EPIDEMIOLOGY OF BREAST CANCER IN KOREA

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1. Estrogen-augmented-by-progesterone hypothesis

There is overwhelming evidence that ovarian hormones play a crucial role at all stages in the development of breast cancer, and many clinically evident breast cancers remain sensitive to ovarian hormones. Both major ovarian hormones, estradiol and progesterone, play important roles in increasing breast cancer risk.

1) Key epidemiologic evidence

The key epidemiologic observations on the relation of ovarian hormones to breast cancer risk are as follows. (1) Early menopause, whether it occurs naturally or through bilateral oophorectomy, reduces risk. (2) Postmenopausal obesity increases risk, but premenopausal obesity decreases risk. (3) Menopausal estrogen replacement therapy increases risk, but only to a relatively small extent. (4) Use of combination type oral contraceptives does not decrease the risk. (5) Use of depot medroxyprogesterone acetate does not decrease breast cancer risk (Pike et al. 1993).

2) Estrogen-augmented-by-progesterone hypothesis

The key epidemiologic hormonal risk factors for breast cancer are all explicable in terms of the estrogen augmented by progesterone hypothesis. Early menopause reduces the risk of breast cancer by reducing levels of both estrogen and progesterone. The increased anovulation and increased frequency of lower progesterone levels in the luteal phase that are associated with premenopausal obesity markedly decrease breast exposure to progesterone, while bio-available estradiol appears to be almost unchanged during ovulatory cycles (Kelsey et al. 1993). The contrasting effects of obesity in the premenopausal and postmenopausal periods can thus be readily explained by the estrogen augmented by progesterone hypothesis. The hypothesis predicts that estrogen replacement therapy will increase breast cancer risk, and that the addition of a progestogen will increase risk further (Pike et al. 1993).
2. Epidemiology of breast cancer in Korea

1) Magnitude of the problem in Korea

As a cause of death in women, breast cancer ranks third to uterine cervix cancer and stomach cancer in Korea. It has been reported that 983 new deaths attributable to breast cancer in women were certified in Korea in 1996 (Ministry of Health and Welfare 1998). A nation-wide survey estimated that age-adjusted incidence rates for breast cancer was 10.9 per 100,000 women (Ahn et al. 1994). It can be estimated that 3,447 new cases were diagnosed as having female breast cancer in 1995 in Korea (Ministry of Health and Welfare 1997).

2) Risk factors and high risk group for female breast cancer in Korea

There have been several epidemiologic studies on risk factors of breast cancer in Korea. Table 1 lists high-risk group of breast cancer based on breast cancer risk factors identified through epidemiologic studies in Korea.

Table 1. High-risk group for female breast cancer in Korea

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>High-risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Women with age over 50</td>
</tr>
<tr>
<td>Family history</td>
<td>Women who have a family history of breast cancer among the first-degree relatives</td>
</tr>
<tr>
<td>Menarche</td>
<td>Women with age at menarche before 14</td>
</tr>
<tr>
<td>Menopause</td>
<td>Women with age at menopause after 50</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Nulliparous women</td>
</tr>
<tr>
<td>Breast feeding</td>
<td>Women who have never experience breast feeding</td>
</tr>
<tr>
<td>Obesity</td>
<td>Women with body mass index over 25 kg/m² or with body weight more than 64 kg</td>
</tr>
</tbody>
</table>

Source: Yoo et al. (1998)
3. Is the incidence of breast cancer increasing in Korea?

1) International comparison of incidence rates

One of the most dramatic feature of breast cancer is that there is a large difference in incidence rates between highly westernized and non-westernized countries (Parkins et al. 1992). For many years, breast cancer incidence and mortality rates have been highest in North America and Northern Europe, intermediate in Southern Europe and Latin America, and lowest in Asia and Africa. In recent years, steep increase in breast cancer incidence and mortality rates have been reported in several Asian and Central European countries (Table 2). Thus, the magnitudes of differences in incidence rates between countries such as Korea or Japan and the United States are less than they were previously.

