An Overview of Hormone-associated Cancers

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Abstract

Data on the etiology of hormone-associated cancers are reviewed. Although for breast cancer many risk factors point to the relevance of hormonal factors, findings are not uniform. Evidence points to the importance of dietary factors, and one study appears to confirm an association with high total fat intake. Dietary factors, although possibly mediated through a hormonal mechanism, may eventually be found to play a major role in the etiology of breast cancer.

Studies of both endometrial and ovarian cancer also show the importance of hormonally associated factors, although not always in the same way as for breast cancer. In addition, both for these sites and for cancer of the prostate, dietary factors may also be relevant in their etiology. As yet, no direct assessment of the importance of diet has been attempted for these sites, but this could be rewarding.

Introduction

In presenting an overview of the hormone-associated cancers, it was initially my intent to concentrate on endogenous hormones. However, it soon became clear that the subject of endogenous hormones was bound up with other factors, so a more general overview will be presented, concentrating on breast cancer and presenting some of our own data and that of others to widen our considerations beyond the purely hormonal aspects. This wider overview is necessary if we are going to place the deliberations of this and succeeding sessions in their proper context. The issue of exogenous hormones will not be addressed.

Table 1, based on data from the Third National Cancer Survey (12), provides the cumulative incidence rates to age 75 for each of the sites of hormone-associated cancers for which incidence data were published in the survey. The cumulative rate is a method of age standardization giving equal weight to incidence at all ages (13). It is a useful approximation of the lifetime risk of developing cancer up to the upper age limit, on the assumption that individuals do in fact survive to be exposed to the risk of developing cancer up to that age. For females, the major sites are clearly the breast, cervix, corpus and ovary, and for males the prostate is the major site. Some of the other sites are not often regarded as hormone-associated cancers. If all are accepted as hormone associated, it becomes clear that they comprise in total less than one-third of the cancer load in males but approximately one-half of that in females.

Breast Cancer

MacMahon et al. (27) summarized the data available up to 1972 and indicated a number of promising areas for exploration. Early age at menarche, late age of menopause, a low frequency of artificial menopause, nulliparity, and delayed age at first pregnancy as risk factors all suggested the overwhelming importance of hormonal factors in the etiology of breast cancer. Their estriol ratio hypothesis (10), although challenged (25), has been productive of many investigations and is the subject of at least 3 of the presentations in this symposium (17, 26, 45). Some commentators (2, 16, 43), evaluating trends of mortality or of incidence of breast cancer, have been able to detect fluctuations in age-specific rates that appear to correspond with variations in cohort-specific fertility rates, particularly with patients at ages under 60. This has led to suggestions that breast cancer incidence will continue to increase in the future (43). However, the changes seen were not all consistent (16), and it is possible that other factors may be relevant or that relatively minor variations in rates may be overinterpreted.

Blot et al. (5) have recently pointed out that geographical variations in breast cancer in the United States can be linked to fertility patterns and ovarian cancer mortality in premenopausal women, while socioeconomic status and colon cancer mortality were strong indicators of rates in postmenopausal women. They suggested that extrinsic risk factors remain to be identified for older women, whereas reproductive and genetic patterns have the primary role in younger women.

Nevertheless, although there seems little doubt that genetic factors can have a strong effect in young women (1), it is difficult, even in younger women, to discriminate adequately between those at highest and lowest risk of subsequently developing breast cancer with the use of factors related to family and reproductive history (35).

Effects of Parity and Nulliparity on Breast Cancer Incidence. In a population study based on the 3 cancer registries in the provinces of Alberta, Saskatchewan, and Manitoba utilizing all registrations for women who were ever married over a 3-year period, with data from the Canadian census of 1971 as a control, we found only a weak effect of nulliparity as a risk factor, even when related to women with 4 or more births. However, the relative risk for breast cancer (1.4) was significantly different from 1, while the relative risk for other uterine cancer, largely cancer of the endometrium and ovary, was similar (1.4 and 1.3, respectively). Nevertheless, we had anticipated an effect of a
higher order, suggesting that in this relatively sociologically uniform group of people other factors were probably more relevant. This was heightened by the finding that the relative risk for cervical cancer was only just below unity (0.9). When we looked at the findings for breast and corpus cancer by age, we found that the increase in risk for nulliparity for breast cancer was restricted to women aged 44 or more, whereas the risk for endometrial cancer was greatest in younger women, with a diminishing effect in older ages (Table 2).

