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Commonly used medications associated with reduced risk of cancer – evidence and pitfalls

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The list of commonly used medications possibly associated with a reduction in the risk of cancer is growing. Among these drugs are aspirin, NSAIDs, Cox-2 inhibitors, statins, bisphosphonates, HRT, levothyroxine, colchicin, allopurinol and the anti-glycemic drug metformin. Most medications show a similar association of cancer risk reduction across different cancer sites; some are more specific to one type of cancer while others may reduce risk in one site and increase risk in another.

Most data on common drugs come from observational studies since most of these drugs have not been studied in randomized controlled trials (RCTs) with cancer as a predefined endpoint. Data from observational studies are prone to a variety of biases making its use problematic. Data from retrospective studies on medications used for one clinical indication are also problematic as it is hard to separate the preventive effect of the drug from the possible association between the disease (for which the drug was given) and cancer. Most of these commonly used medications are off patent and therefore there is no incentive for the drug industry to test them in RCTs for anti-cancer effects. RCTs might not be feasible at all for widely used drugs, both because of the high risk of contamination of the control arm as well as the selectivity of controls who will end up not taking the drug of interest. Thus, whether such common drugs actually have a cancer prevention effect can only be alluded to through a natural experiment where reduction in cancer or a specific cancer occurs concurrently with an increase in the use of these drugs.

The literature is full of conflicting reports on the association of medications with cancer risk. There are many factors that can contribute to this – differences in types of studies, in types of medications within classes (for example simvastatin vs. atorvastatin), doses, length of use, mode of delivery (oral, IV, patch), different populations with possible differences in drug metabolism.

While the current data are very promising, all of these pitfalls add to the difficulty in understanding the true association between commonly used medications and cancer risk.

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Physical activity and breast cancer risk: epidemiologic evidence and biologic mechanisms

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To date, 98 observational epidemiologic research studies have been conducted worldwide on the association between physical activity and breast cancer risk. Of these studies, 73 met the inclusion criteria for this review. A reduced breast cancer risk associated with the highest levels of physical activity, regardless of the physical activity assessment methods used in these studies, was found in 41 of these studies. The strength of the risk reduction is approximately 25–30% when comparing the participants with the highest to lowest physical activity levels in these studies. Evidence of a dose-response effect of increasing cancer risk reduction with increasing levels of activity was also found in the studies that demonstrated a benefit of physical activity on breast cancer risk. All types of activity have been shown to reduce breast cancer risk, with somewhat stronger evidence for recreational activity. Sustained activity done throughout lifetime appears to have the most benefit, however, activity done in the postmenopausal period has been shown to reduce breast cancer risk even more than activity done before menopause. Both moderate and vigorous intensity activity decrease breast cancer risk with a somewhat greater benefit with vigorous activity. Several other factors may act as effect modifiers of the association between physical activity and breast cancer. The effect of physical activity appears to be somewhat stronger in normal weight women, in women of non-white racial background, with hormone receptor negative tumours, in women without a family history of breast cancer and with parous women. Randomized controlled trials are investigating the exact biologic mechanisms whereby physical activity influences breast cancer risk. The main hypothesized mechanisms include an effect on sex steroid hormones, insulin resistance, inflammation and body composition. Evidence is emerging that these hypothesized mechanisms are involved in the etiology of physical activity and breast cancer risk. Understanding these mechanisms will provide important evidence, along with the observational epidemiologic data, to refine the public health recommendations regarding the exact dose, type and timing of physical activity that is required to reduce breast cancer risk.

Session 6. Chemoprevention of Breast Cancer: The Trial Facts

S18

Chemoprevention of breast cancer by tamoxifen and raloxifene: the US-experience in NSABP-prevention trials

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The Breast Cancer Prevention Trial (BCPT; NSABP P-1) was a randomized, placebo-controlled, double-blind clinical trial initiated in June 1992 by collaboration of the National Cancer Institute and the National Surgical Adjuvant Breast and Bowel Project (NSABP) to evaluate whether tamoxifen reduced risk of invasive breast cancer in women at increased risk. The primary aim of the trial was to evaluate the effectiveness of 20 mg/day of tamoxifen orally for five years in preventing the occurrence of invasive breast cancer in women at high risk. Secondary aims of the trial assessed osteoporotic fractures and cardiovascular disease in women on tamoxifen compare to control group. Tamoxifen reduced the risk of invasive breast cancer by 49%, with cumulative incidence through 69 months of follow-up of 43.4 versus 22.0 per 1000 women in the placebo and tamoxifen groups, respectively. The decreased risk occurred in women aged 49 years or younger (44%), 50–59 years (51%), and 60 years or older (55%); risk was also reduced in women with a history of lobular carcinoma in situ (56%) or atypical hyperplasia (86%) and in those with any category of predicted 5-year risk. Tamoxifen reduced the risk of noninvasive breast cancer by 50%. Tamoxifen reduced the occurrence of ER-positive tumors by 69%, but no difference in the occurrence of estrogen receptor-negative tumors was seen. Tamoxifen administration did not alter the average annual rate of ischemic heart disease, but a reduction in fractures was observed. The rate of endometrial cancer was increased in the tamoxifen group. The rates of stroke, pulmonary embolism, and deep-vein thrombosis were elevated in the tamoxifen group; these events occurred more frequently in women aged 50 years or older. The annual event rate for invasive breast cancer was 3.4/1000 in the tamoxifen group and 6.8/1000 in the placebo group. There was a 50% reduction in rate of noninvasive breast cancer in women taking tamoxifen. The annual event rate for noninvasive breast cancer was 1.35/1000 in the tamoxifen group and 2.68/1000 in the placebo group. The relative risks (RR) for invasive breast cancer reduction were 0.56 for women less than 50 years of age; 0.49 for women 50 to 59 years of age; and 0.45 for women