Table 2. International comparison of age-standardized incidence rates for breast cancer (ICD-9 174/175)

<table>
<thead>
<tr>
<th>Countries</th>
<th>Age-standardized incidence rate (per 100,000 persons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US, SEER, White (1983-1987)</td>
<td>89.2</td>
</tr>
<tr>
<td>Denmark (1983-1987)</td>
<td>68.6</td>
</tr>
<tr>
<td>Switzerland, Basel (1983-1987)</td>
<td>68.5</td>
</tr>
<tr>
<td>Italy, Florence (1985-1987)</td>
<td>65.4</td>
</tr>
<tr>
<td>Sweden (1983-1987)</td>
<td>62.5</td>
</tr>
<tr>
<td>Australia, New South Wales (1983-1987)</td>
<td>59.6</td>
</tr>
<tr>
<td>France, Doubs (1983-1987)</td>
<td>59.2</td>
</tr>
<tr>
<td>Germany, Saarland (1983-1987)</td>
<td>56.3</td>
</tr>
<tr>
<td>UK, England and Wales (1983-1987)</td>
<td>56.1</td>
</tr>
<tr>
<td>Finland (1982-1986)</td>
<td>52.5</td>
</tr>
<tr>
<td>Hungary, County Vas (1983-1987)</td>
<td>45.0</td>
</tr>
<tr>
<td>Brazil, Goiania (1988-1989)</td>
<td>40.5</td>
</tr>
<tr>
<td>Hong Kong (1983-1987)</td>
<td>32.3</td>
</tr>
<tr>
<td>Poland, Opole (1985-1987)</td>
<td>28.5</td>
</tr>
<tr>
<td>Japan, Miyagi (1983-1987)</td>
<td>27.8</td>
</tr>
<tr>
<td>India, Ahmedabad (1983-1987)</td>
<td>22.7</td>
</tr>
<tr>
<td>China, Shanghai (1983-1987)</td>
<td>21.2</td>
</tr>
<tr>
<td>Korean, nationwide (1988-1989)</td>
<td>10.9</td>
</tr>
</tbody>
</table>

Source : Parkin et al. (1992)
2) Studies in migrants to the United States

Studies in migrants to the United States suggest that the environmental factors rather than genetic factors are mainly responsible for the variation in breast cancer rates among countries (Kelsey and Horn-Ross 1993). Table 3 shows that both Japanese and Chinese migrants had fundamentally higher incidence rates than women in their mother countries, approaching those of their adopted country (American Cancer Society 1995). Even though Korean migrants to L.A., United States, had slightly higher breast cancer incidence rates than women in Korea, they still maintain a relatively lower level in the incidence rate of breast cancer. The speed with which incidence rates among migrants and their offspring, who were potentially exposed to a new environment and culture at an early age, has varied considerably from one ethnic group to another.

Table 3. Age-standardized incidence rates for breast cancer by ethnic groups (ICD-9 174/175)

<table>
<thead>
<tr>
<th>Population groups</th>
<th>Age-standardized incidence rate (per 100,000 persons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White, Connecticut (1983-1987)</td>
<td>88.9</td>
</tr>
<tr>
<td>White, LA (1983-1987)</td>
<td>88.5</td>
</tr>
<tr>
<td>Black, LA (1983-1987)</td>
<td>73.1</td>
</tr>
<tr>
<td>Japanese, Miyagi (1983-1987)</td>
<td>27.8</td>
</tr>
<tr>
<td>Korean, Seoul (1991-1992)</td>
<td>17.0</td>
</tr>
<tr>
<td>Korean, nationwide (1988-1989)</td>
<td>10.9</td>
</tr>
</tbody>
</table>

Source: Parkin et al. (1992); Ahn et al. (1994); Kim et al. (1995)
3) Trends in mortality and morbidity for breast cancer in Korea

Age-standardized mortality rates for breast cancer have been steadily increasing during 1981-1990, showing the increment ratio of about two (Fig. 1). As a proxy estimate of incidence, age-standardized admission rates of breast cancer, as well as proportion index of admission due to breast cancer, showed an increasing trend in Korea since 1981 (Yoo and Kim 1992).

Fig. 1. Trends in age-adjusted admission rates and mortality rates for female malignancies in Korea, 1980-1990.

