Can Nutrition Explain the Pattern of International Epidemiology of Hormone-dependent Cancers?

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Summary

International data on the distribution of hormone-dependent cancers suggest that they are cancers of affluence. Their occurrence parallels that of bowel cancer fairly closely in population and less closely with regard to individual patient risk. The most plausible hypothesis, although based on extremely incomplete knowledge, is that some components of the Western high-protein, high-fat diet acting in early life make individuals prone to develop these cancers.

Introduction

For the purposes of this presentation, the "endocrine-dependent" cancers to be considered will be cancers of the testis, ovary, prostate, breast, and uterine corpus. It may well be that cancers of other endocrine organs and target tissues have related epidemiologies, but current information is sparse. Of these others only cancer of the thyroid has been well studied. Its incidence certainly is diet dependent but the diet factor, iodine, represents a special problem outside the scope of the present discussion.

This presentation will review evidence that has suggested that endocrine-dependent cancers are related causally to nutrition. The presentation will concentrate on descriptive and population epidemiology, using vital statistics data. It will not attempt to discuss separately cancers of different epidemiologies occurring in the same organ, although for each of these cancer sites histological differences have been associated with epidemiological differences (1, 2, 10, 38, 61). Rather the approach of this discussion will be to consider endocrine-dependent cancers as much as possible as a single group, seeking the epidemiology that they have in common. No attempt will be made to bring out all the special characteristics of each type of cancer. Recent reviews that do this include Refs. 12, 23, 35, 37, 41, 54, 56, 59, 60, and 62. The justification for the group approach lies mostly in the tendency of these cancers to occur in the same populations, but they can also cluster in the same family (55).

The 1st question to be answered about the role of nutrition in the etiology of endocrine-dependent cancers is whether there is evidence that any environmental factor is involved. The alternative is to ascribe at least the major variations in risk to genetic inheritance, be it racial, familial, or a random convergence of events that lead perhaps to ovarian dysfunction. If we decide that important risk variations are related to environment, there is a 2nd and more difficult question. Are the environmental factors primarily carcinogens, such as those that cause most lung and skin cancers, or are they factors that in a more general way serve to raise or lower those thresholds for the action of ubiquitous carcinogens or for "spontaneous" mutation?

Endocrine-dependent Cancers as Cancers of Affluence

In Iowa, as elsewhere in the United States 3rd National Cancer Survey areas, endocrine-dependent cancers were extremely prominent (7). Breast cancer was the single most common cancer in women. Prostate cancer was the 2nd most common cancer in men and, of course, would have undisputed 1st place were it not for cigarette smoking. Overall, the endocrine-dependent cancers comprised 30% of all non-skin cancers in Iowa. They represented 40% of all cancers in women and 19% of all cancers in men. Not including cigarette smoking, we estimate that endocrine-dependent cancers would make up 27% of all cancers in men and 36% of all non-skin cancers in the population.

This importance is not a general situation throughout the world (Table 1). In India and Japan endocrine-dependent cancers together represent only about 3% of the total in men and 16% in women (15). In African blacks the figures were about 5 and 20%, and in Latin Americans 8 and 18%. Figures from Central Europe suggest an increased importance in women (25%) but not in men (5%). Earlier but more extensive figures are given by Segi (48).

In terms of actual incidence the Japanese present the lowest incidence of endocrine-dependent cancer (15). The male rate of about 7.5/100,000 is about 10% of the United States incidence. The female rate of about 20/100,000 is 16% of the United States rate. The rates for both men and women are about twice as high in India and Central Europe as in Japan. In black Africans, the female rate is about twice that of Japan, but the male incidence is 4 times higher because of the high incidence of prostate cancer.

