The Cause of Breast Cancer*

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THE prominent location, characteristic clinical course and high fatality rate of cancer of the breast make its official mortality returns a particularly reliable index to its actual occurrence.[1] Examination of the data for different times and places reveals variations in its incidence deserving analysis and interpretation that may well be withheld from forms of cancer offering greater difficulty in recognition.[2]

The number of deaths from cancer of the breast in any particular time and place tells us little regarding its relative importance unless this is expressed in terms of the number of persons exposed to such a possibility. The rate for the entire population is usually the most readily ascertainable figure. This may be, however, quite misleading, if variations in the composition of the population affecting this rate are not recognized.[3]

Since nearly 99 per cent of all cancers of the breast occur in women,[4] the rate for the entire population may be expected to be low in regions where males predominate, as in Nevada with 14 males to each 10 females, and high in places where there is an excess of females, as the District of Columbia with only 9 males to each 10 females.[5] This source of error is eliminated in tables in which the deaths are expressed in terms of the number of females living, but for most large populations it is of little importance.

The age distribution of the population constitutes a much greater source of variations and misconceptions. Cancer of the breast, as most other forms of cancer, is almost unknown in childhood and youth, and extremely rare in young adults, but its incidence increases rapidly during middle life and continues to rise up to extreme old age. The greatly higher death rate from breast cancer in older people is shown in practically all statistics that have been examined (Table I).

TABLE I

AGE AND BREAST CANCER, U. S. REGISTRATION STATES, 1930

Age (Years)	*Population*	*Deaths, Breast Cancer*	*Rate per 100,000 Population*	*Per Cent of All Cancers*
0- 4..	10,833,222	2	0.02	0.02
5-14..	23,347,523	3	0.01	0.03
15-24..	21,235,387	21	0.10	0.20
25-34..	18,017,199	290	1.61	2.68
35-44..	16,451,562	1,441	8.76	13.32
45-54..	12,487,707	2,671	21.42	24.68
55-64..	8,086,614	2,935	36.30	27.10
65-74..	4,559,756	2,107	46.20	19.44
75-....	1,841,550	1,354	73.60	12.53
Total ..	116,950,331	10,831	9.27	100.00

The actual number of deaths from breast cancer at the different ages, accordingly, varies with the age composition of the population concerned. Not only will there be a lower incidence of breast cancer in places with relatively few old people than in places where there are more aged inhabitants, but the age at which the majority of

* Read before the Vital Statistics Section of the American Public Health Association at the Sixty-third Annual Meeting in Pasadena, Calif., September 3, 1934.

the cancers actually appear will be correspondingly lower. Thus, in New Mexico, where less than 18 per cent of the population is over 45 years of age, only 61 per cent of the deaths from breast cancer occur after this age; while in New Hampshire, where more than 30 per cent of the population is over 45 years of age, more than 87 per cent of the breast cancer deaths occur in this age group.

A similar change in the age distribution of the persons dying with breast cancer as a result of the aging of the entire population may be seen in the returns for the U. S. Registration States of 1910 during the past two decades (Table II).

TABLE II

BREAST CANCER DEATHS IN THE U. S. REGISTRATION STATES OF 1910

	1911	*1920*	*1930*
Population	*48,295,860*	*56,080,552*	*66,442,606*
Breast Cancer....	3,610	4,900	7,409
Rate All Ages *..	7.5	8.8	11.2
Rate Age 15–44..	2.9	3.1	3.6
Rate Age 45–64..	22.1	25.6	34.0
Rate Age 65–....	49.8	55.0	61.6
% Population over 45	20.9	24.0	25.6
% Breast Cancer over 45.....	80.6	82.7	84.4

* All rates, per 100,000 aggregate population.

Most, but not all of the increase in the proportion of breast cancer deaths occurring above 45 years of age in recent years may be ascribed to this change in the age distribution of the entire population. A small but significant lowering of the mortality rates from this cause at the younger ages, however, and a definite increase in the older age groups, may be seen (Table III). The prolongation of life through palliative surgical and radiation therapy, even in incurable cancer of the breast, may be, at least in part, responsible for this change.[6] This is supported by the fact that the average age of breast cancer cases reported in hospital statistics and in surgical reports is distinctly lower than that found in mortality reports.[7]