4) Variation in age-specific incidence curve of breast cancer

The variation in incidence rates from one part of the world to another has been associated with different shapes in the age-specific incidence curves. Fig. 2 shows that in areas of high incidence, illustrated by the US state of Connecticut, a slight leveling off in the increase in incidence rates with age occurs during the menopausal years, followed by a continued rise during the postmenopausal years, but at a slower rate of increase. In localities with intermediate incidence rates, such as Slovenia, the rates tend to level off and stay relatively constant among women over 50-55 years of age. In regions with low incidence rates, represented by Miyagi Prefecture, Japan, the rates decline after about age 50 years (Kelsey and Horn-Ross 1993).
It is well known that the relative steep increase in incidence rates in Japan over the past few decades and in Iceland over most of this century had shifted the age incidence curve of the country to those observed in Western industrialized countries. Among women in Korea in 1988-1989, breast cancer incidence rates increase steeply with age until the late forties, then decrease less steeply with age for the rest of the life span (Fig. 3). Currently, the age incidence curve in Korea is quite similar to those in countries with low incidence rates. Will it be changed to the inverted-V shape of incidence curve? It seems to be attributable to the burden of the disease in the future in Korea, which is partially related to the breast cancer risk factor. International differences in breast cancer incidence rates have been hypothesized to be partially related to variation in risk factors, such as body weight, some aspect of diet, hormonal levels, and reproductive characteristics.
4. Concluding remarks

Epidemiologic features, i.e., trends in morbidity and mortality of breast cancer, various shape of age-specific incidence curves, and migrants study results, observed in various countries of high and low incidence for breast cancer, suggest that the incidence of breast cancer might be further increasing in Korea. Age-specific incidence curve would also be changed to those of countries with high incidence when the incidence rate of breast cancer reaches around 50 per 100,000 in Korea. Under these assumptions, control strategies including screening guidelines against breast cancer should urgently be established in the nation.

References

Introduction

Estrogens are needed for the proper development of breast but there are several evidences indicating that estrogen might affect the risk of breast cancer. Recently use of exogenous estrogen in the form of postmenopausal hormone replacement therapy has been increasing largely from clinical experiences. Estrogen replacement therapy for the postmenopausal women with estrogen deficiency has been demonstrated to relieve the early postmenopausal vasomotor and psychological symptoms such as hot flush, night sweat, depression and so on. This treatment is also able to improve urogenital atropy and reduce the incidence of cardiovascular disease and osteoporosis with resultant fracture by almost fifty percent respectively.

There is also evidence of positive effect on Alzheimer's disease and colorectal cancer.

But some adverse effect have been shown. Estrogen replacement therapy can increase the risk of endometrial cancer and possible adverse effect on thromboembolic disease and breast cancer.

Estrogen and breast development

Anatomy of breast involves 4 major tissues: glandular tissues producing milk secretion, ductal tissues transporting milk secretion to nipples, fibrous tissues supporting the breast and fatty tissues producing the bulk & characteristic shape. Fatty tissues comprise 85% of the substance of breast.

Developmental changes of breast are noted throughout life cycle. Phylogenetically breast arises as a modified apocrine sweat gland. Embryologic breast development starts in uterus & is independent of hormones. During the 3rd trimester of pregnancy, placental sex hormones cause epithelial buds to be converted into hollow ducts. Witch's milk of newborn is produced by these structures, which cease as the effects of placental hormones wane. Mammary gland is almost inactive up to puberty, when breast is developed as thelarche.
Breast development depends on the interaction and synergism among various hormones which are increased in production and act intensively during puberty and pregnancy.

Two ovarian sex steroid hormones, estrogen and progesterone, play a central role in breast development during puberty.

Estrogen mainly promotes epithelial proliferation of ductal tissues but in high concentrations estrogen may also stimulate the acinar system. On the other hand, progesterone promotes the growth of alveolar-lobule system after beginning of ovulatory cycle but the total differentiation of breast to occur, synergistic action of thyroxine, prolactin, growth hormone, insulin and cortisol is required.

**Estrogen and mammary cycle**

Mammary cycle differs substantially from endometrial cycle. Maximum proliferative activity is observed in luteal phase of menstrual cycle, around the 21st day. In luteal phase of cycle, the nuclear volume of epithelial cells is bigger than in proliferative phase. Apoptotic index is also higher in luteal phase of cycle in order to compensate the increase in mitotic index.

Cell culture studies revealed that estrogen is capable of stimulating breast epithelial cell growth. Studies of cell proliferation in mammary gland in vivo showed that estrogen increases the proportion of cells engaged in DNA synthesis by recruiting non-cycling cells into cell cycle and reducing the duration of G1 phase. Mitogenic effects of estrogen is via early G1 phase site of action.

