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WHO consensus conference on diet and cancer*

Members of the breast cancer panel

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Do the epidemiological or laboratory data support the ingestion of supplemental micronutrient(s) as a primary preventive measure for breast cancer?

Although anti-oxidant vitamins and minerals, such as vitamin A (including beta-carotene), vitamins E, C and F and selenium, have been widely suggested as potential anti-cancer agents against a number of malignancies, epidemiological studies have failed to show a consistent protective effect of such compounds against breast cancer.

Laboratory studies in animal models of vitamins C. D and E have failed to show a protective effect. Investigations of the role of selenium alone or in combination with vitamin E remain open. There is therefore insufficient supportive evidence to justify any new clinical or population-based trials of dietary anti-oxidants or vitamins as a primary or secondary preventive measure in breast cancer. In general, a better understanding of oxidant and anti-oxidant status in humans (particularly as related to breast cancer) and the mechanisms that lead to unfavourable or favourable effects is necessary before additional exploration of the compounds at the clinical or population level as preventive measures is warranted.

What is the relationship between weight, dietary fat and exercise in breast cancer pathogenesis?

This general area was easily the most contentious considered by the committee, to a significant degree, because of the complexity of the inter-relationship of these three factors and the difficulty in determining the contributions of each, and because of the relative weight given to the various types of evidence by different members of the panel. In arriving at a 'consensus', more weight was put on analytical epidemiological data (which supports causal inference) than ecological epidemiological data (which does not support causal inference). Additionally, more weight was given to direct than indirect evidence in experimental systems.

Epidemiological studies are concordant in demonstrating that overweight increases breast cancer risk in postmenopausal women. As overweight is the result of an imbalance between energy intake and energy expense, all factors increasing energy intake appear to be risk factors. Fat is a highly caloric nutrient that has often been incriminated as contributing to breast cancer risk. Whether the effect of alcohol is mediated through overweight, and especially abdominal obesity, is unknown, but epidemiological studies are consistent in demonstrating that increased alcohol intake is associated with increased breast cancer risk.

Animal data show a promoting effect of polyunsaturated fatty acids on carcinogenesis. This was confirmed in an ecological study, showing that polyunsaturated fat in humans increased the risk, but less than saturated fat. Several studies found a protective effect of mono-unsaturated fat (the Mediterranean diet). Analytical epidemiological data based on different statistical models favour a role for the energy content of dietary fat, but not for a specific fatty acid. Other macronutrients, if ingested in excess, might be found to be risk factors, especially in the absence of physical exercise, the other arm of energy balance. Indeed, when physical exercise has

been evaluated in analytical epidemiological studies, a reduction of breast cancer risk has been consistently observed, especially for exercise at a younger age.

The interaction of physical exercise and hormonal status is important. Regular physical exercise reduces oestrogen levels in pre- and postmenopausal women, reduces fat deposits and improves insulin sensitivity. Physical activity started in young adult life reduces the risk of breast cancer in pre- and peri-menopausal women. The risk reduction may be hormonally mediated, since the onset of menarche is delayed and the number of ovulatory menstrual cycles is decreased in these women. In retrospective studies, the breast cancer risk of women practising regular exercise since their menarche is markedly reduced. No clinical trials have directly attempted to answer the question of whether a decrease in dietary fat intake, reduction of body weight or increased exercise can have an impact on breast cancer pathogenesis; although the Women's Health Initiative, the largest clinical trial ever mounted, addresses the first two parameters in its complex 3 × 2 factorial randomized design.

What is the relationship of obesity, hormones and breast cancer?

Several lines of evidence indicate that the effect of obesity, energy imbalance and sedentarity on breast cancer risk is mediated by hormones and growth factors. Extragonadal oestrogen synthesis, through aromatization of androstenedione in adipose tissue, has long been evoked as the major mechanism underlying the relationship between obesity and breast cancer, explaining both the early menarche and late menopause via elevated oestrogen levels. Since abdominal (visceral) obesity, however, seems to be specifically associated with the risk of breast cancer, an alternative hypothesis (but not mutually exclusive) has developed strong support, and proposes that abdominal obesity is part of the insulin-resistance syndrome in which hyperinsulin-aemia, low levels of sex hormone-binding globulin and insulin-like growth factor binding protein, and, consequently, high levels of testosterone and high level of insulin-like growth factor-1 (IGF-1) result; the latter is a potent growth factor for breast cancer cells. Increased IGF-1 might also underlie the relationship between height and breast cancer. An affluent Western diet increases the production of a

growth hormone, which stimulates hepatic IGF-1 synthesis, and combined with decreased physical exercise results in an early age at menarche.

