

## Diet, Lifestyle and Breast Cancer

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### Introduction

Breast cancer is the most commonly diagnosed malignancy in women and is one of the leading causes of mortality in Canada and the United States<sup>1</sup>. Although the exact causes have not yet been established, the risk of developing breast cancer can be modified by genetic, hormonal and environmental factors. A recent study involving almost 90,000 twins suggests that environmental factors are the major cause of breast cancer<sup>2</sup>. The *World Cancer Research Fund* and the *American Institute for Cancer Research* published a comprehensive guide to cancer prevention that estimated that as many as 30-40% of all cancer cases could be prevented by changes to modifiable risk factors such as to diet and lifestyle factors<sup>3</sup>. There is growing evidence that diet has a major impact on the risk of breast cancer, however, the precise role of specific dietary factors needs to be elucidated.

### Lifestyle factors

#### Reproductive History

Women who reach menopause at a later age or those who began menstruation at an early age, have a higher risk of developing breast cancer<sup>1</sup>. This may be due to an increased lifetime exposure to ovarian hormones that are known to promote carcinogenesis. An early age of first full-term pregnancy lowers the risk of breast cancer partly by inducing mammary gland differentiation, thereby making the epithelial cells less susceptible to malignant transformation. Prolonged lactation has also been associated with a reduced risk of breast cancer although the exact mechanisms are not clear<sup>4</sup>. Oral contraceptives are not considered a major risk factor for breast cancer, but hormone replacement therapy has been associated with a small increase in risk.

#### Obesity, Physical Activity, Weight gain

The relation between obesity and breast cancer differs for premenopausal and postmenopausal breast cancer<sup>5</sup>. Higher body mass is associated with an increased risk of postmenopausal breast cancer, but a lower risk of premenopausal breast cancer. The inverse association between higher body mass and premenopausal breast cancer may be caused by the reduction in ovulatory cycles among obese women. Weight gain during adulthood increases the risk of breast cancer, whereas physical activity decreases risk, especially among postmenopausal women.

#### Smoking

Although smoking is a well known risk factor for several cancer sites it seems that it is

not a significant risk factor for most breast cancers. However, a recent report found that a subset of postmenopausal women with a specific genotype may be at a higher risk for developing breast cancer due to smoking<sup>6</sup>.

### Dietary Factors

#### Fat and Fiber

Women living in countries with a high incidence of breast cancer typically consume diets that are high in animal fat and protein, and low in whole grains, fruits and vegetables<sup>3</sup>. The effects of dietary fat on breast cancer have been extensively investigated but the association remains an issue of considerable debate<sup>7</sup>. Since fat provides more energy on a gram per gram basis than protein or carbohydrate it is difficult for studies to control the intakes of both energy and fat while keeping the intakes of other nutrients constant. Animal studies are often cited as providing compelling evidence for the effects of fat on breast cancer, yet even these studies do not make a clear distinction between the effects of fat *per se*, and the effects of excess calories. The distinction between a low-fat diet and a low-calorie diet is crucial because many low-fat foods are high in sugar and remain high in total calories. In animal studies, caloric restriction has consistently been shown to be a strong inhibitor of mammary tumors. The findings from epidemiological studies of dietary fiber and breast cancer have also been equivocal<sup>8</sup>. Inconsistencies between studies may be due to the different types and sources of fiber (e.g. grains, fruits, or vegetables). Direct evidence for the protective effect of fiber has come from animal studies but, like the effects of fat, it is not clear how much of an effect is due to a displacement of calories, and how much is caused by some other component of fiber. Although high-fiber diets are more commonly associated with a reduced risk of colon cancer, the lack of effect in recent clinical trials<sup>9,10</sup>, along with the inconsistent findings on breast cancer, suggests that fiber is unlikely to have a major impact on breast cancer risk.

#### Fruits and Vegetables

Fruits and vegetables are an excellent source of several micronutrients and phytochemicals that are purported to have anticancer effects. A meta-analysis of fruit and vegetable consumption and risk of breast cancer shows a protective effect with vegetables, but not with fruits<sup>11</sup>. More recently, a large prospective study involving more than 350,000 women found no association between the intake of fruits or vegetables and risk of breast cancer<sup>12</sup>. However, certain vegetables such as spinach, broccoli,

brussels sprouts and string beans were associated with a non-significant reduction in risk. Thus, it is possible that specific phytochemicals found in some of these foods could be effective in lowering the risk of breast cancer. However, many fruits and vegetables are excellent sources of several of the key nutrients. The individual effects of a number of these nutrients have been investigated in association with breast cancer risk.

#### Folate

Folate is a water soluble B vitamin that plays an essential role in one-carbon metabolism. A folate deficient diet is associated with a high spontaneous mutation rate and could increase the initiation of breast carcinogenesis<sup>13</sup>. Indeed, women who consume a low folate diet have an increased risk of developing breast cancer<sup>14,15</sup>. This effect is more pronounced in women with higher intakes of alcohol<sup>14</sup>, which is known to affect folate metabolism<sup>16</sup>. However, the effects of folate have not been supported by animal studies<sup>17</sup>. This may be due, in part, to the difficulty in inducing folate deficiency in some animals, and the limited knowledge of the effects of folate on different stages of carcinogenesis.