The rate of cell division is controlled by speed with which cells pass through G1 phase. Within G1 phase, critical restriction point is existed through which all the cells should pass. The restriction point is now known to be retinoblastoma tumor suppressor protein (pRB). pRB is hypophosphorylated during early G1 and in this form is growth-inhibitory. Phosphorylation of pRB during G1 phase relieves this inhibition and allows S phase entry.

Transient accumulation of cyclins, consequently assembly and activation of cyclin/cyclin-dependent kinase (CDK) complexes leads to phosphorylation of specific substrate, pRB.

Estrogen increases induction of cyclin D1 mRNA and protein, activity of CDK4, major
catalytic partner for cyclin D1 and cyclin E-associated kinase activity. Meanwhile progesterone/progestogen has two distinct effects on cell cycle progression within one cell type. These effects result in biphasic change in rate of cell cycle progression, consisting of initial transient acceleration followed by cell cycle arrest and growth inhibition. The predominant effect of progesterone on mammary cell cycle seems to be long-term growth inhibition.

**Estrogen replacement therapy and breast cancer**

The relationship between estrogen administration and development of breast cancer comes from epidemiological evidence in vitro and animal studies.

Many epidemiological risk factors for breast cancer are related to prolonged cumulative exposure to an excessive number of ovulatory menstrual cycles, such as early menarche, and later menopause. However, after more than 50 years of research, the role of estrogen as initiator of breast cancer has not been proven and there is no clear proof that estrogen causes breast cancer in women.

The studies about risk of breast cancer in women on ERT/HRT are imperfect and no large, prospective double blind randomized trial have not been conducted yet.

Six meta-analyses have been published to attempt to clarify the situation and the results of these meta-analyses are summarized in table 1. The results showed that ERT/HRT was not associated with increased risk of development of breast cancer in all meta-analyses except one from Spain, in which a very small but significant, increased relative risk was noted. Although not entirely consistent, findings also suggested that no increased risk was noted in ever users or short term users but increased risk in two subgroups of users, that is, users of long duration and current users.

Increased risk of breast cancer was associated with duration of estrogen use in 4 meta-analyses (table 2) and higher estrogen dosage in 3 meta-analyses. Breast cancer risk was not increased in ERT/HRT-users with benign breast disease in 3 meta-analyses.

Two meta-analyses from Australia and Nurses' Health Study found no realtionship between positive familial history and estrogen users but meta-analyses from Centers for Disease Control and Prevention(CDC) confirmed this relationship.
Recently, the Collaborative Group on Hormoneal Factors in Breast Cancer has reanalysed more than 90% of the accumulated worldwide data on risk of breast cancer associated with use of hormone replacement therapy over past 25 years or so. The results showed that risk of development breast cancer is significantly increased and risk increases with increasing duration of use, that is, 2.3% for each year of use, but there was no significant excess of risk 5 or more years after cessation of HRT.

Case-controlled studies do not reveal any protective effect for breast cancer by addition of progestogen to estrogen. Only more larger long-term randomized prospective trial can definitely be conclusive.

The breast cancers developed on or after ERT/HRT have been found to be clinically less advanced with few metastases, higher grade & better prognosis than those of non-users.

There is no evidence of increased mortality from breast cancer among estrogen users, even though higher incidence(table 3). This apparent survival advantage is due to better medical surveillance with earlier detection and/or hormonal impact on the type or aggressiveness of the developing cancer.

**Estrogen replacement therapy after breast cancer**

Clinical trial of breast cancer survivors who have been prescribed HRT have not shown increased risk of tumor recurrence or death from progressive disease(Table 4).

Eden et al treated with continuous combined estrogen/progestogen therapy using moderate dosage of (50mg daily) medroxyprogesterone acetate(MPA) and usual dose of estrogen. There were no death among HRT-users compared with 10% among nonusers and risk of recurrence was significantly lower in ERT/HRT-users.

Even these results, caution of ERT/HRT use in women with history of breast cancer is still necessary until randomized prospective trial is undertaken.

Alternatives to ERT/HRT for postmenopausal breast cancer survival were tibolone, tamoxifen, newer selective estrogen receptor modulator(SERM) such as raloxifene & phytoestrogen.