TABLE III

BREAST CANCER DEATH RATES PER 100,000 WHITE FEMALES, 1911–1930

METROPOLITAN LIFE INSURANCE COMPANY INDUSTRIAL DEPARTMENT *

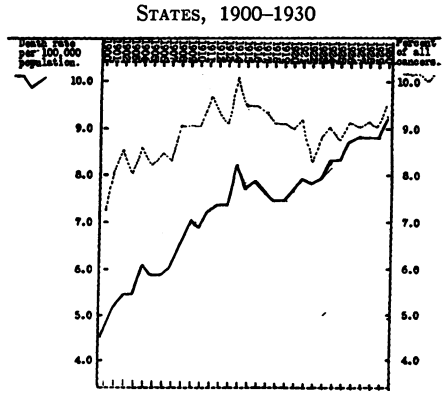
Age Period (Standardized)	*Average Annual Death Rate*	*Mean Annual Change*	*Standard Error*
25–44.....	8.8	—0.09	±0.031
45–74.....	50.9	+0.42	±0.109
1–74.....	12.3	+0.05	±0.021

* Courtesy of Dr. Louis I. Dublin.

The crude mortality rate from breast cancer in the U. S. Registration Areas, as in most other countries, has been steadily rising during the past 30 years. By far the greater part of this change is obviously due to the change in the age distribution of the population. Even in the standardized or the age specific rates, however, an upward trend may be observed (Table II).

With the improvement in diagnostic methods, and the wider use of medical services, more cancers of inaccessible sites are being recognized, with consequent increase in the total number of cancer deaths reported.[8] Accessible tumors such as those of the breast may be expected to share but little in this increased recognition. Accordingly, the fact that there has been no decrease in the proportion of breast cancers to the

FIGURE I—BREAST CANCER IN THE UNITED STATES, 1900–1930



total number of cancers also indicates that there has been an increase in the real prevalence of this condition (Table IV and Figure I).

TABLE IV

BREAST CANCER IN THE UNITED STATES, 1900 TO 1930

Year	Death Rate per 100,000 Population	Percentage of All Cancers
1900	4.5	7.3
1901	5.2	8.0
1902	5.4	8.5
1903	5.4	8.0
1904	6.1	8.6
1905	5.8	8.2
1906	5.8	8.4
1907	6.0	8.3
1908	6.5	9.1
1909	7.0	9.1
1910	6.9	9.1
1911	7.2	9.7
1912	7.3	9.4
1913	7.3	9.2
1914	8.2	10.1
1915	7.7	9.5
1916	7.8	9.5
1917	7.6	9.4
1918	7.4	9.2
1919	7.4	9.2
1920	7.6	9.1
1921	7.9	9.3
1922	7.8	8.3
1923	7.9	8.9
1924	8.3	9.1
1925	8.3	8.8
1926	8.7	9.2
1927	8.8	9.1
1928	8.8	9.2
1929	8.8	9.1
1930	9.2	9.5

Since these mortality figures do not include the increasing numbers of persons who have been successfully operated upon for cancer of the breast in recent years,[9] there seems little doubt that the actual incidence of breast cancer is increasing, at least in this country and Great Britain.

The frequency of breast cancer in different countries varies widely.[10] The data need to be adjusted for the large variations in the age distribution in different countries, but this does not suffice to remove the marked discrepancies noted. Deficiencies in the completeness of death registration and in the accuracy of diagnosis in different countries, it would seem, should lead to an apparent lowering of the absolute incidence of breast cancer, but to an apparent increase in the proportion which it constitutes of all cancers. The close parallelism between these two types of data, however, indicates that the differences observed between countries is not generally due to variations in the age and sex distribution, or in the adequacy of death registration (Table V).

The rarity of all cancers in primitive peoples has been seriously questioned,[11] but as to its relatively infrequent localization in the female breast there appears little doubt. Available information from Japan and India, and from Chile and Uruguay, reveals breast cancer in these countries extremely seldom as compared to the European countries, while the English speaking countries report much higher figures.[12]

Different states in the United States show similar differences, which may not be entirely explained away by variations in the age and sex distribution of the population, or by differences in the adequacy of registration and diagnosis, although these may play a part. Thus, in 1920 the breast cancers in Massachusetts, with an adjusted mortality rate of 11.2 per 100,000 population, constituted 11.3 per cent of all cancers in that state, while in Mississippi, with an adjusted mor-

TABLE V

BREAST CANCER IN DIFFERENT COUNTRIES, 1930

Country	Rate per 100,000 Females	Per Cent of All Cancers	Birth Rate per 1,000 Population	
			1930	1910
England and Wales	29.2	19.1	16.3	23.8
Scotland	23.4	15.0	19.5	26.1
Denmark, urban	22.6	17.3	18.7	25.6
New Zealand	22.4	20.0	18.8	26.0
Switzerland	21.2	11.0	17.2	23.9
Netherlands	19.3	13.8	23.1	28.2
United States	17.6	16.1	18.9	24.9
Australia	16.5	17.2	19.9	28.1
Ireland	16.0	16.0	20.2	22.6
Norway	14.5	7.4	24.5	25.3
Canada	11.5	17.6	24.5	26.6
Italy	6.0	10.0	26.2	31.7
Spain	3.6	7.0	29.0	31.2
Ceylon	3.6	7.6	39.0	38.1
Japan	1.8	3.0	32.4	34.1
Chile	1.2	2.0	39.8	37.0

tality rate of 3.4 per 100,000 they constituted only 6.8 per cent of all cancers.[13]

