Expert Interview with Professor Jack Cuzick, Director of the Wolfson Institute of Preventive Medicine and Head of the Centre for Cancer Prevention, London, UK

Professor Jack Cuzick is a pioneer in the field of cancer prevention. His work has played a vital role in bringing the drugs, tamoxifen and anastrozole to breast cancer prevention. Over the years, he has also perfected mathematical models to measure an individual's risk of developing cancer. In recognition of his contribution to the field of cancer prevention, he has received multiple distinguished awards and has been elected a Fellow of the Academy of Medical Science, a fellow of the Royal Society and also appointed a Commander of the Order of the British Empire by the Queen. In addition to his research activities, Professor Cuzick dedicates his time to increasing awareness about cancer prevention so that more individuals can benefit from it. In this interview, Professor Cuzick takes CPI's readers through his professional journey, discusses challenges associated with developing cancer preventives as well as future opportunities in cancer prevention.

Professor Cuzick, thank you for being with us today. Please, could you tell our audience about your career path and how you became interested in cancer prevention research?

Although I was trained as a pure mathematician, I have always had an interest in applied activities. My undergraduate degree is in mathematics and my PhD is in theoretical probability theory. After my PhD, I took a job in the Statistics Department at Columbia University in New York. I then went to work with Richard Peto in Oxford, originally for just a year, to do some work on real clinical trials and add more experience to my theoretical work. I liked the challenges in the real clinical trials more than the theoretical ones. So, I stayed on in Oxford for 5 years before coming to London, working on a range of clinical trials and related issues. ***I always liked to sit at the border between 2 subjects, and here I was between mathematics and medicine.*** I was also interested in epidemiology. At the boundary between epidemiology and clinical trials, there are prevention trials, which combine a need to understand risk factors for a disease and clinical trials methodology. This is a how I got where I am now.

What was the first clinical trial you were involved with?

The first clinical trial I was involved with was coordinated by the Medical Research Council at the Marsden Hospital in London. We did some of the early trials for the treatment of multiple myeloma, a type of cancer of blood cells like leukaemia. These trials offered a great opportunity to learn more about the natural history and causes of this cancer. We were the first to clarify that radiation is an important risk factor for multiple myeloma, and that this cancer probably also has to do with animal viruses, because those who worked in agriculture had a higher risk. That was one of the early links between clinical trials and epidemiology that stimulated me to continue to work in this area.

What achievements are you most proud of so far?

The one I am the most proud of is the first IBIS trial. Against all odds we got the drug tamoxifen to be used as a treatment for prevention. We had any number of obstacles that almost made it impossible to do this work. There was a study in which researchers had chosen to give tamoxifen at high doses to rats and found that the rats would get liver cancer. Even though millions of women who had taken tamoxifen at standard doses had no increased risk of liver cancer, there was a general reluctance to offer healthy people any kind of preventive therapy. The fact that we pushed through and got this study done and carried on to do the long term follow up was a great achievement. Recently we published that the benefits of taking tamoxifen for 5 years are continuing for at least 20 years. Of course we will continue to follow the subjects for another 10 years to document the extent of long term protection.

What are the challenges associated with running cancer prevention clinical trials?

One of the biggest challenges in running any kind of trials is the extreme bureaucratic complications that are now imposed. For

example, when we ran IBIS-1, we were allowed to label the drug for our 7000 patients ourselves. We had a well-defined and controlled procedure. Unfortunately, all the labeling has now to be done by a company that charges £15 (~$20) a label. We have been trying to run big trials to test the cancer preventive effect of aspirin. With the price of the label, it makes drugs like aspirin, where the part of drug is £0.25 ($0.32), really expensive and the trial impossible because of the cost. This is an example of the bureaucratic requirements are inhibiting the ability to run large-scale public health trials of drugs that are not that expensive. An organization based in Oxford, has been set up (MoreTrials - see www.moretrials.net) which now has support from the Gates foundation and Wellcome Trust to address these issues. It lobbies to get good clinical trial practices reformulated, especially for trials that are not commercial and are using readily available inexpensive drugs. It would be a major breakthrough if we could get more rationale regulation of trials. No one is arguing that you don't need to be careful with trials, but there are silly things that make trials impossible to do and are not in the patient's benefit, because of the excessive bureaucratic requirements.

How difficult was it to recruit patients for the trials?

Tamoxifen got a bad start in the United States. There was a certain amount of controversy with Bernie Fisher, which had nothing to do directly with tamoxifen but made the legislators concerned about these trials. And tamoxifen got confused in the popular press with taxol, which is highly toxic. There was this widespread belief that tamoxifen is far more toxic than any of the data actually showed.