Fibre may also be protective, through indirect (a low-calorie food, decreased nutrient density and increased insulin sensitivity) and direct actions by directly interfering with hormone metabolism and physiology. In the colon, through its action on the bacterial flora, fibre decreases the unconjugation of oestrogens, reduces enterohepatic recirculation and increases faecal excretion. In addition, diphenolic compounds, lignans and isoflavonoids are present in some fibre, especially soya beans, and, to a lesser extent, other legumes. These compounds are modified by the colonic flora to biologically active substances with tamoxifen-like activity. The binding of these compounds to the oestrogen receptor may result in a predominant antagonistic, anti-oestrogenic effect. Wheat bran supplementation showed reductions in serum oestrogen and oestradiol in premenopausal women. In addition, a high-fibre diet has improved insulin sensitivity, and hyperinsuli-naemia is a known risk factor for breast carcinoma in pre- and postmenopausal women.

Do the current clinical trials of breast cancer prevention take dietary influence into consideration?

Unfortunately, neither the tamoxifen nor the 4-hydroxyphenylretinamide trials include assessment of dietary factors. However, retrospective analysis of the effect of lipids and serum lipids should be possible. The Women's Health Initiative is testing the effect of a low-fat diet on breast and colon cancer incidence as well as cardiovascular disease morbidity and mortality, but physical activity *per se* is not being assessed.

Is the precursor lesion of breast cancer sufficiently defined to measure the effect of dietary or other compounds?

The consensus of the committee was 'no, not yet'; although the more frequent use of mammography has led to the increasing recognition of diffuse carcinoma *in situ* (DCIS). To date, no non-invasive test, including magnetic resonance imaging, positron electron tomography or mammography has been able to consistently define a precursor lesion. It is not

known whether diet changes or supplementation with vitamin E or other vitamins can change the natural history of this lesion.

Can a high-risk population for breast cancer prevention trials be defined?

At the time of this conference, the impact of molecular genetics and the identification of the BCRAI and BCRAZ and ATM genes as significant contributors to risk were just becoming understood. It is clear that this group of individuals represents a subset of at-risk individuals in whom there is a strong genetic influence on breast cancer pathogenesis. Nevertheless, as a subset, these individuals should represent a useful group in which to study the influence of diet, obesity and physical exercise on the natural history of breast cancer.

However, for approximately 85% of women who develop breast cancer, the underlying hereditary risk is polygenic. Both the NNSABP and London tamoxifen trials define a high-risk group by a combination of familial and non-familial factors that in the median case result in a score equivalent to the risk of a 60-year-old woman.

What evidence is there that dietary intervention used as a treatment affects the clinical outcome of breast cancer?

To date, there is no dietary manipulation that has been shown to affect clinical outcome, and therefore no recommendation can be made. However, postmenopausal patients with breast cancer who are less overweight and eat less fat showed a better survival than their counterparts in the highest tertile of body mass index.

Do current animal models provide a means to study human breast cancer development?

Yes, but there are major limitations. These include the fact that:

● the metabolism of nutrients and oestrogens in available animal models is different from that in humans, and
● carcinogens are routinely used in animals to induce tumours, and these compounds do not appear to play a role in human breast cancer pathogenesis.

What general recommendations can be given for primary prevention of breast cancer?

The recommendations include:

● fruits and vegetables should be eaten at every meal and whole grains at least once a day;
● caloric intake should be decreased and exercise increased so that overweight/obesity does not occur;
● total fat intake should be reduced by limiting meat and fatty dairy products and increasing consumption of the fish and oils rich in mono-unsaturated fats (olive oil, grape seed oil);
● intake of alcoholic beverages should be decreased; and
● healthy eating and exercise habits should be started early in life.

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