial groups followed by a gradual decrease after the menopause. Although the decrease corresponds to cessation of ovarian function, between 30 and 40% of white women were secretors at age 60 and older—a finding that we attribute in part to therapeutic estrogen use and in part to probable endogenous extraglandular estrogen production. In confirmation of our earlier findings, Chinese and Japanese women are characterized by significantly lower frequencies of secretors than are white and black women in the same age groups.

In another study Buehring (3) found no significant differences in frequency of secretors between Asian, white, and black women. However, her Asian group consisted of only 65 women for whom age distribution and cerumen type are not given. We have shown a strong association of both these characteristics with variations in the frequency of secretors.

The age-related changes in secretory activity that we report appear to parallel the biologic involution of the ovary and decline in estrogen and progesterone production associated with the menopause. Breast development in adolescence, its maintenance in adult life, and involution in the postmenopausal period are dependent primarily on the ovarian hormones estrogen and progesterone and on prolactin (11). The ovarian hormones are known to be required for alveolar-ductal growth and alveolar secretion, but the role of prolactin in the nonlactating breast is not yet understood. Women with early menarche and late menopause have been shown to have increased risk of breast cancer, possibly related to the increased number of menstrual cycles and resulting longer exposure of the breast

epithelia to estrogen and other hormones. In contrast, women with late menarche and early menopause have a decreased risk (12). Our findings on secretions are consistent with these risk factors. They show a higher frequency of secretors among women with early menarche compared to women with late menarche and that the frequency of secretors among women between 40 and 54 years is higher in those who are still menstruating than in those who have experienced natural or surgical menopause.

Parous women have been shown to have a lower risk of breast cancer than nonparous ones (13, 14). In our study a significantly increased proportion of secretors was found among parous women than among nonparous women. These findings are similar to those of Buehring (3). Our age-specific secretory frequencies point to striking differences between parous and nonparous white (and black) women that are associated with advancing age and that we believe to be of physiologic and clinical relevance. A higher proportion of parous than of nonparous women between 20 and 49 years are secretors; but after age 50 the greater proportion of secretors is among nonparous women, until at ≥ 70 years when approximately 45% of nonparous women are secretors in contrast to 25% of the parous ones. This difference between parous and nonparous women is not seen among Chinese, possibly because of the overall marked decrease in secretion after menopause and the negative association of secretion with dry cerumen.

Age at first pregnancy is believed to be of significance in determining breast cancer risk, with a higher risk among women whose first pregnancy occurs after age 30 (15). We, however, found an association between the frequency of secretors and age at first pregnancy in which the proportion of secretors among postmenopausal women was significantly lower among those who had a late first pregnancy. We cannot offer an adequate physiological explanation for this finding; we can only speculate on some underlying processes. Possibly, early primiparas used more estrogen replacement therapy after menopause. These questions are under investigation.

The source of the presumed estrogenic stimulus for continuing postmenopausal breast fluid secretion is unknown. The smaller proportion of secretors among women with natural or surgical menopause would indicate that premenopausal secretory activity is related to ovarian activity. The secretory activity in many postmenopausal women may be due to estrogen stimulation from endogenous extraglandular sources, use of exogenous estrogen, or, possibly, an age-related altered sensitivity of breast epithelium to estrogen. Our data suggest that estrogen therapy is associated with a higher proportion of secretors among postmenopausal women than among women not using exogenous estrogens.

In contrast to the report by Buehring (3), we found that the use of oral contraceptives is not associated with a reduction in the proportion of secretors, possibly

because Buehring did not make age-specific comparisons of users and nonusers and so could not take into account the relationship of age to the frequency of secretors. We found no statistically significant differences in the frequency of secretors and the use of tranquilizers, although the slightly higher proportion of secretors among postmenopausal users suggests a stimulative effect of these drugs. A much larger sample of women using tranquilizers would be needed to definitively test this relationship.

Fibrocystic breast disease has been reported to be associated with an increase in breast cancer risk (16, 17). Our studies show significantly higher proportions of secretors in all age groups among women who have a clinically palpable fibrocystic disease compared to women who have clinically normal breasts. It is reasonable to interpret these findings as being related to the reported altered estrogen (18) and progesterone levels (19) associated with fibrocystic disease.

Previously, we reported that the frequency of secretors was significantly higher among premenopausal Chinese women of the genetically dominant wet-cerumen phenotype than among those of the dry-cerumen type recessive gene (1). The present study provides ample confirmation of these findings in a larger sample of Chinese women and is supported by similar observations in premenopausal white women. The results demonstrate that the quantity of secretion obtained is associated with cerumen type. A similar relationship between cerumen type and amount of axillary apocrine sweat was reported by Yamashita (20). The evidence supports our earlier hypothesis that genes determining cerumen type and axillary apocrine secretion may also influence breast secretory activity (1).

