

# Breast Cancer Incidence and Nutritional Status with Particular Reference to Body Weight and Height<sup>1</sup>

F. de Waard

Department of Epidemiology, Institute of Social Medicine, University of Utrecht, Utrecht, The Netherlands

## Summary

The epidemiological literature on breast cancer is reviewed with particular emphasis on the possible etiological role of nutritional status as reflected by weight and height. The results of a prospective study and preliminary results of a population-based case-control study seem to indicate that body size or body mass rather than overweight (obesity) is a risk factor. A considerable proportion of the differences in incidence between the Netherlands and Japan can be explained by differences in body mass. The biological mechanisms mediating nutritional status and breast cancer are believed to be of an endocrinological-metabolic nature.

## Introduction

Environmental factors apparently have a profound influence on breast cancer risk. This may seem strange to those who consider a hormone-related cancer to fall into a class of endogenous etiology. Throughout this paper, I will stress that environmental factors, by affecting nutritional status, have an effect upon hormonal metabolism in animals including humans.

Convincing evidence for the existence of environmental factors in breast cancer etiology is available in the form of incidence patterns throughout the world. It is well known (10, 11) that cancer of the breast is much more frequent in Western Europe and Northern America than in Asia and Africa, with Eastern and Southern Europe and Latin America taking an intermediate position. Australians, New Zealanders, and South African Whites have an entirely Western incidence level.

Japan, although a highly industrialized country, still provides an example of the Asian type of breast cancer incidence, the age-specific curve of incidence bending down at menopausal age. However, when Japanese migrate to Hawaii or California, their incidence rate gradually increases; the adaptation to Western ways of life apparently proceeds more slowly than in the case of colon cancer (1), a cancer that is highly correlated geographically with mammary cancer.

In the old textbooks, international differences in breast

cancer frequency were often interpreted as being the result of different lactation experience. In the international study by MacMahon *et al.* (19, 20), statistical evidence was provided that lactation is probably not a factor in human breast cancer etiology, whereas the case-control differences regarding parity could largely be explained by the determinant of age at 1st pregnancy.

In order to be of practical importance in public health, a factor bearing a certain amount of risk should be sufficiently prevalent in the population. This notion has been given the name of attributable risk by epidemiologists. Thus, differences in breast cancer incidence between, say, Japan and the United States, could be partly explained by age at 1st birth only if (a) this factor would be operating in both countries, and (b) the relative frequency distributions of age at 1st baby were sufficiently different between countries. The former condition is true; the latter, as Yuasa and MacMahon (30) have shown, is not fulfilled. Neither did we find such differences between Tokyo and samples from the Netherlands (Chart 1).

Thus, after decades of painstaking efforts, we seem to be more ignorant than ever about possible explanations of international differences in breast cancer incidence.

## A Hypothesis on the Effect of Nutrition

In 1960 and 1964 (7, 8) we published a hypothesis on the possible relationship between nutritional status and breast cancer risk. It was assumed that there are 2 etiological types of mammary cancer; one mainly restricted to reproductive life in which ovarian factors are present, the other type being more prevalent at menopausal and postmenopausal age, in which hormonal factors related to overnutrition play a role. The degree of affluence through overnutrition and obesity was to determine the slope of the age-specific incidence curve of this 2nd type of breast cancer. This model for explaining the differences in both level and shape of the incidence curve between countries is presented in Chart 2. By adding linear incidence figures at each age to the figures of Miyagi prefecture, Japan, thereby increasing the slope of the straight line in each successive diagram, one obtains incidence curves strongly resembling those seen in countries of increasing affluence. Different ways of presenting the model have been attempted in previous papers (3, 4).

The hypothesis has been tested partly by case-control and prospective studies. A prospective study (6) conducted in

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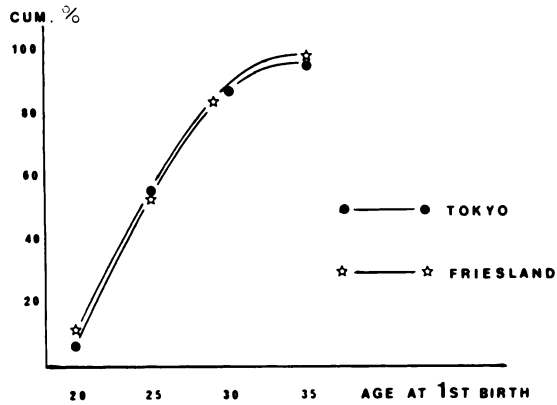


Chart 1. Cumulative (CUM.) percentage distribution of age of women upon birth of first child.