All postmenopausal women should be affected ERT with full explanation of potential benefits and risks, especially including current medical knowledge about breast cancer.
Table 1) risk of breast cancer associated with HRT

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>year</th>
<th>Study</th>
<th>RR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armstrong</td>
<td>1988</td>
<td>23</td>
<td>1.01</td>
<td>0.95 - 1.08</td>
</tr>
<tr>
<td>Dupont &amp; Page</td>
<td>1991</td>
<td>31</td>
<td>1.07</td>
<td>1.0 - 1.15</td>
</tr>
<tr>
<td>Steinberg</td>
<td>1991</td>
<td>16</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Grady</td>
<td>1992</td>
<td>10</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Sillero - Arenas</td>
<td>1992</td>
<td>37</td>
<td>1.06*</td>
<td>1.00 - 1.12</td>
</tr>
<tr>
<td>Colditz</td>
<td>1993</td>
<td>31</td>
<td>1.02</td>
<td>0.93 - 1.12</td>
</tr>
</tbody>
</table>

Table 2) risk of breast cancer among long-term HRT users

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>year</th>
<th>RR(CI)</th>
<th>duration of use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armstrong</td>
<td>1988</td>
<td>no effect</td>
<td></td>
</tr>
<tr>
<td>Dupont &amp; Page</td>
<td>1991</td>
<td>no conclusion</td>
<td></td>
</tr>
<tr>
<td>Steinberg</td>
<td>1991</td>
<td>1.30 (1.26 - 1.6)</td>
<td>8 yrs</td>
</tr>
<tr>
<td>Grady</td>
<td>1992</td>
<td>1.25 (1.04 - 1.51)</td>
<td>8 yrs</td>
</tr>
<tr>
<td>Sillero - Arenas</td>
<td>1992</td>
<td>1.23 (1.07 - 1.42)</td>
<td>12 yrs</td>
</tr>
<tr>
<td>Colditz</td>
<td>1993</td>
<td>1.23 (1.08 - 1.40)</td>
<td>&gt; 10 yrs</td>
</tr>
</tbody>
</table>

Table 3) Summary of mortality estimates

<table>
<thead>
<tr>
<th>Authors</th>
<th>year</th>
<th>relative risk</th>
<th>confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunt et al</td>
<td>1987</td>
<td>0.55</td>
<td>0.28 ~ 0.96</td>
</tr>
<tr>
<td>Hunt et al</td>
<td>1990</td>
<td>0.76</td>
<td>0.45 ~ 1.06</td>
</tr>
<tr>
<td>Yuen et al</td>
<td>1993</td>
<td>0.81*</td>
<td>0.64 ~ 1.02</td>
</tr>
<tr>
<td>Persson et al</td>
<td>1996</td>
<td>0.5</td>
<td>0.4 ~ 0.6</td>
</tr>
<tr>
<td>Colditz et al</td>
<td>1995</td>
<td>1.14**</td>
<td>0.85 ~ 1.51</td>
</tr>
<tr>
<td>Ettinger et al</td>
<td>1996</td>
<td>1.89</td>
<td>0.43 ~ 8.36</td>
</tr>
<tr>
<td>Willis et al</td>
<td>1996</td>
<td>0.84</td>
<td>0.75 ~ 0.94</td>
</tr>
</tbody>
</table>

Table 4) HRT in Women with a history of breast cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>year</th>
<th>Number</th>
<th>Follow-up</th>
<th>Relapse (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stoll</td>
<td>1988</td>
<td>24</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Wile</td>
<td>1993</td>
<td>25</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>Disaia</td>
<td>1993</td>
<td>77</td>
<td>59</td>
<td>8</td>
</tr>
<tr>
<td>Powles</td>
<td>1993</td>
<td>35</td>
<td>43</td>
<td>6</td>
</tr>
<tr>
<td>Eden</td>
<td>1995</td>
<td>90</td>
<td>&gt;72</td>
<td>7</td>
</tr>
</tbody>
</table>
References


Collaborative Group on Hormone Factors in Breast Cancer. Breast cancer and hormone replacement therapy: Collaborative reanalysis of data from 51 epidemiologic studies of 52705 women with breast cancer and 108411 women without breast cancer LANCET 1997; 350: 1047

Dupont WD, Page DL. Menopausal estrogen replacement therapy and breast cancer, Arch Intern Med 1991; 151; 67


EFFECTS OF TAMOXIFEN ON THE BREAST

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A. The Estrogen Receptor Hypothesis

1900: Stanley Boyd collected the records of 46 premenopausal women with advanced breast cancer and documented their responses to oophorectomy.

