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Cancers of the Breast, Endometrium and Ovary: Geographic Correlations

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Abstract—*Patterns of incidence of breast, endometrial and ovarian cancer show strong similarities in both international and inter-regional comparisons, similarities readily confirmed by the calculation of coefficients of correlation. Migrant studies suggest that environmental factors are more important than genetic differences between populations. Correlation studies have shown that dietary factors can explain much of the international variation, and most suspicion has fallen on dietary fat. Differences in fertility between populations also correlate with the variations in incidence. For breast cancer, the latter may be an important determinant of variation within countries in the pre-menopausal age group, with dietary differences accounting for variations in post-menopausal rates internationally. There is scope for improving upon earlier studies, and for investigating the relative contributions of diet and fertility to the geographic patterns of endometrial and ovarian cancers.*

1. INTERNATIONAL PATTERNS

THERE ARE estimated to be 572,000 new cases of breast cancer in the world per year (18.4% of all female cancers), 61% of which occur in the so-called developed countries [1]. Cancers of the endometrium and ovary are considerably less frequent, comprising 4.8% and 4.4% of female cancers respectively.

Internationally, the patterns of occurrence of the three cancers have marked similarities, as shown in Figs. 1–3 [2].

1.1. *Breast cancer*

The highest recorded incidence rates are in Hawaiian women (age-standardized rate 93.9 per 100,000) and in U.S. white women (70–90 per 100,000). Incidence rates are high (60–90 per 100,000) in most industrialized countries, with the notable exception of Japan, and in southern Brazil and Argentina. In these populations, breast cancer is responsible for more than 25% of all cancers in women. Incidence rates are intermediate (40–60 per 100,000) in eastern and southern Europe, and low (less than 40) in central and tropical South America, Africa and Asia.

The ranking of mortality rates internationally [3] contrasts a little with incidence. The highest rates are in Europe (U.K., Scandinavia, The Netherlands), and the U.S.A. appears rather lower in the sequence with age standardized rates only slightly above those in Argentina, and inferior to those of Uruguay.

1.2. *Corpus uteri*

Cancer of the corpus uteri is now numerically slightly more important than cervix cancer in developed countries [1]. The highest recorded incidence rates are from La Plata in Argentina with an age standardized rate of 31.1 per 100,000 [4]. Incidence rates elsewhere are shown in Fig. 2. They are highest in U.S. whites, in Canada, in Hawaiians and Maoris and in western Europe. Low rates of incidence (2–4 per 100,000) are seen in Asian populations, except for Jews in Israel, and Chinese in Singapore and Hong Kong.

1.3. *Ovary*

Cancer of the ovary includes several distinct histopathological entities, with probably different aetiologies. However, when incidence rates for the entire age range are considered, the great majority of tumours are epithelial in origin. The pattern of incidence is shown in Fig. 3. The highest rates are reported among white females in northern and western Europe and in North America, where age-standardized rates are 8–15 per 100,000. In the three Nordic countries shown in Fig. 3, incidence rates exceed 14 per 100,000; however, in Finland the rate is less than 10. Incidence is also high