These investigations indicate that secretory activity of the breast epithelium, as determined by nipple aspiration, is consistent with many reported risk factors for breast cancer. The finding is not unexpected because many presently known risk factors are associated with ovarian and reproductive characteristics of women and because the secretory activity of the breast as indicated by clinical nipple aspiration appears to be a measure of the hormonal effect on the breast. The results lend additional support to our working hypothesis of the pathogenesis of breast cancer, which suggests that the endocrine-dependent secretory activity of the nonlactating breast epithelium can provide a physiologic mechanism whereby initiating mutagens and cocarcinogenic factors can reach the epithelia (21-24). In genetically and metabolically predisposed women, the process may lead to the initiation and promotion of mutant epithelial cells and eventually to the emergence of atypical malignant cells.

REFERENCES

- (1) PETRAKIS NL, MASON L, LEE RE, SUGIMOTO B, PAWSON S, CATCHPOOL F. Association of race, age, menopausal status, and cerumen type with breast secretion in nonlactating women, as determined by nipple aspiration. *J Natl Cancer Inst* 1975; 54:829-834.
- (2) SARTORIUS OW, SMITH HS, MORRIS P, BENEDICT D, FIESEN L. Cytologic evaluation of breast fluid in the detection of breast disease. *J Natl Cancer Inst* 1977; 59:1073-1080.
- (3) BUEHRING GC. Screening for breast atypias using exfoliative cytology. *Cancer* 1979; 43:1788-1799.
- (4) PAPANICOLAOU GB, HOLMQUIST DG, BADER GM, FALK EA. Exfoliative cytology of the human mammary gland and its value in the diagnosis of cancer and other diseases of the breast. *Cancer* 1958; 11:377-409.
- (5) HAAGENSEN CD. Diseases of the breast. Philadelphia: Saunders, 1956.
- (6) LEIS HP JR. Diagnosis and treatment of breast lesions. Flushing, N.Y.: Medical Examinations Publishing Co., Inc., 1970.
- (7) CUTLER M. Tumors of the breast. Their pathology, symptoms, diagnosis and treatment. Philadelphia: Lippincott, 1962.
- (8) PETRAKIS NL, PINGLE U, PETRAKIS SJ, PETRAKIS SL. Evidence for a genetic cline in earwax types in the Middle East and Southeast Asia. *Am J Phys Anthropol* 1971; 35:141-144.
- (9) DEVESSA SS, DIAMOND EL. Association of breast cancer and cervical cancer incidences with income and education among whites and blacks. *JNCI* 1980; 65:515-528.
- (10) WATERHOUSE J, MUIR C, CORREA P, POWELL J, eds. Cancer incidence in five continents. Vol III. Lyon: IARC, 1976 (IARC publication No. 15).
- (11) VORHERR H. The breast. New York: Academic Press, 1974.
- (12) MACMAHON B, COLE P, BROWN J. Etiology of human breast cancer: A review. *J Natl Cancer Inst* 1973; 50:21-42.
- (13) LOGAN WP. Marriage and childbearing in relation to cancer of the breast and uterus. *Lancet* 1953; 264:1199-1202.
- (14) GILLIAM AG. Fertility and cancer of the breast and uterine cervix. *J Natl Cancer Inst* 1951; 12:298-304.
- (15) MACMAHON B, COLE P, LIN TM, LOWE CR, MIRRA AP, RAVNINHAR B, SALBER EJ, VALAORAS VG, YUASA S. Age at first birth and breast cancer risk. *Bull WHO* 1970; 43:209-221.
- (16) DAVIS HH, SIMONS M, DAVIS JB. Cystic diseases of the breast: Relation to carcinoma. *Cancer* 1964; 17:957-978.
- (17) PAGE DL, VANDER ZWAAG R, ROGERS LW, WILLIAMS LT, WALKER WE, HARTMANN WH. Relation between component parts of fibrocystic disease complex and breast cancer. *JNCI* 1978; 61:1055-1063.
- (18) GRATTAROLLA R. Anovulation and increased androgenic activity as breast cancer risk in women with fibrocystic disease of the breast. *Cancer Res* 1978; 38:3051-3054.
- (19) SITRUK-WARE LR, STERKERS N, MOWSZOWICZ I, MAUVAIS-JARVIS P. Inadequate corpus luteal function in women with benign breast disease. *J Clin Endocrinol Metab* 1977; 44:771-774.
- (20) YAMASHITA S. On the offensive odor of the armpit and the soft earwax among Formosans in Canton. *Jap J Anthropol* 1939; 54:444-446.
- (21) PETRAKIS NL. Breast secretory activity in nonlactating women, postpartum breast involution, and the epidemiology of breast cancer. *Natl Cancer Inst Monogr* 1977; 47:161-164.
- (22) ———. Genetic factors in the etiology of breast cancer. *Cancer* 1977; 39:2709-2715.
- (23) PETRAKIS NL, GRUENKE LD, BELEN GC, CRAIG JC, CASTAGNOLI N. Nicotine in breast fluid of nonlactating women. *Science* 1978; 199:303-304.
- (24) PETRAKIS NL, MAACK CA, LEE RE, LYON M. Mutagenic activity in nipple aspirates of human breast fluid. *Cancer Res* 1980; 40:188-189.