1923: Drs. Allen and Doisy identified chemicals produced by the ovaries and named estrogens.

1962: Drs. Elwood Jensen and Herb Jacobson synthesized radioactive estradiol, injected radioactive estradiol into immature female rats. They found that the radioactivity was initially bound to all tissues but was only retained in the estrogen target tissues (uterus and vagina). They reasoned, a receptor that enabled the target tissues to retain estrogen.

1966: The estrogen receptor protein was subsequently isolated from the rat uterus. Dr. Jensen established in the laboratory that some breast cancers did indeed contain the estrogen receptor, he conducted the initial clinical studies illustrating the principle that patients whose tumor contains the estrogen receptor will respond to are endocrine maneuver such as oophorectomy or adrenalectomy.

1974: This principle was established in Bethesda, Maryland at a National Cancer Institute-sponsored meeting.

B. The First Antiestrogens

There might be a better way to treat patients-by blocking estrogen action in the tumor itself. If estrogen is the key that unlocks the growth mechanism in breast cancer, perhaps a drug that blocks the lock could be found and ablative surgery to remove the source of hormones could be avoided (Fig. 1.).

1930: The most potent nonsteroidal estrogen, diethylstilbestrol had been discovered by Sir Charles Dodds. The triphenylethlenes, structural analogue of
diethylstilbesterol, were subsequently found to be potent, long-acting estrogenic drugs.

1967: Drs. Harper and Walpole discovered that the trans-isomer of a triphenylethylene, ICI 46,474, was the antiestrogenic compound (Fig. 2.).

1973: Nolvadex, the ICI brand of tamoxifen (as its citrate salt), was approved in the United Kingdom for the treatment of breast cancer.

C. The Clinical Development of Tamoxifen

1977: Advanced breast cancer in postmenopausal women by FDA in USA.
1989: ER(+), advanced breast cancer, premenopause women.
1990: ER(+), LN(-), pre/postmenopausal women.
1993: Male breast cancer.
1994: Approved by the FDA of prolonging the overall survival.

D. Effects of Tamoxifen Treatment

1) Laboratory Studies
Lippman describe the ability of tamoxifen to inhibit the growth of MCF-7 estrogen-receptor-positive breast cancer cells in culture and to demonstrate that the addition of estrogen could reverse the action of tamoxifen.

Kent Osborne described the blockade by tamoxifen of breast cancer cells at the G1 phase of the cell cycle.

The mammary carcinogens dimethylbenzanthracene(DMBA) and N-nitrosomethylurea(NMU) induce tumors in young female rats. The administration of tamoxifen to carcinogen-treated rats prevents the initiation of carcinogenesis-animals remain tumor-free.

Mechanism of action of tamoxifen (Fig. 3.)

a. antiestrogenic effects-blockage of estrogen receptor
b. local effects-independent of estrogen receptor, blockage at G1 phase

2) Increased survival of breast cancer patient by preventing disease recurrence (Fig. 4.)

Figure 3

Figure 4

3) Reduction in contralateral breast cancer incidence (Fig. 5.)

4) Reduction of local recurrence in breast conserving operated patient (10yr local rec. rate: 10% vs 3.5%)

5) Prevention of Breast Cancer

Report of the National Surgical Adjuvant Breast and bowel Project P-1 Study
The finding of a decreased in contralateral breast cancer incidence following tamoxifen administration for adjuvant therapy led to the concept that the drug might play a role in breast cancer prevention.

Women (N=13388) at increased risk were randomly assigned to receive placebo (n = 6707) or 20mg/day tamoxifen (n = 6681) for 5 years.

Tamoxifen reduced the risk of invasive breast cancer by 49% (two-sided \( P<.0001 \)), with cumulative incidence through 69 months of follow-up of 43.4 versus 22.0 per 1000 women in the placebo and tamoxifen groups.

Tamoxifen reduced the risk of noninvasive breast cancer by 50% (two-sided \( P<.002 \)) (Fig. 6.).