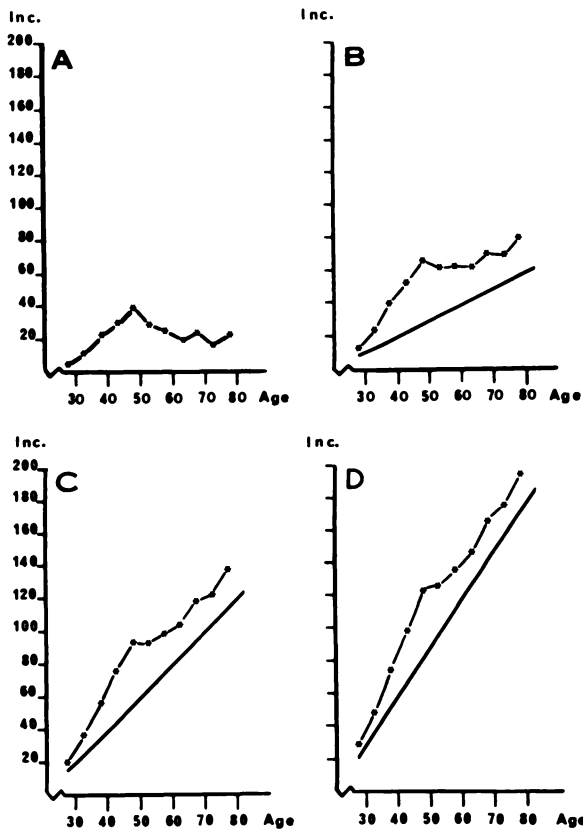


Chart 2. Proposed model of breast cancer incidence (Inc.) assuming 2 etiologies types: (a) an "ovary-related" type with fixed incidence form part A of the chart and (b) a nutrition-related type of linear form with slope depending on the degree of nutritional abundance. Incidence rates of the first type have been added to those of the second in parts B, C, and D of the chart. Consult the text for further explanation.

women 55 to 75 years of age at entry has taught us several important facts (Tables 1 to 3): (a) body weight is a determinant of breast cancer risk in postmenopausal women; (b) body height is also an important risk factor. By "correcting" weight for height a substantial part of the risk disappears (Table 2). Thus, it is not so much the overweight women who are at risk for breast cancer but rather those who are both heavy and tall. Body surface area reflects body

Table 1  
Results of the prospective study (6)

	< 60 kg	60-69 kg	> 70 kg	Total
> 165 cm	(0.0) <sup>a</sup>	2.1	3.6	3.1
	0.01	0.05	0.16	0.22
	0.00	0.04	0.31	0.35
160-164 cm	1.7	2.8	2.8	2.7
	0.02	0.09	0.18	0.29
	0.01	0.12	0.25	0.38
< 160 cm	1.0	1.8	1.9	1.7
	0.10	0.20	0.21	0.51
	0.00	0.12	0.14	0.26
Total	1.0	2.1	2.7	2.3
	0.13	0.34	0.55	1.02 <sup>b</sup>
	0.01	0.28	0.70	0.99 <sup>b</sup>

<sup>a</sup> In each of the cells the upper figure gives the risk ratio relative to that experienced by women < 60 kg and < 160 cm, the middle figure gives the proportion of women at risk, and the lower figure states the proportion of the excess risk relative to the total risk attributable to the weight-height factor complex.

<sup>b</sup> Not equal to 1.00 due to rounding-off procedure.

Table 2

Relative risk of breast cancer in postmenopausal women according to degree of overweight (Quetelet's index)<sup>a</sup>

Quetelet's index	Risk ratio
< 25	1.0
25-26	0.8
27-28	0.9
29-30	1.3
> 31	1.2

<sup>a</sup> See also Table 6 in Ref. 6.