Within a country the association of endocrine-dependent cancers with social class will be best seen when the country shows a wide range of economically determined cultural patterns. This has been particularly well documented for breast cancer (e.g., Ref. 4). The other endocrine-dependent cancers are less well documented in this respect, and the
J. W. Berg

Table 1
Selected international incidence rates* for endocrine cancers

<table>
<thead>
<tr>
<th>Population</th>
<th>Men</th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Breast</td>
<td>Prostate</td>
<td>Testis</td>
<td>Breast</td>
<td>Corpus</td>
<td>Ovary</td>
</tr>
<tr>
<td>Japan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miyagi</td>
<td>0.3</td>
<td>3.2</td>
<td>0.4</td>
<td>11.0</td>
<td>1.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Okayama</td>
<td>0.9</td>
<td>4.3</td>
<td>1.2</td>
<td>12.4</td>
<td>2.2</td>
<td>2.8</td>
</tr>
<tr>
<td>India</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bombay</td>
<td>0.2</td>
<td>6.5</td>
<td>1.2</td>
<td>20.4</td>
<td>1.5</td>
<td>6.1</td>
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<tr>
<td>African blacks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibadan</td>
<td>0.0</td>
<td>9.7</td>
<td>0.1</td>
<td>13.7</td>
<td>1.9</td>
<td>7.5</td>
</tr>
<tr>
<td>Bulawayo</td>
<td>0.2</td>
<td>29.1</td>
<td>0.0</td>
<td>35.5</td>
<td>3.6</td>
<td>9.7</td>
</tr>
<tr>
<td>South African Cape</td>
<td>0.5</td>
<td>19.2</td>
<td>0.0</td>
<td>13.6</td>
<td>4.1</td>
<td>7.7</td>
</tr>
<tr>
<td>South African Natal</td>
<td>0.0</td>
<td>23.2</td>
<td>0.1</td>
<td>11.9</td>
<td>4.7</td>
<td>6.4</td>
</tr>
<tr>
<td>Latin America</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cali</td>
<td>0.2</td>
<td>23.2</td>
<td>2.2</td>
<td>27.3</td>
<td>6.8</td>
<td>9.2</td>
</tr>
<tr>
<td>Jamaica</td>
<td>0.0</td>
<td>28.2</td>
<td>0.0</td>
<td>33.5</td>
<td>6.4</td>
<td>8.3</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>0.7</td>
<td>17.2</td>
<td>0.8</td>
<td>20.9</td>
<td>4.6</td>
<td>5.1</td>
</tr>
<tr>
<td>California, Alameda</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>0.5</td>
<td>38.0</td>
<td>3.5</td>
<td>62.4</td>
<td>16.8</td>
<td>12.6</td>
</tr>
<tr>
<td>Black</td>
<td>1.0</td>
<td>65.3</td>
<td>0.0</td>
<td>38.6</td>
<td>18.1</td>
<td>10.4</td>
</tr>
</tbody>
</table>

* Rates per 100,000 population age adjusted to "European" standard (15).

results have not been suggestive of any strong or simple relationship to socioeconomic class (16).

A marked sociometric gradient in a genetically homogeneous culture is 1 type of evidence that environment, not heredity, is responsible for high cancer incidence. Even for breast cancer we may not have this situation. Hence to settle the nature-nurture question one turns to the data on migrants. Data on Poles migrating to the United States and Australia indicate that endocrine-dependent cancer risk shifts to the pattern of the host country but does so more slowly than does the risk for intestinal cancer (51, 52). The older but more complete United States data show the shift to be weak over the age of 70, and the Australian data on breast cancer do not contradict this picture.

The Japanese migrants show the same phenomena in that endocrine-dependent cancers are more frequent than in Japan, but the approach to the United States rate is slower than for bowel cancer, and the shapes of the curves do not exclude the possibility that a major racial difference in cancer incidence will remain even when the cultural differences have disappeared (5, 25). For the purposes of this conference, however, I believe that it is safe to conclude that many if not all of the international differences in endocrine-dependent cancer incidence are environmental and that these cancers will increase importantly in incidence in individuals migrating from low- to high-incidence regions. The available data, however, leave many unanswered questions, and more information certainly could be utilized.

There are many ways in which affluent culture can affect cancer incidence. One of the more unusual suggestions is that the increase in artificial lighting may act through the pineal to produce earlier menarche (33). This would in turn produce a higher risk for at least breast (41) and possibly endometrial cancer (34).

The general picture, then, is that endocrine-dependent cancers are 1 of the 3 major environmental cancer problems of this country along with cigarette-caused cancers and bowel cancers. We know from many studies that cigarettes are not epidemiologically linked with endocrine-dependent cancers. The next problem is whether the endocrine-dependent cancers have an epidemiology sufficiently similar to the epidemiology of bowel cancer that we should seek a common cause for both or whether the discrepancies favor essentially different causal situations.