Tamoxifen reduced the occurrence of estrogen receptor-positive tumors by 69% but no difference in the occurrence of estrogen receptor-negative tumors was seen.

Additional benefit in postmenopausal women
- Maintain bone density
- Lowering circulating cholesterol level

* Adverse Side Effects

Minor side effect:
- Hot flashes, weight gain, fluid retention, vaginal discharge, nausea, irregular menses, weight loss, skin change, increased BUN, diarrhea
- Increased GOT
major side effect: endometrial cancer

Incidence: 2/1000 woman-year of adjuvant tamoxifen treatment
Mainly confined to postmenopausal women
Distribution of early stage of endometrial cancer (74%-79%)

The rate of endometrial cancer was increased in the tamoxifen group predominantly in women aged 50 years or older. All endometrial cancer in the tamoxifen group were stage I (localized disease); no endometrial cancer deaths have occurred in this group. (NSABP-P1 study)

E. Conclusions

First, it is now clear that adjuvant tamoxifen has a substantially greater impact on the survival of postmenopausal women and about the same impact on the survival of premenopausal women with receptor-positive tumors as that seen with chemotherapy.

Second, tamoxifen decreases the incidence of invasive and noninvasive breast cancer. Despite side effects resulting from administration of tamoxifen, its use as a breast cancer preventive agent is appropriate in many women at increased risk for the disease. (J Natl Cancer Inst 1998;90:1371-88)
Estrogen receptor mediated signal transduction pathway

**Ligand binding domain**

- E2
- H2N

**DNA binding domain**

- A/B
- C
- D
- E
- F
- COOH

**Response**

- Estrogen response element
- Progesteron Receptor
- TGF-alpha, TGF-beta
- IGF (insulin like growth factor)

**Transcriptional activation**

- Conformational change and Dimerization
Structural fomular of triphenylethylene compounds

* cis and trans isomer
* only trans isomer
Mechanism of action of tamoxifen as an antitumour agent

Antioestrogen effects - blockage of estrogen receptor

Local effects - independent of estrogen receptor (blockade at G1 phase)

- Decrease TGFα
- Increase TGFβ
The absolute benefits from the use of adjuvant tamoxifen, however, were greater in node-positive than in node-negative patient.
### Overviews of Adjuvant Tamoxifen Therapy (VII)

**Reduction in Contralateral Breast Cancer Incidence**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Tamoxifen</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Reduction in incidence</td>
<td>39% °αe</td>
<td>18% °φ</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt;0.00001</td>
<td>NS</td>
</tr>
</tbody>
</table>

- No. of contralateral breast cancer observed: T/C
  - Tamoxifen: 122/184
  - Chemotherapy: 40/42
- % Reduction in incidence with duration of:
  - <2 yr: 26% °αf
  - 2 yr: 37% °αg
  - >2 yr: 54% °αh

T: treatment group, C: control group

Lancet 339:1, 71, 1992
Cumulative rates of invasive and noninvasive breast cancers occurring in participants receiving placebo or tamoxifen.

The p values are two-sided.
Hormonal replacement therapy (HRT) is an important component of preventive health care for postmenopausal women. This lecture will review the normal and abnormal mammographic and ultrasound (US) findings related to HRT and to evaluate cancers found in these women. Mammography and high-resolution US of 5,000 women before and during HRT were analyzed and correlated with pathology in 69 patients (24 preHRT lesions and 45 lesions during HRT). Related literatures were reviewed (1-3).

Ten cancers were detected by preHRT mammography. Increased parenchymal density developed in 2050 patients (41%) and stabilized usually within 1.5 years after HRT. Mammographic abnormalities seen in these women included asymmetric increase in breast density and development or increase in size of nodules or microcalcifications. Common US findings were increased parenchymal layer, ductal dilatation or prominence, small hypoechoic nodules or multiple cysts. Most (34/45) were proved to be benign (22 fibrocystic changes, 4 epithelial or lobular hyperplasias, 5 fibroadenomas, and 3 cysts). Of 11 breast cancers detected during HRT, five (45%) were intraductal cancers. For assessing the focal density or mass seen on mammograms or the palpable mass, US examination was of assistance in the decision for follow-up versus biopsy without cessation of HRT.