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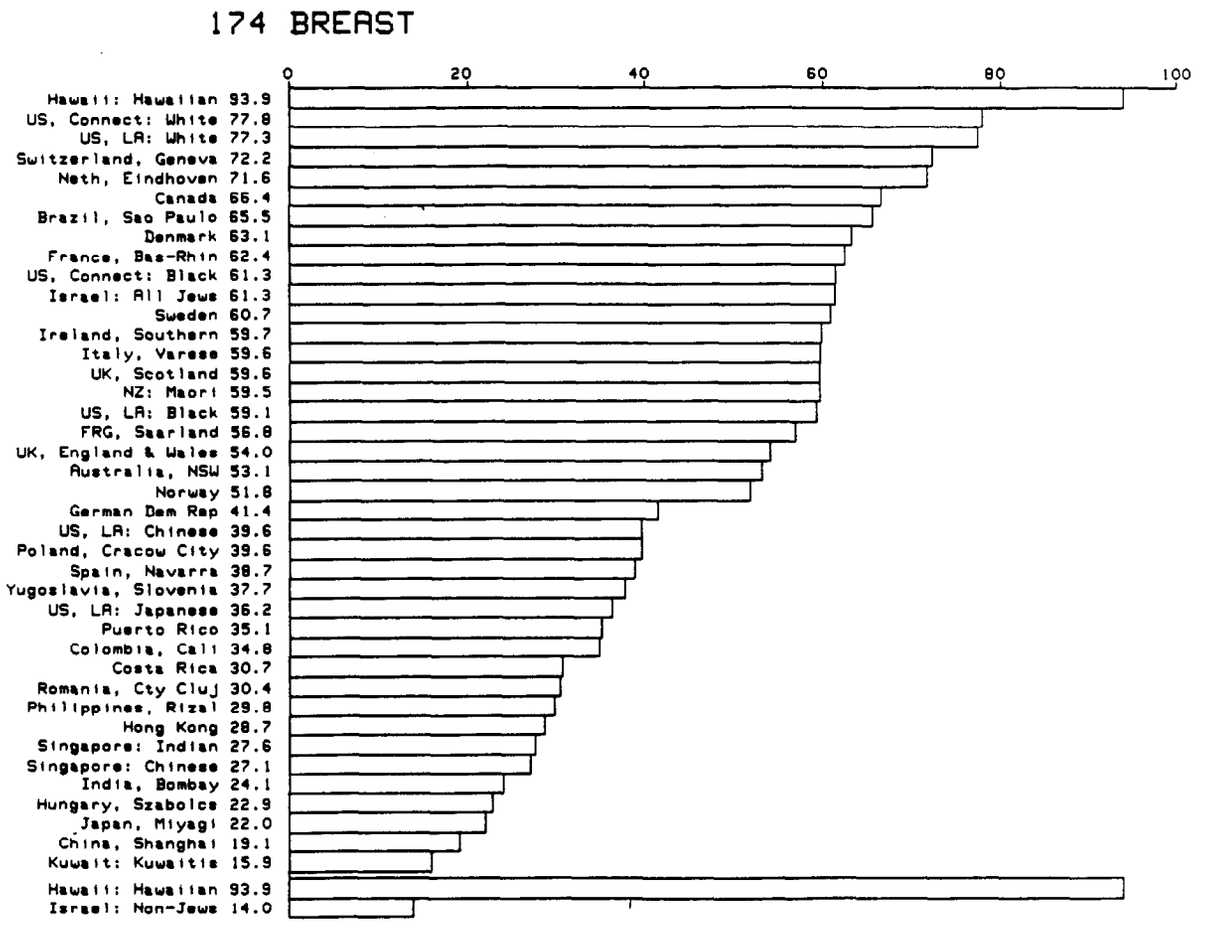

Fig. 1. Incidence rates of breast cancer around 1980 (*source Ref.* [2]).

in Israeli Jews. It is interesting that the highest recorded incidence is in the Pacific Polynesian Islanders of New Zealand, since there is also a moderately high incidence in Maoris (10.9) and in Hawaiians (14.1). Ovarian cancer is less common in Indian, Chinese and Japanese populations, with rates of 2–5 per 100,000. Mortality patterns are similar to those for incidence [3].

2. VARIATIONS WITHIN COUNTRIES

In general, less variation in incidence is observed between different regions of the same country than internationally. This is because the populations are rather more genetically homogeneous, so that regional variations may be particularly revealing of possible environmental influences.

A very large number of cancer atlases have appeared in recent years. Even a relatively superficial inspection reveals that the geographical patterns for breast, endometrial and ovarian cancers show marked similarities. In the U.S.A., for example [5], mortality rates are highest for all three cancers in the North East and northern Mid-west, and low in the southern and central states. In the Nordic countries, the highest incidence rates for all three cancers are observed near to Copenhagen and Stockholm, and in southern Sweden [6].

3. CORRELATIONS BETWEEN RATES

The similarities in the geographical patterns of the three cancers between and within countries described above in semi-quantitative terms can be formally tested by correlating measures of occurrence such as incidence and mortality rates, or, when these are not available, relative frequency data.

