PREVENTION OF BREAST CANCER

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The best therapy for cancer is prevention. Primary prevention involves health promotion and risk reduction in the general population so that invasive cancers do not develop. These primary preventive measures include the cessation of smoking, lifestyle and diet modification, vitamins and micronutrients supplementation. Identification of genetic risk, understanding of carcinogenesis, development of effective screening tools, avoiding risk factors and effective chemoprevention can lead to decreased morbidity and mortality of cancers in general and more importantly breast cancer. Secondary prevention is the identification and treatment of premalignant or subclinical cancers. Screening by means of mammography is a typical example of secondary prevention. Tertiary prevention is defined as symptoms control and rehabilitation. These definitions may become less useful in the future as they do not account for the new incoming data such as molecular data.

Key Words: Prevention, Cancer, Breast.

SIGNIFICANCE

Breast cancer is the most common lethal neoplasm in women. In the United States of America, breast cancer is second only to lung cancer as a cause of cancer mortality in women. In the kingdom of Saudia Arabia, breast cancer is the most common cancer among women accounting for 20.6% of cancer diseases (Cancer Incidence Report Saudi Arabia 1999-2000) as shown on Table 1. The frequency of treatment failure and cause specific-death is directly related to the stage of the cancer at the time of presentation. More than 90% of patients with stage I disease remain without evidence of breast cancer 10 years after appropriate treatment, while patients with stage VI disease are incurable and require only palliative therapy. It is therefore imperative to diagnose breast cancer in the early stages, to reduce toxicity and improve the efficacy of treatment. In addition to that, there has been growing interests in the development of preventive measures. Among these are diet, lifestyle, selective estrogen receptor modulators (SERMs) and hormonal interventions.

DIETARY PREVENTION

The role of a low fat diet in prevention of breast cancer needs to be verified; however, there are
indications that breast cancer risk is increased with consumption of food rich in fat and low fiber. A low-fat diet might decrease the risk of breast cancers through hormonal mechanism. It has been reported that dietary fat and postmenopausal estrogen levels are directly related. Low-fat and high carbohydrate diet lead to a significant reduction in mammographic breast density and serum estradiol levels in the intervention group as compared to control after 2 years of follow up. A long follow-up may determine if there is a decrease in the incidence of breast cancer in either arm of the study. However, there is no evidence today for an association between total dietary fat intake and breast cancer risk. Dietary modification to increase vegetables and fruits did not show a significant association between any of the specific fruits and vegetables and the reduction in the breast cancer risk. However, many case-control studies suggest that fruit and vegetable consumption may be associated with reduced breast cancer risk. Micronutrient and vitamin intake may play a role in reducing the risk for breast cancer. Some clinical studies have found an inverse association of dietary intake of vitamin E and breast cancer incidence. In the USA, a prospective study of over 80,000 nurses did not find an association between breast cancer risk and dietary intake of vitamin C, vitamin E, or B-carotene. A high intake of folate, Beta-carotene, Vitamin A and vitamin C may reverse the increased risk associated with alcohol consumption. Soya beans contain isoflavones, which are converted in the bowel to antioxidative and antiestrogenic compounds and there are epidemiologic data suggest that the consumption of soya products is associated with reduced risk of breast cancer. The data available today about the preventive effect of fiber-rich and low-fat diet, vitamins and soya are inclusive and information gained from an ongoing large scale randomized clinical trials may help to clarify these issues.

**LIFESTYLE FACTORS**

Lifestyle factors which may affect breast cancer risk include sexual behavior pattern, alcohol intake, physical activity and obesity. Women who do heavy manual labor or strenuous exercise have a low breast cancer risk. The protective mechanism of physical activity is not known but physical activity may have an effect on the endogenous hormone. Epidemiologic data indicate that obesity (body mass index $\geq 30$kg/m$^2$) increases the risk of breast cancer. The risk for breast cancer in a postmenopausal woman who gained more than 20 kg after age 18 and had never had hormone therapy is approximately twice the risk for women who did not gain weight.