In a recent case-control study of breast cancer conducted in 4 areas of Canada (Sherbrooke, Toronto, Winnipeg, and northern Saskatchewan) with controls selected from the neighborhood of the cases in an endeavor to match fairly closely for socioeconomic status, we could find no evidence that early age at menarche was a risk factor in this population (8). We also found hardly any effect of parity until we looked at the duration of pregnancy (Table 3). Thus, the mean number of pregnancies for cases and controls was identical, but when we analyzed the data separately according to pregnancies carried to full term, to 5 months or more, or to 4 months or less, we did find differences. Full-term pregnancies resulting in a live birth or pregnancies of 5 months or more occurred slightly less frequently in cases than in controls, but the difference was not significant. Pregnancies of 4 months or less, however,

<table>
<thead>
<tr>
<th>Site</th>
<th>Rate (%)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td></td>
<td>White</td>
<td>Black</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>0.1</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td>5.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>1.4</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>2.2</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>1.4</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>4.4</td>
<td>8.4</td>
<td></td>
</tr>
<tr>
<td>Testis</td>
<td>0.3</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Melanomas of skin</td>
<td>0.4</td>
<td>0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Kidney and renal pelvis</td>
<td>0.8</td>
<td>0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.2</td>
<td>0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>1.1</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Leukemias</td>
<td>1.0</td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>All hormone-associated</td>
<td>8.3</td>
<td>11.2</td>
<td>14.7</td>
</tr>
<tr>
<td>sites</td>
<td></td>
<td></td>
<td>12.4</td>
</tr>
<tr>
<td>All sites</td>
<td>31.1</td>
<td>37.6</td>
<td>25.0</td>
</tr>
</tbody>
</table>

Table 2

Risk for nulliparity, relative to 1.0 for women with 4 or more births, by age

Data from study of cancer and parity based on all registrations from married women to the provincial cancer registries of Manitoba, Saskatchewan, and Alberta.

<table>
<thead>
<tr>
<th>Site</th>
<th>Relative risk by age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20-44</td>
</tr>
<tr>
<td></td>
<td>45-54</td>
</tr>
<tr>
<td>Cancer of the breast</td>
<td>1.09</td>
</tr>
<tr>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Cancer of the endometrium</td>
<td>3.62</td>
</tr>
<tr>
<td></td>
<td>2.45</td>
</tr>
<tr>
<td></td>
<td>1.53</td>
</tr>
</tbody>
</table>

\[ a p < 0.05. \]
\[ b p < 0.01. \]

Table 3

Breast cancer and parity according to duration of pregnancy (8)

<table>
<thead>
<tr>
<th>Duration of pregnancy</th>
<th>Mean no. of pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (irrespective of duration)</td>
<td>Cases</td>
</tr>
<tr>
<td></td>
<td>3.5</td>
</tr>
<tr>
<td>Full-term (resulting in a live birth)</td>
<td>2.7</td>
</tr>
<tr>
<td>5 mos. or more</td>
<td>2.9</td>
</tr>
<tr>
<td>4 mos. or less</td>
<td>0.6</td>
</tr>
</tbody>
</table>

\[ a p = 0.04 \text{ (2-sided).} \]

Table 4

Risk of breast cancer, relative to nulliparous, according to age at first birth

<table>
<thead>
<tr>
<th>Area</th>
<th>Nulliparous</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parous, at following age (yr) at first birth</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;20</td>
<td>20-24</td>
</tr>
<tr>
<td>Boston (28)</td>
<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Glamorgan (28)</td>
<td>1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Los Angeles (18)</td>
<td>1.0</td>
<td>0.7</td>
</tr>
</tbody>
</table>

did occur significantly more often in cases than in controls. Although this could be an artifact of rather finely divided data, there is still a suggestion that the pregnancy experience of cases and controls is likely to be similar, except for a tendency for cases to complete pregnancies less often than do controls. This suggests some greater tendency to hormonal instability in women who subsequently become candidates for breast cancer.