Most correlation studies have examined the relationship between the risk of a particular cancer and the prevalence of some environmental agent in the same population, a positive association implying, with the methodological limitations described later (section 5), a possible causal association. A different approach is simply to correlate the measures of disease risk for different cancers; a positive association suggesting that there may be common aetiological factors for the two, without providing any information as to what these might be. Despite this limitation, there are certain advantages to studies which simply correlate rates. Firstly, the data for the different cancers come from identical sources

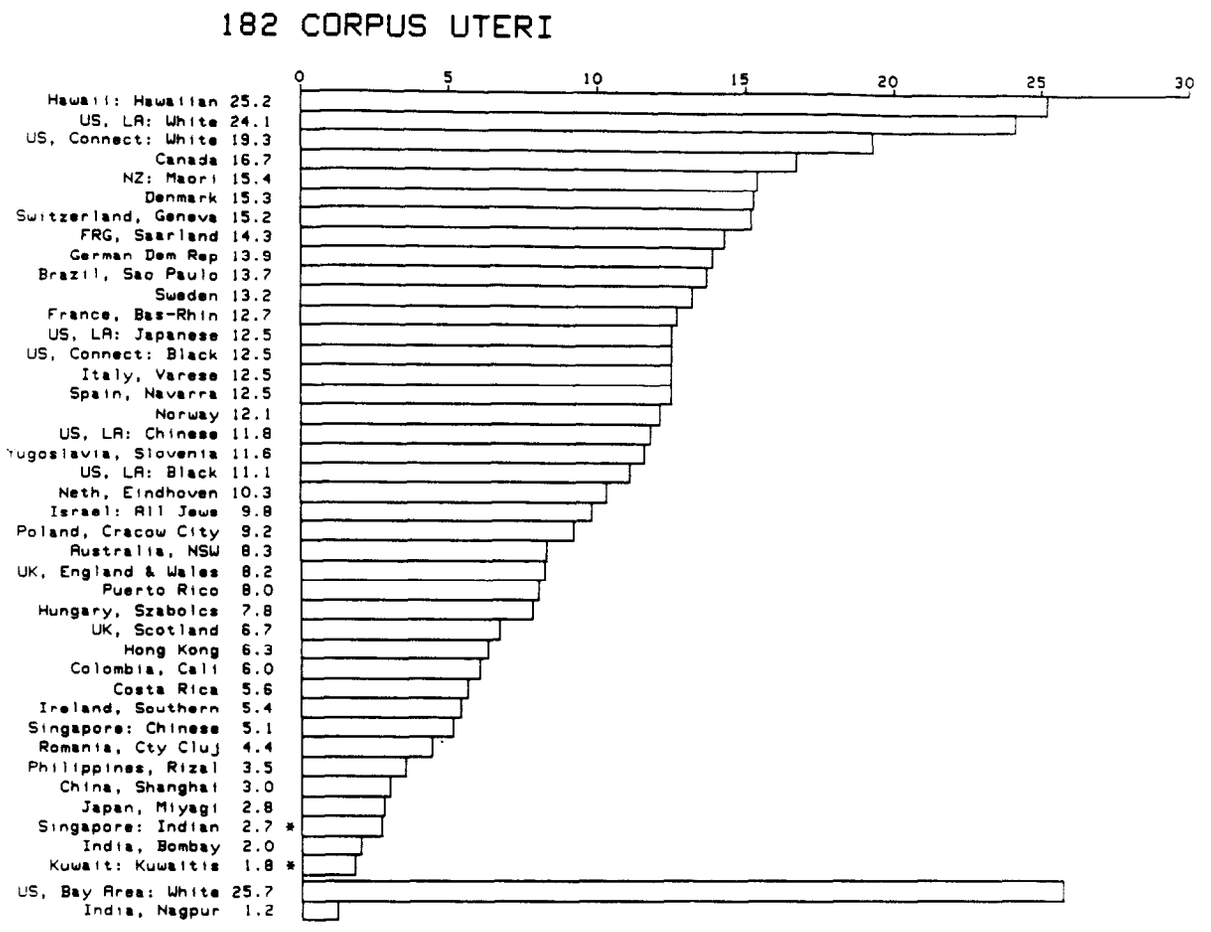

Fig. 2. Incidence rates of cancer of the corpus uteri around 1980 (*source Ref.* [2]).

within each population unit and are therefore subject to identical biases; when correlations are with risk factors, the populations studied within each country or region may differ for exposure and outcome, and there are frequently differences in the methods used for the different countries or regions studied. Secondly, incidence (or mortality) rates for the same time period can be compared; there is no need to introduce an arbitrary latent period between the measure of exposure prevalence and disease occurrence.