Endocrine-dependent Cancers and Bowel Cancers

At the moment most of us believe that bowel cancer is almost surely a cancer of affluent nutrition (31). To the extent that bowel cancers and endocrine-dependent cancers occur together, endocrine-dependent cancers also could be nutritional cancers. Internationally, the incidence and rates for the endocrine-dependent cancers follow fairly closely the rates for bowel cancer. Table 2 presents some of these correlations. Breast cancer is linked particularly closely with bowel cancer. The associations between bowel cancer and corpus, ovarian, testis, and prostatic cancers become progressively weaker in that order, but still all are statistically highly significant.

Within individual countries the correlations are weaker, but the extent to which intracountry distributions can be relied on for epidemiological clues is a moot point in any case. Certainly, the lack of correlation of rates for Japanese prefectures (29) can be explained by the low rates for all of the cancers in question. Burbank's (6) stepwise analysis of United States mortality rates links breast cancer fairly closely with bowel cancer in white women, ovary and corpus cancer fairly closely, but prostate and testis cancer not at all to bowel cancer in white men. The links between these cancers are stronger for United States black men and women. Overall, population risks suggest a parallel between bowel and endocrine-dependent cancer risk factors but not necessarily an equivalence.

Another way to look for evidence of a common cause of cancer is to see whether individuals who are victims of one of the diseases in question are at special risk for the others. We have not yet reached much sophistication in the interpretation of these results. When we are convinced of a common cause but find no association (e.g., the relationship of diet fat to coronary heart disease and bowel cancer), we postulate alternate metabolic pathways. When we report associations we usually have not studied the individual case material thoroughly enough to rule out genetic rather than environmental linkage.

The studies that I was involved with (Table 3) showed that patients with endometrial and ovarian cancer had somewhat later bowel cancer than expected. There was no increased risk of breast or prostate cancer in bowel cancer patients, nor was there appreciable increased bowel cancer in patients...
with these latter cancers. This contrasts with the clear association between breast, ovarian, and endometrial cancer (see also Ref. 40). The associations of intestinal with breast, ovarian, and endometrial cancer mortality, which also was increased, also was influenced by marital status and infertility as it seems to be in the general population. It is not clear whether the excess bowel cancer mortality in nuns and other single women is truly excess incidence or to what extent it could be related to special nutritional problems.

Another link pointing to some underlying common thread is the close genetic linking of bowel and breast cancer in a number of families (39). Further study of the gene lesions behind such linkage might indicate ways in which the environment affects the target organs. Other families, however, certainly show endocrine-dependent cancer risk without especial bowel cancer risk and vice versa. Overall, there seem to be enough hints that bowel and endocrine-dependent cancers could have etiological factors in common so that the search for these factors should go on, but there is not enough evidence to guarantee success in the search.

### Endocrine-dependent Cancers and Food Patterns

Given the noted close country-by-country associations between endocrine-dependent cancers and bowel cancer, it is not surprising that international studies show correlations at least between breast and prostate cancer and the same food types that have been associated with bowel cancer, i.e., meat, animal fat, and sugar. The other endocrine-dependent cancers have not been studied from this point of view. Drasar and Irving (17) showed high correlations between national levels of breast cancer and per capita consumption of total fat, animal protein, animal fat, eggs, and total protein intake (Table 4). Sugar and sweets were somewhat less correlated with breast cancer ($r \approx 0.5$), but this correlation still is stronger than that of sugar with bowel cancer ($r \approx 0.3$). Howell (30) reports that prostate cancer mortality correlated with meats, fats, milk, and sugars in particular, all of the associations being slightly weaker than for intestinal cancers. In another review (31) Howell relates national rates of cancer mortality from intestinal, breast, and prostate cancer to the sugar, meat, fat, and milk food group. Hems (26) has shown that the diet-breast cancer correlations improve when only "postmenopausal" breast cancer rates are utilized. However, Howell in unpublished