In this study we also confirmed an increased risk with later age at menopause but confirmed, as has been noted before (38), that this was an effect largely restricted to those age 70 or more.

Effect of Age at First Pregnancy. The major study that most investigators have regarded as clarifying the whole relationship of pregnancy with breast cancer is that conducted by MacMahon et al. (28) in a number of international centers. This was primarily directed toward finally clarifying the role of lactation, which most would now accept as not a risk factor for breast cancer. Table 4 summarizes the findings from 2 of the western centers in that study, Boston and Glamorgan, although in fact the findings of all centers, whether middle-risk areas such as Athens or low-risk areas such as Taipei, Taiwan, and Tokyo, were very similar. In contrast, the findings from a study conducted in Los Angeles and reported in 1974 (18) are presented. Both related risk to the nulliparous, and it is interesting that in the larger international study the increase in risk beyond that for the nulliparous occurs only with patients at age 35 or over, whereas in the Los Angeles study the change occurs 1 decade earlier. Furthermore, the proportion of nulliparous was substantially higher in nearly all centers in the international study than in the Los Angeles study.

We took little note of these discrepancies until in our own study we found no effect of age at first pregnancy whatsoever. No matter how we look at our data, according to menopausal status or according to area, we find, if anything, an increased risk in women who were at an early age.
at first pregnancy. The summary point estimate comparing women whose age at first birth was 25 years or over with those whose age at first birth was less than 25 was 0.7 compared to 1.7 both for the Boston component of the international study and for the Los Angeles study. Our proportion of nulliparous was almost identical with that of the Los Angeles study but was substantially less than the proportion noted in Boston. Other studies have also not inevitably confirmed the effect. Discrepant findings have been reported showing increased risk only in premenopausal (11) and in postmenopausal women (36), while another study (19) has also shown no effect. In Iceland an independent effect of both parity and age at first pregnancy has, however, been found (39), as distinct from the finding in the international study that the parity effect was eliminated when age at first pregnancy was taken into account.

**Dietary Factors.** It is one of the acknowledged tenets of epidemiology that an effect should be seen consistently if it is a truly etiological factor (21) unless it can be demonstrated that the absence of an effect is due to some methodological flaw. Although there may have been some overmatching in our study, this should not result in the elimination of an effect. Rather, it will increase the number of discordant pairs and make it more difficult to demonstrate a significant effect. We also find it difficult to accept methodological flaws as an explanation for all the discrepancies reported. It is possible, therefore, that age at first pregnancy is not the primary factor but is an indicator of some other factor that may be extrinsic and may mediate an effect partly through a hormonal mechanism. There is absolutely no question that there are a number of pointers to external environmental influences relevant to the etiology of breast cancer. The substantial international differences (40), the changes in rates that occur on migration, although they seem to require at least a generation to have an effect (6), have been accepted by many as an indication that environmental influences and possibly (even most particularly) diet or nutrition may be relevant. Diet was, in fact, suggested as an important factor by MacMahon et al. (27) and more recently has been reemphasized by Cole and Cramer (9) as a potentially relevant factor in the etiology of cancer of endocrine target organs, with a postulated but undefined effect through hormonal mechanisms. There is absolutely no question that there are a number of pointers to external environmental influences relevant to the etiology of breast cancer. The substantial international differences (40), the changes in rates that occur on migration, although they seem to require at least a generation to have an effect (6), have been accepted by many as an indication that environmental influences and possibly (even most particularly) diet or nutrition may be relevant. Diet was, in fact, suggested as an important factor by MacMahon et al. (27) and more recently has been reemphasized by Cole and Cramer (9) as a potentially relevant factor in the etiology of cancer of endocrine target organs, with a postulated but undefined effect through hormonal mechanisms. The relevant animal and human data were reviewed in the Symposium on Nutrition in the Causation of Cancer, which appeared in this journal 3 years ago (4, 7).

We felt that indirect assessments of the importance of diet were unsatisfactory and that, despite all of the acknowledged difficulties of dietary studies, a direct assessment of the role of diet should be attempted.