Correlations between incidence and mortality rates have been carried out relatively frequently. Berg [7], for example, using data from 57 cancer registries in *Cancer Incidence in Five Continents*, Vol. II [8] found strong correlations between the incidence rates of cancers of the breast, corpus uteri and ovary. This exercise has been repeated using data from 48 populations in *Cancer Incidence in Five Continents*, Vol. V [9]. The populations chosen represent one per country, or one for the major ethnic groups within a country. The results are shown in Table 1, and include correlations between breast, corpus uteri and ovary, and also colon cancer and cervical cancer. Correlations with colon cancer are almost as strong as those between breast, endometrium and ovary, but the relationships with cervix cancer are all negative and weak.

It is easy to carry out this type of analysis using rates for different regions of the same country, although it appears to have been done relatively infrequently. Winkelstein *et al.* [10] published correlations between incidence rates from nine registries contributing to the Third National Cancer

Table 1. Correlation between age-standardized incidence rates in 48 populations around 1980

Comparison			Correlation coefficient
Breast	vs.	Endometrium	0.79
		Ovary	0.75
		Colon	0.71
		Cervix	−0.19
Endometrium	vs.	Ovary	0.66
		Colon	0.52
		Cervix	−0.14
Ovary	vs.	Colon	0.44
		Cervix	−0.16

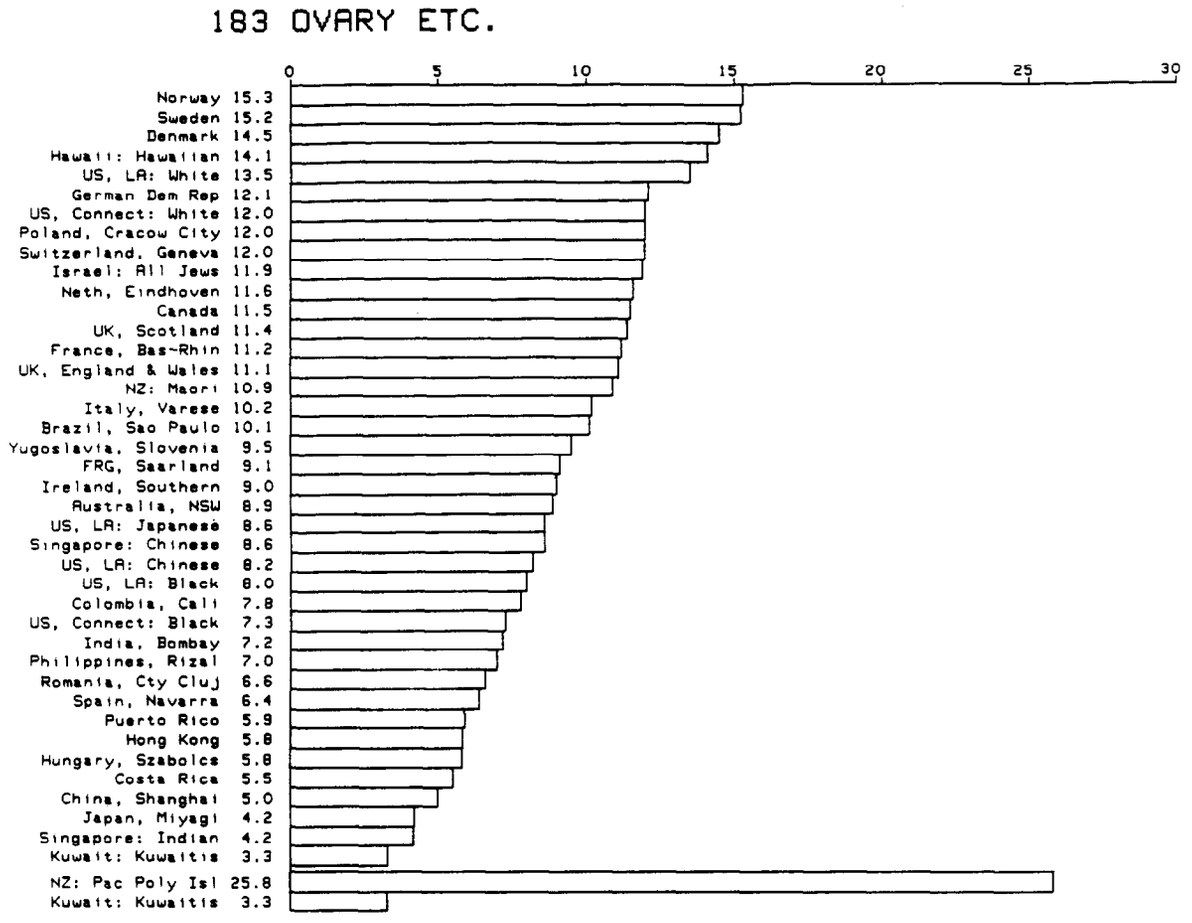

Fig. 3. *Incidence rates of ovarian cancer around* 1980 (*source Ref.* [2]).