#### Vitamin C, Vitamin E and Selenium

Antioxidants protect cells from oxidative damage by scavenging reactive oxygen species. Oxygen free radicals are thought to be involved in the initiation of carcinogenesis by inducing DNA damage, which may give rise to cancer causing mutations. This proposed link between oxidative damage and cancer has prompted a number of researchers to investigate the effects of antioxidants on breast cancer. Vitamin C (ascorbic acid) is the major water-soluble antioxidant in the diet and a few studies have shown an inverse association between intake levels and risk of breast cancer<sup>18</sup>. Vitamin E is a major lipid-soluble antioxidant which may protect against breast cancer, but the studies conducted to date have not been conclusive<sup>18,19</sup>. Animal studies that have assessed the effects of vitamin E on the development of chemically-induced mammary tumors have also been equivocal<sup>20</sup>. It has been proposed that vitamin E supplements at levels that exceed dietary requirements may prevent breast cancer in women, however, such an intervention study has not yet been conducted<sup>21</sup>. Dietary selenium plays an important role in the endogenous antioxidant system. Although animal studies have shown a protective effect<sup>22</sup>, studies in humans have not<sup>23</sup>.

#### Vitamin A and $\beta$ -carotene

Vitamin A can be obtained from the diet as preformed (retinol) from animal sources or as a

precursor ( $\beta$ -carotene) from plants. Retinoids have been shown to affect cell growth and differentiation and synthetic analogs are currently being evaluated in clinical trials.  $\beta$ -Carotene, the most abundant dietary carotenoid, is a strong antioxidant but is known to have other biological effects as well. There is evidence that both retinol and carotenoids lacking vitamin A activity may prevent breast cancer in women<sup>18</sup>. The few animal studies that have evaluated the effects of individual carotenoids on tumorigenesis do not show any clear benefit.

### Calcium and Vitamin D

Vitamin D is best known for its role in regulating calcium homeostasis. In addition to the diet, sunlight also provides an important source of vitamin D by enabling the body to synthesize its own supply from cholesterol. Recent evidence suggests that dietary calcium and vitamin D can lower the risk of breast cancer<sup>24</sup>. Some of the earliest evidence supporting a role for vitamin D in preventing breast cancer comes from studies linking sunlight exposure to a lower incidence of breast cancer<sup>25</sup>. The geographical distribution of breast cancer in the US shows higher rates among women living in the northeast, where exposure to sunlight is low, compared to those living in the southwest, where sunlight exposure is considerably higher. The hormonal form of vitamin D (1-25-dihydroxyvitamin D) affects the growth and differentiation of epithelial cells, and synthetic analogs have been developed as potential anti-cancer agents. Women who have a commonly mutated form of the vitamin D receptor are at increased risk of developing breast cancer<sup>26</sup>. A recent analysis from the NHANES I follow-up study shows that vitamin D from either sunlight or the diet is associated with a lower risk of breast cancer<sup>27</sup>. The *Women's Health Initiative* (WHI) is an ongoing clinical trial designed to evaluate the effects of dietary intervention and hormone replacement on a variety of chronic diseases including breast cancer<sup>28</sup>. One of the intervention groups includes calcium and vitamin D – given primarily to prevent osteoporosis – which could yield valuable information on the effect of these nutrients on breast cancer.

### Phytoestrogens

Phytoestrogens are plant-derived compounds with both estrogenic and anti-estrogenic properties. Soy products commonly consumed by Asian women are one of the richest sources of phytoestrogens such as isoflavones. There is some evidence that women who consume higher levels of phytoestrogens have a reduced risk of breast cancer<sup>29</sup>, an observation supported by *in vitro* and animal studies. However, the safety of high levels of phytoestrogens has not been assessed.

### Alcohol and Caffeine

Increased alcohol consumption has been consistently linked to an elevated risk of breast cancer in both human and animal studies<sup>30,31</sup>. As mentioned earlier, the effect of alcohol is most pronounced among women with low intakes of folate<sup>14</sup>, suggesting that the effects of alcohol might be caused by antagonizing folate metabolism. Coffee, the major source of caffeine in North America, does not have any significant effect on the risk of breast cancer<sup>3</sup>.

### Summary

One of the difficulties in establishing a clear association between diet and breast cancer is determining accurately what women eat. Despite a number of studies suggesting a protective effect of certain dietary factors on breast cancer risk, other studies have not observed such associations. Improvements to the methods used to assess dietary intake, the use of biomarkers of long-term exposure and studies that assess gene-diet interactions will provide important new insights into the effects of diet on breast cancer. A diet that is lower in fat and higher in whole grains, fruits and vegetables tends to be less energy dense and more nutrient dense. Adherence to such a diet could help women maintain an ideal body weight and possibly reduce their risk of breast cancer along with other chronic diseases. Ongoing studies assessing the effects of various dietary interventions on breast cancer recurrence such as the *Women's Intervention Nutrition Study* (WINS) and the WHI will improve our understanding of the role of diet in breast cancer prevention.

TABLE 1: Risk Factors for Breast Cancer

- Age
- Family history
- Genetic mutations in BRCA1, BRCA2, ATM
- Early menarche and/or late onset of menopause
- Nulliparity
- Weight gain during adulthood

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