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**Table 2**

<table>
<thead>
<tr>
<th>Cancer A</th>
<th>Cancer B</th>
<th>Pearson's $r$</th>
<th>$n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowel (F)</td>
<td>Breast (F)</td>
<td>0.79</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Corpus</td>
<td>0.76</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Ovarian</td>
<td>0.59</td>
<td>57</td>
</tr>
<tr>
<td>Bowel (M)</td>
<td>Testis</td>
<td>0.54</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td>0.43</td>
<td>58</td>
</tr>
<tr>
<td>Breast (F)</td>
<td>Corpus</td>
<td>0.66</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Ovarian</td>
<td>0.77</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td>0.61</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Testis</td>
<td>0.67</td>
<td>57</td>
</tr>
<tr>
<td>Prostate</td>
<td>Testis</td>
<td>0.32</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Corpus</td>
<td>0.61</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Ovarian</td>
<td>0.58</td>
<td>57</td>
</tr>
<tr>
<td>Testis</td>
<td>Corpus</td>
<td>0.46</td>
<td>56</td>
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<tr>
<td></td>
<td>Ovarian</td>
<td>0.61</td>
<td>56</td>
</tr>
<tr>
<td>Corpus</td>
<td>Ovarian</td>
<td>0.65</td>
<td>57</td>
</tr>
</tbody>
</table>

* "World" rates from Cancer in 5 Continents (15).

**Table 3**

Associations among bowel and endocrine cancers in the same patient

<table>
<thead>
<tr>
<th>Cancer A</th>
<th>Cancer B</th>
<th>Relative risk of Cancer A after Cancer B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowel</td>
<td>Breast</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Endometrium</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>Ovary</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td>1.0</td>
</tr>
<tr>
<td>Breast</td>
<td>Endometrium</td>
<td>0.4*</td>
</tr>
<tr>
<td></td>
<td>Ovary</td>
<td>2.1*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.0*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.0</td>
</tr>
</tbody>
</table>

* Statistically significant decrease presumably due to postmastectomy hysterectomies and/or castration.
* Statistically significant increase.
work found that bowel cancer mortality correlated more closely with premenopausal breast cancer rate than with the rates in older women.

One obvious next step is to see whether the parallels in cancer risk hold for special groups. Earlier we emphasized Argentina where a high beef, low-sugar diet was associated with a high intestinal cancer rate but not a high coronary heart disease rate (24). In La Plata breast cancer mortality also was comparable with Anglo American rates (45). The story on breast cancer was not completely clear, however, because Bristol's high death rate arose in a country where the incidence rate is substantially below that of the United States (15). If La Plata had the same incidence-to-mortality ratio as Bristol, its incidence rate would be only about two-thirds of the United States rate. Ovarian cancer mortality was high in Bristol and San Francisco but not in La Plata; therefore a definite discordance exists. The other endocrine-dependent cancers do not show enough difference between Anglo American and Latin American death rates to follow the same lines of logic.

A more explicit and crucial test will come when firm incidence rates are available from the Seventh Day Adventists and Mormons, 2 groups on "prudent" diets. If endocrine-dependent cancer rates are as low, compared to nearby populations, as their bowel cancer rates, we will have substantial evidence that diet plays a major role in the causation of these cancers. Preliminary evidence that this may be true comes from a report on the breast cancer incidence in Utah (18). Only crude incidence is given but the rate of 56/100,000 is substantially below the rate of 79/100,000 reported for white women in the 3rd National Cancer Survey.

Other key evidence comes from Japan and should be analyzed more thoroughly. Presumably because of diet changes, Japanese children have been steadily growing larger (53). Concomitantly with this change, ovarian cancer, prostatic cancer, and testicular cancer although not breast cancer have shown increases (in mortality) of 2- to 4-fold in less than 20 years (36, 49). Further and more detailed studies of these phenomena might well prove the most direct way of linking diet and endocrine-dependent cancer risk more closely.

### Hypotheses Regarding the Endocrine-dependent Cancer-Food Associations

If we accept the initial hypothesis that the geographic and socioeconomic distribution of endocrine-dependent cancers implies an environmental factor (as opposed to inborn genetic susceptibility), we must postulate either a specific environmental carcinogen such as a virus or a general enhancement of host susceptibility by affluence. As long as we lack the evidence for the specific carcinogen, susceptibility must be a viable alternative. We know that at least for breast cancer both the endocrine state of the patient and the past reproductive history are determinants of cancer risk. The most economical hypothesis is to postulate that the environmental factors act by modifying the endocrine status and balance (58). Evidence for this now is available from Hawaii. Dickinson et al. (14) have shown that the endocrine profile of young Japanese women in Hawaii has become much more like that of Caucasian women, and quite altered from the profile of women in Japan. To me, one of the most important facts about the endocrine story is the great influence on breast cancer risk exercised by events in early reproductive life (41). It seems most logical to assume that the environmental factor must be most influential when it is cotemporal with these early reproductive events. The culture in which a woman lived during her early reproductive period would be the culture most influencing her breast cancer risk. The parallel would be with stomach cancer, where risks are set early in life rather than with bowel cancer, or lung cancer, where risk seems to relate in good part to exposures of middle age.