Table 3

Relative risk of breast cancer in postmenopausal women according to estimated body surface area

Surface area (sq m)	Risk ratio
< 1.64	1.0
1.64-1.75	2.5
1.76-1.87	2.1
1.88-1.97	3.0
> 1.98	3.8

size; it can be estimated by synergistic interplay of weight and height (14). Relative risk of breast cancer according to body surface area in our prospective study is shown in Table 3.

In view of the above-mentioned principles regarding differences in incidence attributable to postulated factors, the following questions have to be answered. (a) Has the effect of weight and height on breast cancer risk been demonstrated outside the Netherlands? The answer is positive since MacMahon *et al.* (19) included these measurements in their international study. A marked effect of weight (particularly strong in postmenopausal women) and a smaller effect of height were observed in São Paulo, Brazil

(22), and in Taiwan (18). In Athens, Greece, not only weight and height (29) but also overweight, as defined by Quetelet's index (weight/height<sup>2</sup>), was associated with increased risk. The findings in Slovenia, Yugoslavia (24), and the United States (28, 31, 32) were less clear. (b) Are the differences in weight and height between populations in various countries large enough to account for a substantial proportion of the international differences in breast cancer risk? The answer is again positive. A large body of data from epidemiological and anthropological studies (e.g., Ref. 21) is ample documentation of this kind of variation in body weight and height. Not only weight but also height depends on environmental factors. Recent trends in Japan (15) seem to indicate that the short stature of the Japanese is not so much a racial characteristic as it is the result of exogenous (probably nutritional) factors. The long latency period of the expected epidemic of breast cancer in Californians of Japanese origin might be explained by the fact that only the Nisei and those Issei who migrated before puberty could attain American levels of height, which (in conjunction with increased body weight) seems to be needed for maximum incidence of breast cancer.

### Recent Studies

Recent work by the Cancer Registry in the Netherlands is being reported here as an attempt to quantitate the order of magnitude of the differences in breast cancer incidence attributable to body weight and height.

The Cancer Registry has been operating in the cities of Rotterdam and The Hague and in the province of Friesland. Over the last 2 years we have collected data on the weight, height, and age of women upon birth of the first child in a large proportion of all breast cancer cases occurring in those areas and in samples from the normal population taking part in population-screening programs (routine chest X-ray examinations and special surveys).

### Methods

In an area where a population-based cancer registry is operating it is possible, by comparing all (or almost all) cases with normal population controls, to estimate not only relative risks of certain factors but also absolute risks (namely, incidence rates) in persons having these factors. If we define  $I_t$  as incidence in total population,  $I_e$  as incidence among persons exposed to a factor,  $I_o$  as incidence among persons not exposed to this factor,  $p$  as proportion of population exposed, and  $r$  as relative risk when exposed, then:

$$I_t = pI_e + (1 - p)I_o$$

and since  $I_e = rI_o$

$$I_t = prI_o + (1 - p)I_o$$

$$I_t = (pr + 1 - p)I_o$$

$$I_o = I_t / (pr + 1 - p)$$

$$I_e = rI_o$$

$I_t$  is known from the registry, at each age;  $r$  can be computed for each age group by comparing cases with controls; and  $p$  is estimated from the proportion of persons having the risk factor among controls.

Up to now we have been rather successful in securing the desired information from the province of Friesland. This is a rural province (which does not mean isolated or deprived of facilities) in the northern part of the Netherlands. In just 90% of cases data on weight and height have been obtained. The population-based case-control study presented here is based on 332 new breast cancer patients and 1982 controls aged 35 to 74 years.

### Results

According to the above-mentioned formula, we have split up the age-specific incidence curve of breast cancer in Friesland in curves for certain subpopulations, e.g., those weighing less than 70 kg versus those weighing 70 kg or more (Chart 3).