**SERMS AS PREVENTIVE MEASURES OF BREAST CANCER**

The term SERM is an abbreviation for selective estrogen receptor modulators. These agents include tamoxifen, raloxifene and toremifene. The mechanisms of action of these agents are either estrogenic or antiestrogenic effects depending on the specific end organ. The main finding of the breast cancer prevention trial (BCPT) was a 49% reduction in the incidence of breast cancer among the participants who were randomly assigned to receive tamoxifen. Tamoxifen was the first agent for primary cancer prevention to be approved by food and drug administration (FDA) of USA in 1998. Adverse effects of tamoxifen include 2.53 times greater risk of developing invasive endometrial cancer, the risk for pulmonary embolism is three times more and stroke is nearly...
twice as common in patients taking tamoxifen. The number of events in the national surgical adjuvant breast project are shown in Table 2 (NSABP Trial). Other side effects include cataracts, vaginal discharge, hot flushes, dry vagina, weight loss and vaginal bleeding. The net benefit versus risk depends on age, presence or absence of uterus and the baseline risk of breast cancer. FDA approved raloxifene for the prevention of osteoporosis in postmenopausal women in 1997. Generally, the side effects of raloxifene are similar to tamoxifen except that raloxifene did not increase the risk of endometrial hyperplasia. The favorable influence of tamoxifen and raloxifene on lipid metabolism to reduce the risk of coronary heart disease is not yet established. STAR trial will provide a direct comparison between tamoxifen and raloxifene on vascular events such as pulmonary embolism and deep vein thrombosis as well as compare the efficacy of these two drugs as breast cancer preventives. Breast cancer incidence is the primary end point of this study. Study designs, follow up and results of breast cancer prevention trial, international breast cancer intervention study, multiple outcomes of raloxifene evaluation and study of tamoxifen and raloxifene are summarized in Table 3. Taken together, these studies demonstrated a significant reduction in the risk of breast cancers in women on tamoxifen and raloxifene. The drugs, tamoxifen and raloxifene reduce the risk of only breast cancer positive for estrogen receptor (ER) but the risk of breast cancer negative for ER is not affected.

EXOGENOUS ESTROGEN (OC AND HRT)
Epidemiologic evidence strongly suggests a role for estrogen, whether endogenous or exogenous, as a proliferative factor contributing to breast carcinogenesis. It appears there is increased risk of breast cancer in young women (younger than 35 years) with current prolonged use of oral contraceptives (OC) more than 5 years. This risk appears to level off after the use of OC has stopped. We therefore advice women not to use oral contraceptive pills more than 5 years unless it is medically indicated. In relation to menopausal replacement therapy, there are data to suggest that hormone replacement therapy with estrogen is associated with increased risk of breast cancer among recent estrogen users, and this risk is proportional to the duration of use. It appears that combined estrogen and progestin HRT induces higher risk of breast cancer than estrogen replacement therapy alone and this risk is proportional to duration of HRT use. Before considering the use of HRT, patients should weigh the risk of breast cancer against the evidence from observational studies that it may reduce the overall mortality.

PROPHYLACTIC MASTECTOMY
The risk of women developing breast cancer is influenced by a range of factors and it is difficult to find a formal definition of high risk women. Women who carry mutation in BRCA1 and BRCA2, family histories of genetically transmitted breast cancer, women who have received mantle irradiation, women with lobular carcinoma in situ are considered high risk. In a retrospective cohort study, the reduction in risk of death from breast cancer ranged from 100% among moderate risk women to 80% among high risk women. This study provides the best available evidence that prophylactic mastectomy prevents the development of breast cancer in women with moderate and high risk. Women considering bilateral mastectomy as an optional preventive measure need information about both the effectiveness and morbidities of this procedure. This should be done in association with the patient and her doctor.

### Table 2: Numbers of events in NSABP study

| Type of event                  | Placebo | Tamoxifen | Risk Ratio |
|-------------------------------|---------|-----------|------------|
| Invasive breast cancer        | 175     | 89        | 0.51       |
| Noninvasive breast cancer     | 69      | 35        | 0.5        |
| Invasive endometrial cancer   | 15      | 36        | 2.53       |
| Fractures                     | 137     | 111       | 0.81       |
| Stroke                        | 24      | 38        | 1.59       |
| Transient ischemic attack     | 25      | 19        | 0.76       |
| Pulmonary embolism            | 6       | 18        | 3.01       |
| Deep vein thrombosis          | 22      | 35        | 2.60       |

### Table 3: Breast cancer prevention trials

| Trial   | Agents vs. placebo | MFU in months | Odds ratio (IBC) |
|---------|---------------------|---------------|------------------|
| BCPT    | T 20 mg/day         | 55            | 0.51             |
| IBIS    | T 20 mg/day         | 48            | 0.67             |
| MORE    | R, 60 mg or 120 mg/day | 47         | 0.28             |

MFU=Median follow-up, IBC=Invasive breast cancer, BCPT=Breast cancer prevention trial, T=Tamoxifen, IBIS=International breast cancer intervention study, MORE=Multiple outcomes of raloxifene evaluation, R=Raloxifene
with cancer risk assessment and other preventive strategies including tamoxifen.

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