Suvey in the U.S.A.—the results were similar to those for the international studies.

4. ETHNIC VARIATION IN INCIDENCE

The similar patterns of geographical occurrence of breast, endometrial and ovarian cancer (and also cancer of the colon) suggest similarities in aetiology, but do not distinguish between possible genetic determinants or environmental factors, both of which can be associated with a particular geographical location. It is clear that when ethnic differences in incidence are examined, they do appear to be similar for the three sites. Table 2 shows incidence rates by ethnic group within the U.S.A. and Hawaii, and in Singapore; they are very similar for all three sites—except in Singapore, where the pattern is less clear.

Studies of migrant populations are a classic method of examining how much of the difference between ethnic groups is due to genetic similarity, and how much to a common environment. Japanese migrating to the U.S.A. move from a country with very low risk for the three cancers to one where it is very high. The early studies of Haenszel and Kurihara [11] suggested that breast cancer mortality rates increased in the migrants somewhat, but remained well below those for U.S. whites, and that there was little change between first generation migrants (Issei) born in Japan, and the second generation (Nisei) born in the U.S.A. Similar patterns were seen for cancer of the ovary and 'other uterus' (i.e. excluding cervix), although migrant rates showed rather more change than for breast

Table 2. *Variation in incidence by ethnic group* [*age-adjusted rates* (*world std.*) *per* 100,000]

		Breast	Corpus	Ovary
U.S.A. (SEER)	White	82.7	23.4	12.9
	Black	70.0	12.0	9.1
	Indian	19.7	6.8	5.1
Hawaii	White	84.4	23.4	10.4
	Japanese	50.1	15.5	7.8
	Hawaiian	93.9	25.2	13.2
	Filipina	32.0	11.0	8.8
	Chinese	57.5	18.7	7.8
Singapore	Chinese	27.1	5.1	8.5
	Malay	21.1	3.9	9.9
	Indian	27.6	2.7	4.2

Source: SEER program, 1978–1982 (unpublished)
Hawaii (1978–1982) and Singapore (1978–1982) [9].

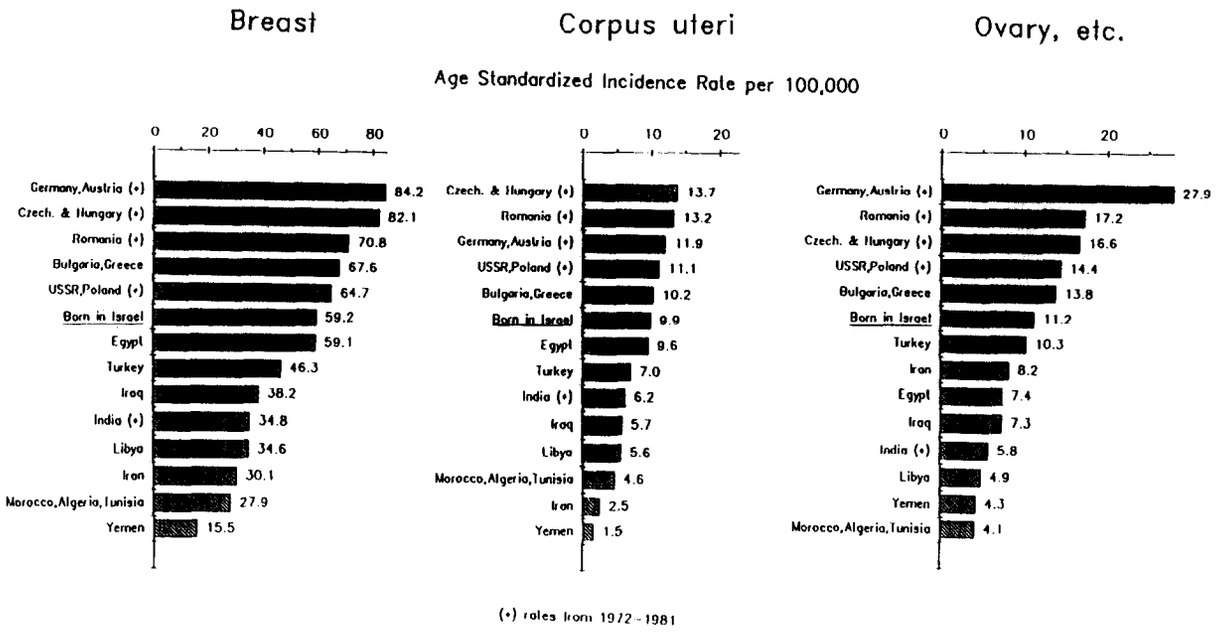

Fig. 4. *Cancer incidence in migrants to Israel* (1961–1981).