Our trials also showed, and that is still not widely appreciated, that the common side effects, for example, the menopausal symptoms in early post-menopausal women or muscular skeletal aches and pains are extremely common even in the absence of a treatment. An example I like to quote is in IBIS-2 with anastrozole. We offered anastrozole for 5 years and 64% women complained about muscular skeletal aches and pains. This sounds terrible until one looks at the placebo arm, in which participants have no treatment, and yet 58% of the women complained about the same side effects. There was a real increase in side effects but the real increment is about 8% and not 64% as sometimes suggested, esp. by those who don't realize this is a common event in the general population of postmenopausal women. **This has been a real concern, as people believe that the side effects are much worse than they are and in fact most have nothing to do with the drug**. These are just symptoms that people have at that age. The expected benefits clearly outweigh the side effects for anyone who would be considered at sufficiently high risk to take it.

General Practitioners also need to be made more aware of the facts regarding risks and side effects. In many cases in our trials, women go to the specialist and are recommended to take preventive drugs like tamoxifen or anastrozole. Then they talk with their GPs who are not expert in the subject and the GP convinces them not to do it because of concerns of the side effects, which are largely exaggerated.

How can we communicate better with patients and doctors?

We have been working with a behavioral psychologist trying to figure out to deliver the true message about preventive therapies. Cardiologists have been successful at this for some time now and, but of course, their drugs have very few side effects. There is a general fear to take drugs that prevent these cancers.

Better communication is the key.

Yes, and it is our job to that. I now try to spend more of my time figuring out how to get preventives used than discovering new preventive treatments. There is a lot to be done here.

Prevention trials are long and difficult by nature. What are your thoughts about surrogate endpoints? Is there an ongoing effort to develop biomarkers to predict the drug response earlier within the treatment?

Because of the cost, large trials are not being done as much as they should be. Surrogate endpoints, if they are reliable, are the way to go

forward. But good ones are really difficult to identify and validate.

Reduction in breast density with tamoxifen seems to be a reasonably good predictor of a lowering of subsequent risk, but some uncertainty remains. Another way of finding out who is likely to respond to preventive treatment is the "no-pain-no-gain result". Women who have endocrine based symptoms seem to respond better to the drugs. These symptoms may be a measure of activity of the drug for the specific person. Nobody has yet developed this approach well enough so that it can be reliably used. We are desperately looking for markers who can help us monitor response.

One of the big additions to improving our ability to assess risk is adding a SNP/polygenic risk score to other markers. That is turning out to be a major biomarker in terms of being able to predict risk.

In addition, we are exploring if methylation profiles can provide good information on the risk of getting cervical cancer. Most of our work uses material coming from smears and early biopsies. The methylation profile seems to be a good indicator if the tissue is going to become a lesion or if the body is going to clear it. It is at an early stage and all our work is in cervical cancer but it does appear promising and may be useful for other cancers as well.

Biomarkers for response to endocrine agents are highly desirable and people are looking at them but we do not really have anything much more than breast density at the moment. We have not done any real work on methylation but it is something that might work.

What level of risk reduction is meaningful for a drug to be considered preventive?

You have to balance the benefits to the risk profile. Something like aspirin, which has very low toxicity and appears to reduce overall cancers by 10%, making it is a good option for a large part of the population. It appears to reduce colorectal cancer, stomach, and esophageal cancer by as much as 30% and lung breast and prostate by about 10%, and because it is a minimally-toxic, well tolerated drug you can consider it even for those at average risk of these cancers. If you start looking at aromatase inhibitors or tamoxifen, where there are some common side effects, it becomes important to focus prevention on those at highest risk, so that the benefits on average will clearly outweigh any risks.

Do you have any advice for organizations like ours who are interested in developing cancer preventatives?

For breast cancer risk-adapted screening should be implemented for the general population. Everyone should get a risk assessment - ideally at their first screening visit to determine what their risk of getting breast cancer is. Some people will be found to have high enough risk that they should be considering therapeutic preventive treatment upfront, while others will have a lesser increase in risk and would benefit from additional screening. Some will also be found to be at very low risk and may need less or even no screening. So there is a potential to tailor screening and prevention activities to the individual women's risk and focus efforts on those who stand to gain the most.

What is coming next in the cancer prevention space?

Now that we know that the standard dose of some drugs also work for prevention, we are interested in knowing if lower doses also work, and if side effects can be reduced.

Another approach is to look at local topical delivery for tamoxifen like drugs to determine whether a cream or gel could prevent cancer.

Finally, we would like to do a big trial to study better how aspirin prevents different cancers, but the bureaucracy is making this difficult. We do not know how aspirin prevents cancer and we are doing a lot of work to find out the mechanism by which this happens. The doses at which it works are too low to act via the known COX2 anti-inflammatory pathway, so there is something very important still to discover. It is a really active research area.

Thank you!