The next question is how does diet affect endocrine profile? Hopefully, the endocrinologists may help us if we can phrase our questions correctly. One lead is in the relationships reviewed by de Waard and Baanders-van Halewijn (13) between somatotype and breast cancer, and it is pointed out that both somatotype and breast biology (11) are influenced by growth hormone while growth hormone activity levels are in turn influenced by the level of dietary protein (42). In speculation one could go as far as to suggest that mankind generally evolved under conditions of prudent (i.e., low-fat and protein) nutrition and that the present affluent diet from childhood onward may overstimulate the endocrine system, producing the same effect that one would obtain running a diesel engine on high-octane airplane fuel. The onset and frequency of menstruation certainly is dependent upon nutrition (21). In this view, overnutrition is a general evil favoring endocrine hyperfunction and hyperstimulation of target organs.

While it probably is worthwhile to see what implications of a very general overnutrition hypothesis can be tested, the possibility of very specific factor-target links should not be ruled out. The inadequately explored high incidence of endometrial cancer in obese diabetic women (22, 43, 57) is a case in point, since these women have not been shown to be
at appreciable excess risk for other cancers. If this is an association in search of an explanation, the suggestion of Hill et al. (28) that gut flora might convert cholesterol and bile steroids into estrogen-like breast carcinogens is a hypothesis in search of more epidemiological and chemical evidence. Perhaps support for this concept is found in the reports [reviewed by Carroll et al. (8)] that adding fat to the diet specifically increases breast cancer incidence in rat and mouse systems.

The cancer most in need of more specific hypotheses is prostate cancer. One could argue that blacks represent a population with specific susceptibility to disease. Certainly, in South Africa there is a contrast between the great white-black differences in breast, endometrial, and testicular cancer and the nearly equal rate for prostatic (and ovarian) cancer (15). Prostate cancer is only 1 of a spectrum of prostatic diseases that are common in Bantus (44). The prostatic cancer incidence in Rhodesia and Jamaica is 50% higher than English and European rates, while of course United States blacks have the highest prostatic cancer rates in the world. However, it seems more productive to avoid the concept of racial predisposition as long as we can and to search for additional etiological factors such as viral or even bacterial infection that might combine with dietary factors to produce an ultra-high incidence rate (32, 62). The suggestion that prostate cancer and heart disease are linked also should be investigated (27).

Other situations where the incidence of 1 or more cancers deviates from what would be expected may also point to unique epidemiological complexes. For example, Maoris appear to be at high risk for endocrine cancer without sharing the high incidence risk of other New Zealanders for bowel cancer (15). Hawaiian Chinese appear to be high in male bowel and female endocrine cancers but low in prostatic and testis cancer incidence (15). Chinese American mortality rates differ somewhat in being low for breast and female endocrine cancers but low in prostatic and testis cancer incidence in Rhodesia and Jamaica is 50% higher than English and European rates, while of course United States blacks have the highest prostatic cancer rates in the world. However, it seems more productive to avoid the concept of racial predisposition as long as we can and to search for additional etiological factors such as viral or even bacterial infection that might combine with dietary factors to produce an ultra-high incidence rate (32, 62). The suggestion that prostate cancer and heart disease are linked also should be investigated (27).

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These and other special risk situations seem to rule out any simple relationship between a specific dietary factor and all endocrine-dependent cancers. Other epidemiological variables may have to be identified and peeled away before we are in a position to see clearly what the key nutritional factors might be and how they operate. It therefore may be premature to consider endocrine-dependent cancers as a group in epidemiological studies. Concern with the peculiarities and local risk factors, however, should not obscure the point that there seem to be underlying forces acting generally to raise the frequency of endocrine-dependent cancers in populations like our own and that these factors could easily be nutritional.

References


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