Table 3. *Cancer incidence in Japanese migrants: Hawaii* (1973–1977) [*age-adjusted rates* (*world std.*) *per* 100,000]

	Japan (Miyagi)	Hawaii Issei	Japanese Nisei	Hawaii Whites
Breast	17.5	35.9	57.2	85.6
Corpus uteri	2.0	15.4	20.3	34.8
Ovary	3.4	7.0		9.4

From Kolonel *et al.* [12].

cancer. More recent data, based on incidence rates in Hawaii, are shown in Table 3. It is clear that the incidence for all three cancers in the migrants is now more similar to the white population of Hawaii than to that of Japan.

Incidence rates for different populations of Jews migrating to Israel are shown in Fig. 4. Even without a formal correlation, it is clear that the pattern of incidence by country of birth is very similar for the three sites. Jews born in Europe have incidence rates higher that those born in Israel, those from Asia and North Africa have lower rates. It is possible to examine how the risk varies according to duration of residence in the new environment—for breast and endometrial cancer Jews born in Africa show an increase in risk with duration of stay, so that after 30 years in Israel it is the same as those born in the country; for Asian born Jews there is almost no change in risk [13]. Similar results are reported from a study of mortality rates in migrants to Australia [14]: southern European migrants have low mortality from breast and ovary cancer compared with the locally-born, but the risk increases with duration of stay in the new host country.

5. CORRELATIONS BETWEEN 'RISK FACTORS' AND CANCER RATES

5.1. *Correlation studies*

Correlation (or ecological) studies compare the prevalence of possible aetiological factors with the risk of disease, using populations rather than individual subjects as the units of measurement. Correlation studies may be international, inter-regional within a country, or compare measurements at different time periods within one population (temporal correlations are not considered here).

There are several well rehearsed problems of interpretation of correlations at the population level. The main defect arises from the so-called 'ecological fallacy', which is the result of the fact that consumption and risk are measured at the population rather than the individual level. In reality, there is considerable variation in exposure in the population, and if the relationship between exposure variable and disease is non-linear (or there are unmeasured synergistic agents present) quite different distributions of exposure levels may be present within an identical average *per capita* figure, but which give rise to different overall incidence (or mortality). Secondly, official statistics on consumption usually concern national populations, whereas data on incidence rarely do so; the alternative is to use national mortality rates, but then the ratio of mortality:incidence may not be the same in all populations. A third problem is that it is not easy to allow for other aetiological agents which may obscure the relationship since comparable data are rarely available, and there may be confounding between them (which is difficult to adjust for in correlation studies). Of course, such factors may equally well give rise to

entirely spurious relationships. For some cancers, the major causative agents may differ according to region (e.g. for oral cancer), so that inclusion of data from all regions would obscure relationships in some of them. Finally, the latent interval exposure–cancer is quite long (20–40 years), so that contemporaneous measures of both are clearly inappropriate, and any attempt to adjust by using consumption data from an earlier time period is inevitably somewhat arbitrary—it makes no allowance for changing consumption patterns with time, nor with possible migration (so that the group exposed at an earlier period may have subsequently moved away).

With so many apparently negative features, it apears paradoxical that some relationships appear to be more clearcut as simple correlations of group data than they do in individual based studies.

This is most evident in the case of the association between breast cancer and dietary fat. For example, Kolonel *et al.* [15] found that there was a close correlation between *per capita* fat intake in the five ethnic groups in Hawaii and their breast cancer incidence, while a case-control study within the Caucasian and Japanese populations [16] failed to find a statistically significant association.