Increased parenchymal density by HRT might diminish the sensitivity and specificity of mammography for the early detection of breast cancer. However, recent population-based studies showed no significant differences in cancer stages or in the number of mammographically detected cancers or false-negative mammograms between the HRT group and non-HRT group (3).

Increasing numbers of women are undergoing HRT and are studied with mammography and US. The knowledge of normal or benign imaging findings related to HRT is important for differentiating these HRT changes from suspicious malignancy.
References


PREGNANCY-RELATED BREAST CANCER

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Normal Breast Changes during Pregnancy and Lactation
- Proliferation of ducts and lobules
- Increased secretion
- Vascular engorgement and breast enlargement
- Diminished intralobular and interlobular connective tissue
- Enlargement of lobular acini filled with colostrum as progression of the pregnancy

Mammography during Pregnancy and Lactation
Findings: Increased the x-ray attenuation of the breast tissue
Density, heterogeneous coarse, nodular, confluent density with decreased fat
Decreased sensitivity on cancer diagnosis
Safety: Raised carcinogenic effects of radiation on the epithelium due to active proliferation (generally avoid screening mammography)
Fetal Radiation Exposure: 0.0004 mR to the uterus using dedicated mammography (essentially zero)
Screening Mammography: At least 3 months after cessation of lactation
Diagnostic Mammography: Performed immediately after emptying the breast

Ultrasound during Pregnancy and Lactation
Findings: Decreased echogenicity of the parenchyma
Homogeneous and finely granular
Distended lactiferous ducts in late pregnancy and lactation: tubular, hypoechoic or anechoic structures
Safe and Accurate
Valuable in evaluation of palpable lesion during pregnancy and lactation
Valuable in differentiating cystic from solid masses
US-guided needle procedure
**Effect of Pregnancy on Breast Cancer**

Def. of Pregnancy-Associated Breast Cancer (PABC): The diagnosis of breast cancer is made during pregnancy or within 1 year afterward.

Incidence: 0.2 % - 3.8 %, 1 / 3,000-10,000 pregnancies

Determining the effect of the hormonal milieu of pregnancy on a breast cancer is a problem. Less agreement in the effect of a pregnancy on a growing cancer.

Prognosis of PABC: Poor

- **Cause:** Unknown
  - More aggressive growth pattern secondary to the biologic effects of pregnancy
  - Delayed diagnosis secondary to the breast changes of pregnancy
  - Combination of the two

- No statistically significant difference in survival rate between PABC and non-PABC when matched state for stage.
- Axillary lymph nodes metastasis at first diagnosis: 53 - 81 %
- 5-year survival rates: 0 - 17 %
- 5-year survival rates without axillary lymph nodes metastasis: 61 %
- Therapeutic abortion can not be proved beneficial
- Improvement of prognosis: Early detection and immediate treatment

**Breast Cancer Diagnosis**

- Before pregnancy, careful physical examination and baseline mammography, as indicated by the patient’s risk factors, are useful.
- Most benign masses excised during pregnancy were present before pregnancy.
- About 20 % of breast biopsies in pregnancy showed malignancy (similar to nonpregnant population)

1. **Physical Examination**

- As pregnancy progresses, the breasts increase in volume, firmness, and nodularity.
- A mass may feel similar to normal hypertrophic thickness or to be nonpalpable.
- There is no recommended interval in which to reexamine.
- Nipple discharge with blood: common
- Inflammatory Cancer vs. Infection: Skin biopsy

2. **Mammography**

- Liberman L, et al. (Radiology 1994;191:245)
  : 78 % mammographic sensitivity in detecting clinically evident PABC.
  : Negative mammograms in 6 of 8 pregnant patients with breast cancer  
- Microcalcifications

3. **Ultrasonography**
- No evidence of any detrimental effect (Safe, Accurate)  
- Useful as initial imaging study in a palpable or questionable mass in pregnant women  
- Differentiating cystic from solid mass  
- US-guided needle procedure

4. **MRI**
- Not indicated during pregnancy and lactation  
- Strong generalized contrast enhancement in the engorged breast tissue  
- Difficult to identify the malignant processes

5. **Intervention**
- Needle Aspiration Biopsy: US-guided fine needle aspiration or core needle biopsy  
- Excisional Biopsy: Local anesthesia, Second trimester

“The greatest risk to the baby is a delay in the diagnosis of the mother.”

**References**