With the same procedure, curves have been computed for women measuring <165 cm and >165 cm, respectively (Chart 4). By choosing a different dividing line between "small" and "tall" women in the dichotomy, namely, at 160 cm or at 170 cm, the effect of height can be studied in more

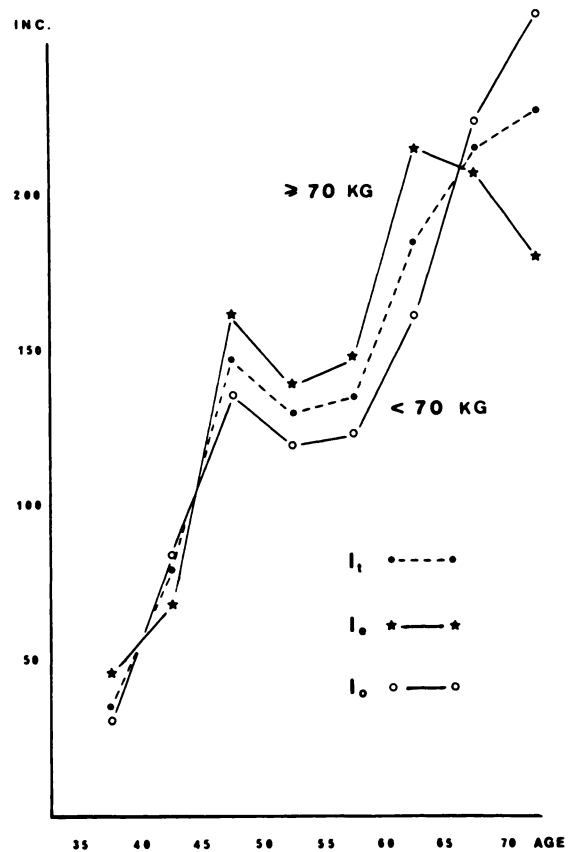


Chart 3. Separation of the age-specific incidence (*Inc.*) curve of breast cancer in the province of Friesland (1968 to 1972) into curves for those with body weight <70 kg and >70 kg, respectively.  $I_t$ , incidence in total population;  $I_e$ , incidence among persons exposed to a factor;  $I_o$ , incidence among persons not exposed to a factor.

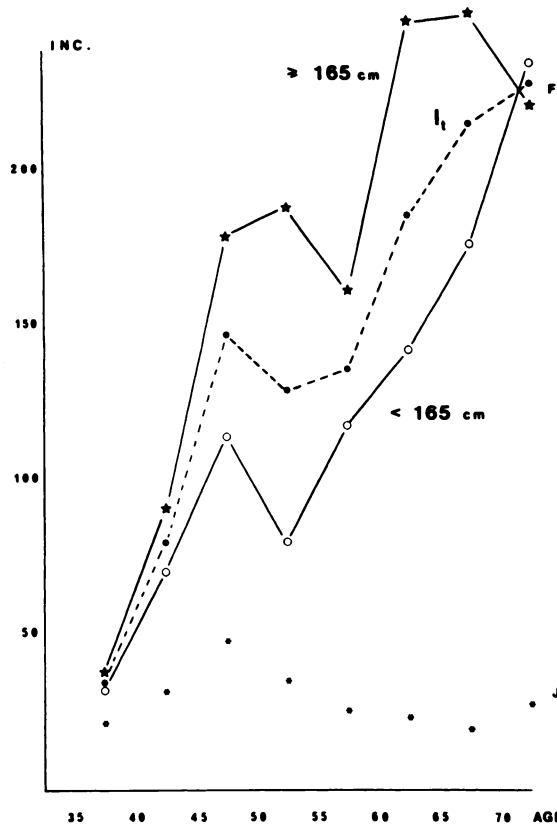


Chart 4. Separation of the age-specific incidence (*Inc.*) curve of breast cancer in the province of Friesland (1968 to 1972) into curves for those with body height <165 cm and >165 cm, respectively. At the bottom, age-specific incidence figures for Miyagi prefecture, Japan, have been plotted.

detail (Chart 5). It will be seen that Clemmesen's hook (2) can be manipulated by choosing different cutoff points for height.

The effect of overweight on the curve has been studied after computation of Quetelet's index (weight/height<sup>2</sup>) of cases and controls. The Belgian statistician Quetelet (1796 to 1874) devised this index because it is almost uncorrelated with height. Its value has been confirmed in recent studies in men (16), but in women the index weight/height may be an equally acceptable alternative (12). The latter corrective manipulation for height leaves a larger share for the overweight factor in breast cancer epidemiology.