The dietary findings in this study may be summarized as showing a difference in intake of a number of nutrients between cases and controls, particularly total fat intake (30). One difficulty in the analysis was that the premenopausal group as a whole consumed more than did the postmenopausal group. Further, matching by neighborhood not only had been successful in largely eliminating confounding by socioeconomic status but also tended to result in relatively few discordant pairs in the risk ratio analysis. We did not have any prior hypothesis as to the appropriate level of division of total fat intake; therefore, the divisions that we elected to use were derived by inspection. Even so, it would seem that for both premenopausal and postmenopausal women the relative risks for total fat intake as estimated from a detailed dietary history are approximately of the same order, although the dichotomy level was different. Thus, for premenopausal women the division was at 90 g, with a risk ratio of 1.6, and for postmenopausal women it was at 50 g, with a risk ratio of 1.5 (30).

**Relevance of These Risk Factors.** Can we now attempt some sort of synthesis? If age at first pregnancy is indeed the prime epidemiological indicator of some largely internally influenced hormonal mechanism and if the risk ratio of approximately 1.7 from the studies reviewed is appropriate, then we can estimate from the controls in our study that the attributable risk for this factor approximates 25% (assuming that we failed to see an effect because of some as yet unidentified error). Family history of breast disease, which seems to be largely independent of other factors, with a risk ratio in our study of 2.4, results in an attributable risk of 20%, a lower proportion because of the lower proportion in the population who do, in fact, have the factor. Finally, total fat intake from our data by an appropriated weighted average over pre- and postmenopausal women results in an attributable risk of 27%. Currently, it would seem that the greatest doubt attaches to the attributable risks for age at first pregnancy and total fat intake, inasmuch as the former may be overestimated and the latter may be underestimated. In addition, there is possibly an interaction between the 2, and neither may, in fact, adequately reflect the true risk factor. Age at first pregnancy does not seem to explain international variation. Total fat intake explains this much more satisfactorily (29). If total fat intake or other dietary factors are relevant, there is possibly some hope, with greater knowledge, of using these factors for control measures. Even so, the mechanism of the action of dietary factors is still in doubt. Is it through some sort of indirect hormonal mechanism (9), mediated through the interaction of bile salts, intestinal bacteria, and fat intake with the production of some carcinogen (22), or does it reflect something even more diverse, mediated as de Waard believes through height and weight (14)? If height is relevant this suggests the action of nutrition in adolescence or earlier; but if height is not relevant [we could not confirm its relevance in our study (8)] and weight is more important, then nutrition could have an effect at any age. In any case it seems possible that dietary factors may yet be shown to have a major role in the etiology of breast cancer.

**Endometrial Cancer**

As already indicated, the data from our population-based study support nulliparity as a risk factor in endometrial cancer but suggest that the effect is greatest at younger ages (Table 2). Elwood et al. (15), who recently reported the findings from a population-based case-control study of endometrial cancer in the Greater Boston area, did not present their data by age. They did, however, confirm reduced risk with increased parity; the relative incidence (RI) for multiparous women was 0.3, compared to a RI of 1.0 for married nulliparous women. Early menarche (RI = 1.6) and late menopause (RI = 1.7) were also associated...
with increased risk of disease. However, an irregular association was found with age at first birth with no indication of a trend as for breast cancer. Other risk factors identified included monthly rental as an index of social class; increased weight but not increased height; previous diagnosis of diabetes, hypertension, and arthritis; and place of birth in other parts of North America or in Europe.

Nulliparity and obesity have been noted previously as risk factors for endometrial cancer (46), and the correlation of endometrial with breast cancer (4, 44) suggests that dietary factors may be relevant for this site also. Armstrong and Doll (3) showed as strong a correlation between total fat intake and endometrial cancer incidence as was shown for breast cancer. Direct assessment of the relevance of dietary factors with endometrial cancer is obviously required, although whether dietary factors work through hormonal factors, as postulated by Cole and Cramer (9), or use another mechanism must be the subject of further study.

