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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

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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

60 years of age and older. To compare the relative effects and safety of raloxifene and tamoxifen on the risk of developing invasive breast cancer and other disease outcomes, the NSABP conducted the Study of Tamoxifen and Raloxifene (STAR) trial, a prospective, double-blind, randomized clinical trial Patients were 19,747 postmenopausal women of mean age 58.5 years with increased 5-year breast cancer risk (mean risk, 4.03±2.17%) as estimated by the Gail model. Participants were randomly assigned to receive either tamoxifen at a dose of 20 mg per day or raloxifene 60 mg per day over 5 years. Outcomes of interest were incidence of invasive breast cancer, uterine cancer, noninvasive breast cancer, bone fractures, and thromboembolic events. The trial was designed to assess statistical equivalence of the two therapies and was powered to report data when 327 cases of invasive breast cancer occurred. After a median of 3.2 years of therapy in the trial, there were 163 cases of invasive breast cancer in women assigned to tamoxifen and 168 in those assigned to raloxifene (incidence, 4.30 per 1000 vs. 4.41 per 1000; RR = 1.02; 95% CI, 0.82–1.28). The cumulative incidence through 72 months for the 2 treatment groups was 25.1 and 24.8 per 1000 for the tamoxifen and raloxifene groups, respectively (P = 0.83). When the treatment groups were compared by baseline categories of age, history of LCIS, history of atypical hyperplasia, Gail model 5-year predicted risk of breast cancer, and the number of relatives with a history of breast cancer, the pattern of no differential effect by treatment assignment remained consistent. There were no differences between the treatment groups in regard to distributions by tumor size, nodal status, or estrogen receptor level. The incidence of noninvasive breast cancer was similar in the two treatment groups.

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Prevention of breast cancer by newer SERMs and the future

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Clinical breast cancer prevention trials in healthy women have shown that tamoxifen and raloxifene will reduce breast cancer risk and both have now been approved in the USA for risk reduction of breast cancer. However neither have been widely used to prevent breast cancer. Further clinical studies have therefore been undertaken with two newer SERMs, arzoxifene and lasofoxifene. Preclinical and early clinical data indicate that arzoxifene, is more potent with better bioavailability than raloxifene. The results of the phase 3, multicenter, placebo-controlled, double-blind GENERATIONS trial of 9354 postmenopausal women with osteoporosis or low bone mineral density (BMD) were reported at San Antonio in 2009. Participants were randomly assigned to arzoxifene 20 mg/d (N = 4676) or placebo (N = 4678). The primary outcomes were radiographic vertebral fracture in the osteoporotic population at 36 months and invasive breast cancer in all study participants at 48 months. The results showed a 41% reduction in the incidence of vertebral fractures ($p < 0.001$) and 56% reduction in incidence of invasive breast cancer (43 placebo vs 19 arzoxifene, HR 0.44 $p = 0.002$) and a 70% reduction in invasive ER-positive breast cancer (30 placebo vs 9 arzoxifene, HR 0.30 $P = 0.001$). Other findings included no significant reduction in ER-negative breast cancer, non-vertebral fractures or cardiovascular events. Generally, arzoxifene was well tolerated, although there was a significant increase in VTE, gall bladder disease, pulmonary disorders, hot flushes, muscle cramps and gynaecological events in the arzoxifene group. In summary although the overall benefit/risk profile of arzoxifene did not represent a meaningful advancement in the treatment of osteoporosis the trial did provide further support for a significant risk reduction of invasive breast cancer by SERMs in postmenopausal women.

Pre-clinical studies and clinical trials in breast cancer patients showed that lasofoxifene is more potent than raloxifene in reducing bone loss and serum cholesterol with no increased risk of endometrial cancer. The results of the phase 3, multicenter, placebo-controlled, double-blind PEARL trial of two doses (0.25 or 0.5 mg/day) of lasofoxifene compared to placebo for 5 years on the incidence of ER+ breast cancer in 8556 postmenopausal women with osteoporosis were presented at San Antonio in 2008 and St Gallen in 2009. Breast cancer (invasive or non invasive) occurred in 24 women in the placebo group compared to 20 women in the lasofoxifene 0.25 mg/day group (HR = 0.82, 95% CI 0.45–1.49, $p = 0.52$) and 5 women in the 0.5 mg/day lasofoxifene group (HR = 0.21, 95% CI 0.08–0.55, $P < 0.001$). ER-positive breast cancer (invasive or non invasive) occurred in 21 women in the placebo group compared to 11 women in the lasofoxifene 0.25 mg/day group (HR = 0.52, 95% CI 0.25–1.08, $P = 0.073$) and 4 women in the 0.5 mg/day lasofoxifene group (HR = 0.19, 95% CI 0.07–0.56, $P < 0.001$). There was no reduction in ER-negative breast cancer. Lasofoxifene 0.5 mg per day caused a significant reduction in the incidence of vertebral fractures at 3 years (HR 0.58, 95% CI 0.47–0.70) and non vertebral fractures at 5 years (HR 0.76, 95% CI 0.64–0.91). However there was an increased risk of VTE events (HR 2.1, 95% CI 1.20–3.60), but not stroke (HR 0.64, 95% CI 0.41–0.99) and the incidence of major CHD events was significantly decreased (HR 0.68, 95% CI 0.50–0.93). There was also an increase in gynaecological toxicity including endometrial thickening, uterine polyps, and fibroids but there was no increase in endometrial atypia or cancer. Overall mortality was similar for lasofoxifene 0.5 mg/d and placebo (HR 1.12, 95% CI 0.80–1.56). In summary, 0.5 mg/day of lasofoxifene significantly reduced the incidence of ER-positive breast cancer, vertebral and non vertebral fractures and major coronary heart disease events with no detected increase in endometrial cancer risk in postmenopausal osteoporotic women. This improvement in the spectrum of benefits and the lower toxicity profile with lasofoxifene 0.5 mg/day may encourage more widespread use of SERMs to prevent breast cancer especially in women with osteoporosis. However, the problem of having to treat many healthy women to prevent a relatively small number of cancers remains an issue. Most prevention trials were of short duration and toxicity with SERMs occurs predominantly during treatment whereas the benefit of breast cancer risk reduction continues for many years after treatment and this cumulative accrual of benefit needs to be considered when calculating the overall benefit. The possibility of identifying more accurately those women who are likely to develop ER-positive breast cancer has become a priority in order to take the strategy of SERM prevention of breast cancer forward. The algorithm for detecting ER-positive breast cancer may need to be integrated into the risk factors for osteoporotic fractures, CHD and stroke to identify a population of healthy women who may really gain overall clinical benefit from SERM intervention. This is likely to be possible once we are able to identify the commonly occurring polymorphisms for risk of these diseases, the interaction of environmental factor with the genetic risks and the phenotypic features of these risk factors.

In conclusion the development of SERMs to prevent breast cancer with low toxicity and a spectrum of other benefits has probably been optimised and now the challenge is to more clearly identify those women who will have a clinically worth while benefit from such medication.