In the present study the overweight factor (on the basis of Quetelet's index) does not seem to contribute to breast cancer risk. The crude effect of height (including the covariation of weight) apparently accounts for all risk attributable to body size or body mass. In our prospective study (6) the effect of overweight proved to be quite small.

In Charts 4 and 5 the incidence curves for Friesian women shorter than 160 or 165 cm may be compared with the curve for the inhabitants of Miyagi prefecture, Japan (11). Since most Japanese women >30 years of age are shorter than 160 cm (26) (Chart 6), these curves may provide an impression of the proportion of breast cancer risk attributable to body size at various ages. Results of the studies in

Rotterdam and The Hague, although less striking than those in Friesland, conform to the observed risk pattern.

**Discussion**

The striking effect of height, although interesting to the epidemiologist, may at first sight be rather puzzling to the biologist who tries to understand mechanisms of cancer initiation and promotion.

In our original hypothesis (7, 8) we focused on overweight as a risk factor because a relationship between

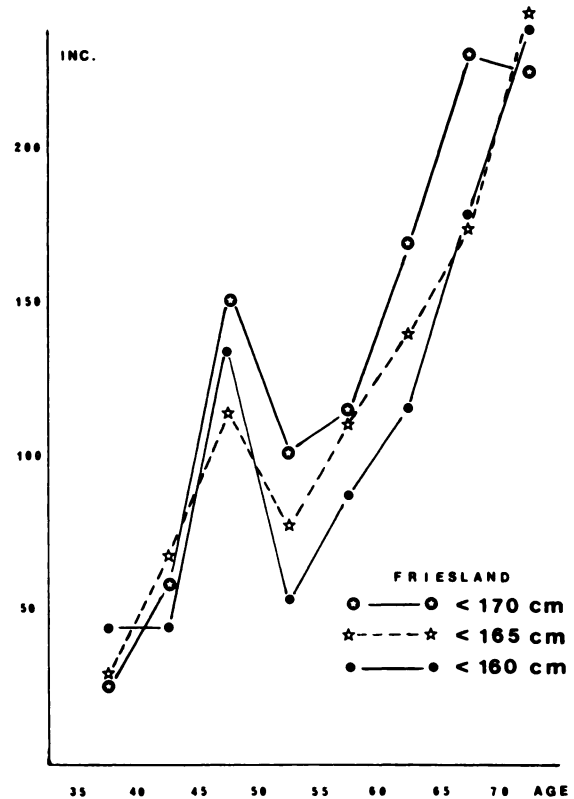


Chart 5. Age-specific incidence (*Inc.*) curves of breast cancer in Friesland for populations of various heights (upper cutoff levels chosen at 160, 165, and 170 cm, respectively).

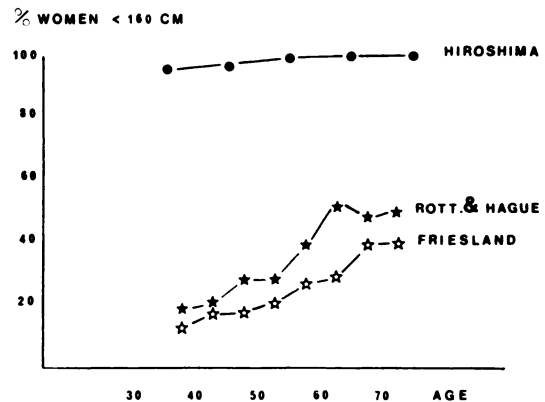


Chart 6. Percentages of women with body height <160 cm in the Netherlands and Japan, according to age. *ROTT.*, Rotterdam.

postmenopausal estrogenic stimulation and overweight had been found. These observations got a firm biological basis when it was shown by Siiteri *et al.* (27), Poortman *et al.* (23), and others that estrogen production after the menopause does not take place in the ovaries or adrenals but in peripheral tissues; adipose tissue is capable of converting androstenedione into estrone (25). Whereas these findings are an attractive explanation for the relationship between obesity and endometrial cancer, the problem of breast cancer seems to be more complex.

