Breast cancer chemoprevention: little progress in practice?

In The Lancet, Jack Cuzick and colleagues report the first results from IBIS-II (International Breast cancer Intervention Study II), in which 3864 postmenopausal women at high risk of breast cancer were randomly assigned to receive the potent, non-steroidal aromatase inhibitor anastrozole or placebo every day for 5 years. After a median follow-up of 5 years, 40 (2%) of the 1920 women in the anastrozole group and 85 (4%) of the 1944 placebo group had developed breast cancer (hazard ratio 0.47, 95% CI 0.32–0.68). This finding is in keeping with those of other similar studies. So far, unsurprisingly, the investigators have not recorded evidence for a difference in breast cancer or all-cause mortality: 18 deaths had been reported in the anastrozole group and 17 in the placebo group. The design of IBIS-II was essentially pragmatic: women enrolled were at increased risk of breast cancer, whether because of family history or previous diagnosis of non-invasive lesions (eg, ductal carcinoma in situ, lobular carcinoma in situ, and atypical ductal hyperplasia). The predicted cumulative incidence of all breast cancers after 7 years in the control group (5.6%) reflects an increased risk in the participants, and is in line with other similar studies of breast cancer prevention. All the women in IBIS-II had a mammogram and physical breast examination at baseline, unless these procedures had been done within 12 months of enrolment, and then at least every 2 years during the treatment period. 78 (62%) of 125 cancers were detected through screening. At the end of the 5 years, follow-up was as per local practice (including imaging), with no central review of imaging from either before or during the study, or of the lesions (invasive or otherwise) diagnosed before or during the trial. The issue with studies of pharmacological breast cancer prevention is whether there is true prevention of clinically significant, life-threatening breast cancers, early treatment of tumours overdiagnosed by intrinsic

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We declare that we have no competing interests. AIZ and AO have an expert advisory role to the UK All Party Parliamentary group on global tuberculosis.

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united voice. We must not miss this unique opportunity to make the strongest possible case for tuberculosis, push it up the political agenda, and secure global commitment and leadership that will steer a new path to end tuberculosis forever.
screening programmes, or some mixture of the two. The consistent finding of an increased effect of prevention therapy on hormone-receptor-positive tumours supports the prediction made by modelling data that pharmacological prevention of breast cancer is actually early treatment of extant subclinical tumours.\textsuperscript{5} With two-thirds of the anastrozole benefit in screen-detected cancers, in view of their better outcomes,\textsuperscript{3} the likelihood of an eventual breast cancer mortality benefit seems small.

Longer follow-up will be important for IBIS-II, as the investigators acknowledge, but without protocol-defined procedures after 5 years, complete data capture might be a challenge. Although the cumulative incidence curves should not be overinterpreted, the annual frequency of breast cancer diagnosis in the control group seems to decrease from about 1\% during the 5-year treatment programme to roughly 0·3\% thereafter, which could suggest less stringent routine mammography or poor follow-up, or both.

Cuzick and colleagues conclude that their results provide strong support for the use of anastrozole in high-risk postmenopausal women. Indeed, 2013 guidance from the UK National Institute of Health and Care Excellence\textsuperscript{7} recommends that tamoxifen be offered to women at high risk of breast cancer. However, the use of primary prevention pharmacological therapy in women at increased risk of breast cancer is nowhere near universal.\textsuperscript{8,9} Will IBIS-II change this situation and, if not, why not?

With the strongest protective effect recorded in hormone-sensitive and screen-detected breast cancers, the overall breast cancer mortality gain with prevention therapy could be small. No such gain has been reported in any of the pharmacoprevention trials so far.\textsuperscript{2-4} Therefore, for any woman considering 5 years’ anti-oestrogen therapy to reduce her risk of breast cancer without evidence to suggest that she will have a longer life, the perceived and actual toxicity of this intervention becomes important. The financial costs of breast cancer chemoprevention might have decreased, but the toxicity cost to women has not.