The reasons for this seeming paradox have been clearly summarized recently by Goodwin and Boyd [17]. The first problem is that cohort and case-control studies are almost always conducted within a single country where the range of exposure to major constituents of diet—such as fat—is likely to be very small in comparison to the range studied in international correlations. Thus, although the range of incidence of breast cancer internationally is at least six-fold (Fig. 1), when a regression line is fitted to the correlation between breast cancer incidence and *per capita* fat intake, it can be estimated that, with the range of fat intake observed in the U.S.A. in the cohort study of Willett *et al.* [18], the risk of breast cancer in the highest quintile of consumption would only be 1.4 times that in the lowest. This is a small relative risk to detect in an epidemiological study, but the problem is further compounded by the considerable degree of measurement error, and hence misclassification of exposure level, that is inherent in most of the methods of estimating dietary intakes. Goodwin and Boyd [17] compared the results obtained from dietary records and diet questionnaires in the study by Willett *et al.* [18] and estimated that the misclassification resulting from the latter would reduce the size of relative risk that it was attempted to detect from 1.4 (the true value) to 1.16.

Some of the measurement error associated with diet questionnaires may be due to a true lack of validity (that is to say, they are incapable of the measurement which they attempt). However, a large component is simply due to lack of reliability in the response obtained, which, in theory at least, might be corrected by questioning each individual many times, to obtain a mean of their responses. In population level measurements, the dietary measures are, of course, already population averages, and so not subject to this type of measurement error.

5.2. *Correlations with diet*

Many correlation studies have been reported, particularly for breast cancer, and they have concentrated primarily upon the relationship between incidence or mortality rates and dietary variables, sometimes investigating also the effects of reproductive and anthropometric factors. Armstrong and Doll [19] in an international comparison found a strong correlation between total fat consumption and incidence and mortality rates of breast cancer (simple correlation coefficients of 0.79 and 0.89), ovarian cancer (0.53 and 0.79) and incidence of cancer of the corpus uteri (0.85). Similar results have been obtained for two or more of these three sites by others [16, 20–22].

Several studies have attempted to investigate the contributions of fat and other relevant factors which are likely to be associated with it at the international level, on the risk of breast cancer. Gray *et al.* [23] found that both incidence and mortality rates of breast cancer remained significantly associated with dietary fat, even after adjusting for height, weight and age at menarche. Prentice *et al.* [24] in a series of regression analyses found that variation in fat calories provided the best explanation for international incidence rates of breast cancer, with no additional contributions from these three variables.

5.3. *Correlations with reproductive variables*

To investigate the extent to which differences in reproductive factors might explain variations in international incidence rates, data on the cumulative incidence (0–64) of cancers of the breast, cervix uteri, corpus uteri and ovary for the period around 1980 were obtained for 32 populations (Table 4). For breast cancer, cumulative incidence in the pre-menopausal (30–44) and post-menopausal (50–64) age groups was also calculated.

For the same populations, the following indices of fertility were obtained from volumes of the UN Demographic Yearbook:

(a) Total fertility rate in 1980
(b) Number of live births per woman at age 44, around 1980
(c) Number of live births per woman at age 64, around 1980
(d) Proportion of first births under the age of 20, in 1960.

Table 4. Correlations between incidence rates and reproductive variables: populations studied

Brazil (four registries)	d	Czechoslovakia (Slovakia)	
Columbia (Cali)	c	Denmark	b,c
Ecuador (Quito)		F.R.G. (Hamburg)	b,c,d
Costa Rica		G.D.R.	
Martinique	c,d	Hungary (Vas)	
Puerto Rico		Iceland	b,c
Canada		Ireland (South)	b,c
U.S.A. (SEER, all races)		Netherlands (Eindhoven)	b,c
China (Shanghai)	d	Poland (Cracow)	
Hong Kong	d	Spain (Zaragoza)	
India (Bombay)		Switzerland (Geneva)	b,c
Israel		England and Wales	b,c
Japan (Miyagi)		Scotland	b,c
Kuwait (Kuwaiti)	d	Yugoslavia (Slovenia)	
Philippines (Rizal)		Australia (1982)	
Singapore (Chinese)	c,d	New Zealand (non-Maori)	

Letters indicate missing reproductive variables—see text.
*Source: *Cancer Incidence in Five Continents* [9], except SEER (unpublished data for 1978–1982), Australia [25] and Ecuador [26].

Table 5. Female cancers: correlations with reproductive variables: 32 populations (1980)

Cumulative incidence (0–64)	Total fertility rate	Live births at age 64*
Breast	−0.58	−0.53
Cervix	+0.38	+0.48
Corpus	−0.63	−0.76
Ovary	−0.55	−0.68

*21 populations only.