Our hopes that hormonal cytology could provide a simple lead to the question of breast cancer risk in postmenopausal women proved idle. In assessing estrogenic status in our prospective study, we distinguished among 3 classes of smears: atrophic, intermediate, and karyopyknotic (estrogenic) smears. Whereas both intermediate and karyopyknotic smears were associated with overweight (5, 9), only the intermediate smears predicted a small increase in breast cancer risk (4). Since estrogenic activity in cytological smears largely reflects effects of estriol, we have wondered whether the ideas of Lemon (17) on a possible protective effect of estriol could offer some explanation for these results.

The recent insight gained in peripheral metabolism of steroids leads us to suggest that more attention be given to hormones in relation to lean body mass. Height correlates fairly well with lean body mass,  $r$  being in the order of 0.5 (13).

A further lead to biological mechanisms might be derived from the fact that several endocrine and metabolic functions (*e.g.*, basal metabolic rate and cortisol production rate) seem to correlate better with body surface area than with body weight. The rationale for using surface area is often lacking except for the fact that it is estimated from both weight and height.

With the modifications described above, we adhere to the hypothesis that socioeconomic factors inherent to Western ways of life through nutrition affect body mass and composition, thereby changing endocrine and metabolic processes that determine breast cancer risk.

## References

- Buell, J. L. Changing Incidence of Breast Cancer in Japanese American Women. *J. Natl. Cancer Inst.*, *51*: 1479-1483, 1973.
- Clemmesen, J. Carcinoma of the Breast. Results from Statistical Research. *Brit. J. Radiol.*, *21*: 583-590, 1948.
- de Waard, F. The Epidemiology of Breast Cancer; Review and Prospects. *Intern. J. Cancer*, *4*: 577-586, 1969.
- de Waard, F. Nurture and Nature in Cancer of the Breast and the Endometrium. *In*: R. Doll, I. Vodopija, and W. Davis (eds.), *Host Environmental Interactions in the Etiology of Cancer in Man*, pp. 121-130. Lyon: International Agency for Research on Cancer, 1973.
- de Waard, F., and Baanders-van Halewijn, E. A. Cross-Sectional Data on Estrogenic Smears in a Postmenopausal Population. *Acta Cytol.*, *13*: 675-678, 1969.
- de Waard, F., and Baanders-van Halewijn, E. A. A Prospective Study in General Practice on Breast Cancer Risk in Postmenopausal Women. *Intern. J. Cancer*, *14*: 153-160, 1974.
- de Waard, F., Baanders-van Halewijn, E. A., and Huizinga, J. The Bimodal Age Distribution of Patients with Mammary Cancer. *Cancer*, *17*: 141-151, 1964.
- de Waard, F., Laive, J. W. J., and Baanders-van Halewijn, E. A. On the Bimodal Age Distribution of Mammary Carcinoma. *Brit. J. Cancer*, *14*: 437-451, 1960.
- de Waard, F., Pot, H., Tonckens-Nanninga, N. E., Baanders-van Halewijn, E. A., and Thijssen, J. H. H. Longitudinal Studies on the Phenomenon of Postmenopausal Estrogen Production. *Acta Cytol.*, *16*: 273-278, 1972.
- Doll, R., Payne, P., and Waterhouse, J. H. *Cancer Incidence in Five Continents*. Berlin: Springer-Verlag, 1966.
- Doll, R., Muir, C., and Waterhouse, J. H. *Cancer Incidence in Five Continents*. Vol. II. Berlin: Springer-Verlag, 1970.
- du Florey, C. V. The Use and Interpretation of Ponderal Index and Other Weight-Height Ratios in Epidemiological Studies. *J. Chronic Diseases*, *23*: 93-103, 1970.