In IBIS-II, many women in both groups reported side-effects associated with oestrogen deprivation: frequency of musculoskeletal and vasomotor symptoms was about 50\% or higher in both groups, and roughly a fifth of women had gynaecological adverse events. Although the increase in frequency with anastrozole was modest for musculoskeletal (6\%) and vasomotor (8\%) events, more than 100–200 additional women had these symptoms in the anastrozole group compared with the placebo group—quite often to a moderate or severe level—to prevent 15 symptomatically diagnosed breast cancers. Compliance with endocrine therapy for invasive breast cancer is known to be suboptimum, and the reported frequency of possible side-effects was higher in IBIS-II than in the ATAC study of anastrozole after potentially curative breast cancer surgery\textsuperscript{36} (vasomotor symptoms: 57\% of women in the anastrozole group in IBIS-II vs 34\% of women in the anastrozole group in ATAC; musculoskeletal symptoms: 64\% vs 28\%), although objective morbidity was more similar (fractures: 9\% vs 6\%; cataracts: 5\% vs 3\%).

In 2002, Kinsinger and Harris\textsuperscript{11} noted on the publication of the IBIS-I tamoxifen chemoprevention trial: “For chemoprevention to find a prominent role in reducing the burden of breast cancer, research must develop along at least three paths. First, longer-term research must find that the reduction in incidence translates into a reduction in breast cancer mortality. Second, newer drugs that have a better safety profile need to be developed. Finally, better ways are needed to target the drugs to those women who will benefit most.” Unfortunately, although Cuzick and colleagues report important data,\textsuperscript{1} IBIS-II has not addressed any of these challenges.

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Almost 40% of the world’s population is at risk of *Plasmodium vivax* infection, with 70–390 million clinical episodes occurring each year.¹ Unlike *Plasmodium falciparum*, *P. vivax* forms hypnozoite stages, which can lie dormant in the liver for months or even years before emerging to cause malaria relapses. The risk, frequency, and timing of these relapses vary with the geographical location of infection and host immunity.² The chronic relapsing nature of the disease can cause severe anaemia, miscarriage in pregnant women, malnutrition, and developmental delay in young children; the associated morbidity and economic burden of these manifestations is considerable.³

A radical cure for malaria requires treatment that targets both the erythrocytic and liver stages of infection. For more than 60 years, radical cure of *P. vivax* has relied on primaquine—the only licensed antimalarial with proven hypnozoitocidal activity. However, primaquine has several major shortcomings. It can cause severe haemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, an X-linked disorder present in 1–40% of the population.⁴ WHO guidelines recommend a 14-day primaquine regimen, but since treatment is usually unsupervised, adherence is generally poor, limiting effectiveness and public health benefit.⁵ Tafenoquine was designed as a synthetic analogue of primaquine with a slower elimination time, allowing shorter courses to be given. Despite its pragmatic advantages over current options, progress in bringing tafenoquine to market has been slow. It has been 20 years since the first reports of its schizontocidal efficacy in rodent malaria⁶ and 10 years since the early clinical studies.⁷

In *The Lancet*, Alejandro Llanos-Cuentas and colleagues⁸ present a much anticipated comparative study of single-dose tafenoquine for the radical cure of *P. vivax*. This multicentre, double-blind, phase 2b clinical trial randomly allocated 329 patients to receive one of six regimens: a single dose of 50 mg, 100 mg, 300 mg, or 600 mg tafenoquine, 14 days of primaquine (15 mg per day), or placebo. All patients received chloroquine for 3 days to ensure initial clearance of the erythrocytic stages of the parasites. The primary objective was to show superiority of chloroquine plus tafenoquine over chloroquine alone, as assessed by recurrence of *P. vivax* infection within 6 months. The results are impressive: 6 months after being assigned chloroquine plus tafenoquine 300 mg, 89·2% (95% CI 77–95) of patients remained free from *P. vivax* recurrence compared with only 37·5% (23–52) of patients assigned to chloroquine alone. The 600 mg dose offered little benefit (91·9% [80–97] efficacy) over the 300 mg dose, and the lower tafenoquine doses were significantly worse (both <58%). As expected, the proportion of patients who had recurrent *P. vivax* infection after chloroquine monotherapy varied substantially between sites, ranging from 10% in India, to 44% in Thailand, 83% in Brazil, and 88% in Peru. The superiority of tafenoquine 300 mg was apparent at all sites except in India, where the sample size was small and risk of recurrence low.

Clinical trials of antirelapse treatment are challenging...