In general, breast cancer mortality rates have been higher in urban than in rural districts, in northern than in southern states, and in whites than in negroes. Although a large part of the apparent differences in the crude rates disappears when they are adjusted for age distribution, the general relations remain, and the proportion of breast cancers to all cancers shows the same relations (Table VI).

TABLE VI

BREAST CANCER AND THE BIRTH RATE IN THE UNITED STATES

State	*Breast Cancer per 100,000 Females, Age 45+* 1930	*Deaths per 100 of All Cancer* 1930	*Births per 1,000 Females, Age 15–44* 1930	1900
Massachusetts	109.4	11.2	70	90
Rhode Island	108.9	10.5	73	93
New York	107.3	10.5	66	93
Connecticut	103.5	10.7	71	96
California	99.4	10.5	62	82
Maryland	95.8	10.1	78	111
Idaho	92.5	11.0	95	155
New Jersey	91.4	10.0	68	102
Washington	90.4	9.5	63	106
Minnesota	89.9	8.4	79	139
Oregon	89.8	9.6	62	94
Missouri	89.5	9.1	71	110
Michigan	89.0	10.0	87	104
New Hampshire	88.6	9.3	81	90
District of Col.	88.4	9.1	63	70
Ohio	88.2	10.1	75	96
Montana	87.8	9.8	85	123
Illinois	87.7	10.1	67	105
Iowa	86.2	9.6	76	113
Kansas	83.9	7.8	78	115
Colorado	83.1	9.2	77	101
Utah	82.4	9.4	113	160
Wyoming	82.3	9.3	89	133
Nebraska	82.1	8.6	84	124
Wisconsin	82.0	8.2	84	123
Delaware	80.0	9.6	81	104
Pennsylvania	79.2	8.9	83	112
Vermont	72.5	8.2	94	96
Maine	71.0	7.1	95	92
Indiana	70.6	8.5	80	105
Louisiana	70.2	9.0	81	134
Florida	69.1	10.0	73	138
Alabama	68.6	10.7	101	142
South Dakota	67.2	8.3	80	150
Kentucky	66.3	9.3	101	133
Virginia	57.6	8.7	98	132
New Mexico	56.2	9.0	126	163
Georgia	54.3	8.8	84	147
Tennessee	53.1	8.7	83	134
Mississippi	52.7	8.3	99	139
West Virginia	52.0	7.5	107	150
Arkansas	50.0	9.6	93	149
North Carolina	49.6	8.3	102	150
Arizona	42.4	5.6	102	133
Oklahoma	40.5	6.6	110	160
Nevada	37.5	4.1	75	100
South Carolina	36.5	7.0	94	152
North Dakota	35.7	4.4	98	168

It has been repeatedly noted in recent years that cancer of the breast is relatively much more frequent in single than in married women.[14] It appears also to be true that among the married women cancer of the breast is more often encountered among the nullipara than among those who have borne children, and there are indications that it is even less frequent among those who have had a large number of children.[15]

These last observations may be readily harmonized with the foregoing mortality statistics, and go far to clarify the differences that are observed. If childbearing and lactation tends to prevent cancer of the breast, it may be readily expected that the incidence of cancer of the breast in recent years would rise in most places with a falling birth rate, and that the countries with higher birth rates, like Japan, or the southern and rural districts in the United States, or the negroes and other population groups having a higher birth rate, would still have a low incidence of cancer of the breast.

If the states are arranged in the order of their breast cancer mortality rates for the female population over the age of 45 only, thus avoiding discrepancies due to age and sex differences, there is found a very high inverse correlation with that obtained by taking them in the order of their birth rate for the female population between the ages 15 and 45. In other words, generally speaking, states with a high breast cancer rate have a low birth rate, and *vice versa*.