- Forbes, G. B. Stature and Lean Body Mass. *Am. J. Clin. Nutr.*, *27*: 595-602, 1974.
- Gehan, E. A., and George, S. L. Estimation of Human Body Surface Area from Height and Weight. *Cancer Chemotherapy Rept.*, *54*: 225-235, 1970.
- Insull, W., Oiso, T., and Tsuchiya, K. Diet and Nutritional Status of Japanese. *Am. J. Clin. Nutr.*, *21*: 753-777, 1968.
- Keys, A., Fidanza, F., Karonen, M. J., Kimura, N., and Taylor, H. L. Indices of Relative Weight and Obesity. *J. Chronic Diseases*, *25*: 329-343, 1972.
- Lemon, H. M. Abnormal Estrogen Metabolism and Tissue Estrogen Receptor Proteins in Breast Cancer. *Cancer*, *25*: 423-435, 1970.
- Lin, T. M., Chen, K. P., and MacMahon, B. Epidemiologic Characteristics of Cancer of the Breast in Taiwan. *Cancer*, *27*: 1497-1504, 1971.
- MacMahon, B., Cole, P., Lin, T. M., Lowe, C. R., Mirra, A. P., Ravnihar, B., Salber, E. J., Valaoras, V. G., and Yuasa, S. Age at First Birth and Breast Cancer Risk. *Bull. World Health Organ.*, *43*: 209, 1970.
- MacMahon, B., Lin, T. M., Lowe, C. R., Mirra, A. P., Ravnihar, B., Salber, E. J., Trichopoulos, D., Valaoras, V. G., and Yuasa, S. Lactation and Cancer of the Breast, a Summary of an International Study. *Bull. World Health Organ.*, *42*: 185, 1970.
- Meredith, H. V. Worldwide Somatic Comparisons among Contemporary Human Groups of Adult Females. *Am. J. Phys. Anthropol.*, *34*: 89-132, 1971.
- Mirra, A. P., Cole, P., and MacMahon, B. Breast Cancer in an Area of High Parity: São Paulo, Brazil. *Cancer Res.*, *31*: 77-83, 1971.
- Poortman, J., Thyssen, J. H. H., and Schwarz, F. Androgen Production and Conversion to Estrogens in Normal Postmenopausal Women and in Selected Breast Cancer Patients. *J. Clin. Endocrinol. Metab.*, *37*: 101-109, 1973.
- Ravnihar, B., MacMahon, B., and Lindtner, J. Epidemiologic Features of Breast Cancer in Slovenia. *European J. Cancer*, *7*: 295-306, 1971.
- Schindler, A. E., Ebert, A., and Friedrich, E. Conversion of Androstenedione to Estrone by Human Fat Tissue. *J. Clin. Endocrinol. Metab.*, *35*: 627-630, 1972.
- Seigel, D. Height-Weight Tables Hiroshima and Nagasaki. Hiroshima-Nagasaki: Atomic Bomb Casualty Commission Technical Report, pp. 1-17, 1962.
- Siiteri, P. K., Hemsell, D. L., Edwards, C. L., and MacDonald, P. C. Estrogen and Endometrial Carcinoma. *In*: R. O. Scow (ed.), *Proceedings of the Fourth International Congress of Endocrinology*, Washington, D. C., pp. 1237-1242. Amsterdam: Excerpta Medica, 1973.
- Stavraky, K., and Emmons, S. Breast Cancer in Premenopausal and Postmenopausal Women. *J. Natl. Cancer Inst.*, *53*: 647-655, 1974.
- Valaoras, V. G., MacMahon, B., Trichopoulos, D., and Poly-

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- chronopoulou, A. Lactation and Reproductive Histories of Breast Cancer Patients in Greater Athens. *Intern. J. Cancer*, 4: 350-363, 1969.
30. Yuasa, S., and MacMahon, B. Lactation and Reproductive Histories of Breast Cancer Patients in Tokyo, Japan. *Bull. World Health Organ.*, 42: 195-204, 1970.
31. Wynder, E. L. Current Concepts of the Aetiology of Breast Cancer. *In: A. P. M. Forrest and P. B. Kunkler (eds.), Proceedings of the First Tenovus Symposium, Cardiff*, pp. 32-49. Baltimore: Williams & Wilkins, 1968.
32. Wynder, E. L., Bross, I. J., and Hirayama, T. A Study of the Epidemiology of Cancer of the Breast. *Cancer*, 13: 559-601, 1960.