Ovarian Cancer

Ovarian cancer has been relatively neglected by epidemiologists, although it is a more important cause of premature mortality than is cancer of the endometrium or cervix (Table 5). This neglect has probably arisen because of the fact that many early cases are treated by general surgeons and do not reach specialized centers until they develop advanced disease. One review of the etiology of ovarian cancer (24), although suggesting an association with environmental carcinogens, could only identify nulliparity, association with breast cancer, and members of rare "ovary cancer families" as established risk factors. Joly et al. (23) in a case-control study, however, identified a number of reproductively associated risk factors that suggested to them that women who developed ovarian cancer had a gonadal status that predisposed them to both ovarian cancer and low fertility. Newhouse et al. (31) in another case-control study largely confirmed this, finding that fewer of the women with ovarian cancer had married and fewer had been pregnant, while the family size was smaller compared to women in a gynecological ward or on the lists of general practitioners living in the same area as the cases.

Weiss et al. (41, 42) have also studied ovarian cancer with the use of Third National Cancer Survey data. They have confirmed an increased risk in the never married (42) and have shown an increased risk of epithelial tumors in white women compared to the incidence in 4 other racial groups, while nonepithelial tumors appear to show a fairly constant incidence in all racial groups (41).

The association noted by Blot et al. (5) between ovarian cancer mortality and mortality from breast cancer in premenopausal women would tend to confirm the importance of reproductive factors in its etiology. However, Armstrong and Doll (3) noted a significant correlation between ovarian cancer incidence and mortality and total fat intake, which (at least for mortality) was not much less than that between total fat intake and breast cancer. Strong correlations have also been noted among breast, endometrial, and ovarian cancer (4, 44). Thus, once again the role of dietary factors, until now largely unexplored in this site, requires investigation.

Prostate Cancer

Prostate cancer, with almost twice as much cumulative incidence in blacks as in whites (Table 1), is possibly like cervical cancer, a disease with a largely extrinsic etiology. However, despite its frequency in the elderly, prostate cancer is a relatively unimportant cause of premature mortality (Table 5). Hence, it has remained somewhat of an enigma epidemiologically, despite the marked international differences in its incidence (47). Some flurry of interest has been renewed interest in its possible association with benign prostate hypertrophy (20), and recently there has been renewed interest in its possible association with sexual activity (37). Thus, evidence is accumulating that suggests an association with various aspects of sexual drive (33, 34) that presumably have a hormonal basis. Once again nutrition has been suspected as being relevant. Armstrong and Doll (3) found a strong correlation between total fat intake and cancer of the prostate in mortality data, although the correlation with incidence data was much lower and nonsignificant.

Discussion

Pregnancy and its readily apparent effect upon subsequent cancer experience has been a fruitful source of epidemiological investigation and subsequent hypothesis derivation and testing. However, the occurrence of pregnancy and particularly the age at which it first occurs is obviously intimately related to life-style, and it is possible that previous studies have failed to take sufficient note of this. For some time it has been recognized that the relative immunity of nuns and other nulliparous women to cervical cancer was not due primarily to hormonal factors but to other extrinsic factors (32), although it was obviously based on an appropriately hormonally prepared site. It does not

Table 5

<table>
<thead>
<tr>
<th>Site</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>0.2</td>
<td>30.7</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>2.5</td>
<td>6.8</td>
</tr>
<tr>
<td>Other uterus</td>
<td>2.1</td>
<td>7.5</td>
</tr>
<tr>
<td>Ovary</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>2.7</td>
<td>4.2</td>
</tr>
<tr>
<td>Testis</td>
<td>2.9</td>
<td>6.8</td>
</tr>
<tr>
<td>Melanomas of skin</td>
<td>2.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Kidney</td>
<td>3.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>11.7</td>
<td>7.8</td>
</tr>
<tr>
<td>Leukemias</td>
<td>14.2</td>
<td>9.2</td>
</tr>
<tr>
<td>All hormone-associated sites</td>
<td>37.5</td>
<td>69.7</td>
</tr>
<tr>
<td>All sites</td>
<td>136.2</td>
<td>124.5</td>
</tr>
</tbody>
</table>

a PYLL, potential years of life lost to age 70.

b Deaths certified to uterine corpus and uterus unspecified.
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References

42. Weiss, N. S., Young, J. L., and Roth, G. J. Marital Status and Incidence
A. B. Miller

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