Logically, of course, we may expect that the birth rate of 30 years or so prior, when the women now developing

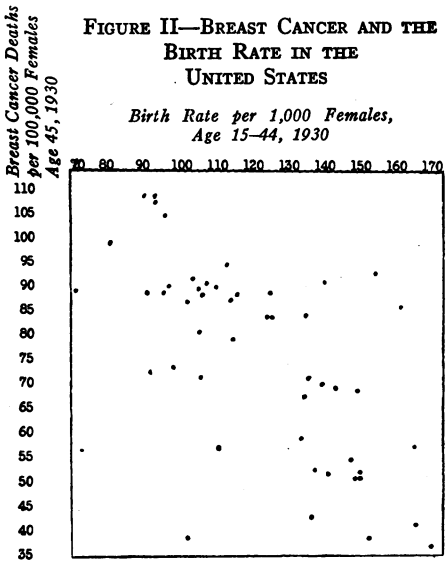


FIGURE II—BREAST CANCER AND THE BIRTH RATE IN THE UNITED STATES

cancer of the breast were in their childbearing age, would better reflect the influences bearing on them than that today. Unfortunately, the U. S. Registration Area for Births is only 18 years old, and has only recently included all of the states. The census for 1900,[16] however, included an attempt at an approximation of the birth rate in the various states at that time, and this may be taken, for want of better, for comparison. It may be seen that although the actual birth rate has decreased markedly in practically all parts of the country, the relative order of the different states shows little change not accounted for by differences in the age and sex composition of the people. Accordingly we find again that the states with the high breast cancer rate in 1930 generally showed a low birth rate in 1900, and the states with the high birth rate in 1900 are found to have a low breast cancer rate in 1930 (Table VI and Figure II).

Available data for the different countries of the world agree with this finding (Table V). Arranging the various countries in the order of increasing birth rate in 1900, or before the war, gives almost the same list as that in the order of increasing mortality rate from cancer of the breast, or the ratio of breast cancer to total cancers. A superficial inquiry into the different countries involved also emphasizes the fact that cancer of the breast is more prevalent where early weaning of the infant is the rule, and is less often met with where breast feeding is common and prolonged.

Clinical investigation of large groups of women suffering from cancer of the breast confirms and amplifies these observations.[17] Not only is cancer of the breast found with disproportionate frequency in single women and in nulliparа, but it is also more prevalent among women who have had miscarriages or stillbirths or for some other reason, although pregnant, have failed to nurse their young. Particularly suggestive are the reports of cases where cancer has developed in an unused breast, and not in the contralateral lactating breast.

These are objective facts gleaned from an impersonal survey of official records and clinical data by a number of different workers, and confirmed by a series of case records personally examined for the present study. They indicate quite definitely that the retention of milk and other secretions in the breast due to non-lactation may be a potent factor in the production of many, if not all, cases of carcinoma of the mammary gland, and that the removal of such substances by suckling exerts a definite prophylactic effect against the development of such tumors.

Animal experimentation sheds further light on this phenomenon. White mice that have had their young removed at birth, so that they cannot suckle them, develop mammary carcinoma quite similar to the breast cancers in women. That this is due to local retention of secretions and not to a general endo-

crine disturbance is shown by the fact that white mice that have had their breasts occluded on one side only by ligature develop cancer on that side, and not on the other. These findings, first reported by Bagg nearly a decade ago,[18] have been amply confirmed in our experience at Olive View (Table VII).

TABLE VII

EXPERIMENTAL INDUCTION OF MAMMARY CARCINOMA IN MICE

Olive View, Calif., 1932–1934

Procedure	*Total Number of Mice*	*Average Number of Litters*	*Average Survival Period, Months*	*Number Developing Breast Cancer*	*Per Cent Developing Cancer*
Young removed at birth.....	18	7	18	10	55
Nipples on left side ligated, suckling with right side	18	4	15	6	33
Normal breeding controls	18	5	18	0	0

Recent investigations into the carcinogenic actions of tars and related substances have shown that a reduced derivative of cholesterol is capable of producing cancer just as effectively as are some of the coal tar and other phenanthrene compounds.[19] Cholesterol is present in the ducts of the non-lactating female breast of the virgin, as well as in the secretions of the lactating breast,[20] and in the absence of the normal drainage that comes with lactation, it may undergo the reductions that would lead to the development of carcinogenic properties. Childbirth and lactation constitute, accordingly, a natural protection against this endogenous carcinogenic agent.

SUMMARY

Analysis of available vital statistics shows that cancer of the breast is strikingly associated with a low birth rate. Clinical investigation confirms this finding and indicates that it is more particularly related to lack of drainage of the mammary glands. Animal experimentation shows that this is due, not to endocrine derangement subsequent to the lack of suckling, but simply to the local retention of secretions in the non-lactating breast. Recent chemical investigations have revealed the existence of chemical substances in the normal breast secretions which may, after many years of retention, exert carcinogenic effects similar to those well known to result from the exogenous application of certain coal tars. The results of the clinical, biological and chemical investigations concur with those of the analysis of the vital statistics in emphasizing the etiological rôle of retained mammary secretions in the development of cancer of the breast.

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