Data were unavailable for some of the populations, as shown in the footnotes to Table 4.

The results of these correlations are shown in Tables 5 and 6. Correlations with measures of population fertility were negative for cancers of the breast, corpus uteri and ovary, and weakly positive for cervix cancer. The association was strongest for cancer of the corpus uteri, and rather weaker for breast cancer (Table 5).

The results for breast cancer alone, including division into pre- and post-menopausal age groups, are shown in Table 6. In general, the associations are strongest in the pre-menopausal age group (30–44). The variable 'Proportion of first births under age 20' had been included as a proxy indicator of the average age at first full-term pregnancy (for which no routine data are available). As shown in the table, the correlation is greatly improved by omitting data from Japan, where low breast cancer incidence was coupled with very few first births under age 20 (3% in 1960); conversely, two high risk countries, U.S.A. and Iceland, showed much higher than expected values (37% and 39%, respectively).

In a previous study relating mortality rates from breast cancer in 26 countries to a measure of fertility (the reciprocal of family size at age 45–49), Hems [27] had found correlations of about the same order as those found in Tables 5 and 6. However, controlling for dietary variables (dietary fat, total calories), the partial correlation coefficient became

Table 6. Breast cancer: correlations with reproductive variables: 32 populations (1980)

Variable	Cumulative incidence rate 30–44	50–64	0–64
(a) Total fertility rate	−0.60	−0.55	−0.58
(b) Live births age 44*	−0.51	—	—
(c) Live births age 64†	—	−0.50	−0.53
(d) Proportion of first births < 20‡	−0.46 (−0.57 excl. Japan)	−0.29 (−0.48 excl. Japan)	−0.36 (−0.53 excl. Japan)

*24 populations.
†21 populations.
‡25 populations.

negligibly small, whereas total fat remained correlated with breast cancer independently of family size. This suggested that reproductive factors may not be important in explaining international variations in risk of breast cancer. In a subsequent analysis [28] using as units 11 regions within the U.K., the very small inter-regional differences in diet were unable to predict variation in breast cancer mortality rates, which did, however, correlate well with fertility differences (expressed as the reciprocal of family size). In a correlation study of breast cancer mortality at county level in the U.S.A. Blot *et al.* [29] concluded that variations in breast cancer mortality in the post-menopausal period (ages 55+) were related to socio-economic factors and ethnicity, both possible markers of dietary differences (for which no direct data were available). Conversely, in pre-menopausal women (age 20–44), the associations were strongest with fertility patterns (birth rates at 25–34 and the ratio of birth rate at 15–24 to that at 25–34) and ovarian cancer mortality rates, suggesting the importance of reproductive factors in aetiology.

6. CONCLUSIONS AND SUGGESTIONS FOR FURTHER STUDIES

Correlation studies provide, at present, the best available evidence concerning the nature of dietary influences on cancers of the breast, endometrium and ovary. Although it is difficult using correlation methods to distinguish causative associations from confounding ones, for breast cancer, at least, the most consistent explanations for international variation in risk are obtained for dietary fat, or fat calories. Whether or not differences in reproductive variables play a role in international variation in incidence of breast cancer is less clear, since the relevant variables (age at first birth, numbers of births) have been measured rather indirectly. It is probably also important to separate pre- and post-menopausal rates when trying to assess effects. For endometrial and ovarian cancers there have been no studies to date investigating the relative contributions of diet and reproduction to geographical patterns of occurrence.

Future studies should attempt to use incidence rather than mortality rates, since the ratio between mortality and incidence is by no means constant from one country to another [19]. Furthermore, several correlation studies have used published mortality rates somewhat uncritically; for several developing countries they are considerable underestimates of the true rates, so that in the case of correlations with variables associated with affluence (dietary fat, protein, etc.) the strength of observed correlations is probably spuriously increased.

Studies of the contributions of fertility to geographical patterns of incidence should attempt to ensure that the two are measured in the same populations. Cross-sectional measures, as used in section 5.3, should be replaced by cohort-specific incidence and fertility. The availability and validity of measures of the average age at first birth in different populations should be investigated.

The importance of correlation studies lies in the fact that, in the absence of helpful data from case control and cohort studies (a situation which, for the reasons discussed, is unlikely to change much in future), they provide the most realistic method of estimating the probable changes in disease risk which will result from preventive measures applied at the population level, particularly in the case of diet.

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