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NEWS...NEWS...NEWS

Launch of IBIS-II

The second phase of the International Breast Cancer Intervention Study (IBIS-II) has been launched in 25 countries among women at increased risk of breast cancer. The study has started recruiting and will run for 4 to 6 years.

IBIS-II is a randomised, blinded, placebo-controlled clinical trial which will be investigating the hormonal therapy, anastrozole (Arimidex). The first part of the study, IBIS-II Prevention, aims to recruit 6000 postmenopausal women at increased risk of developing breast cancer. They must be aged between 40 and 70 years and not taking hormone replacement therapy (HRT).

The second part, IBIS-II (DCIS) aims to recruit 4000 women who have been diagnosed with and had surgery to remove ductal carcinoma *in situ* (DCIS). As well as being at high risk of developing more advanced forms of breast cancer, these women are also more likely to develop a new tumour in the opposite breast. This part of the trial is designed to determine whether anastrozole or tamoxifen can best prevent new cancers, both in the breast affected by DCIS and in the opposite breast.

''WE'D LIKE TO HAVE PREVENTIVE MEDICINES FOR CANCER''

Professor Jack Cuzick (Cancer Research UK, University of London, UK) is co-chair of the IBIS-II Steering Committee. He said, ''It is vitally important that women come forward to participate in the trial – not just for themselves, but for their daughters, their families and for other women around the world. Many of us already take preventive medicines for heart disease and stroke and this is a major attempt to extend this successful approach to cancer.''

IBIS-II is based on the results of the ATAC trial (Arimidex, Tamoxifen, Alone or in Combination) which suggested that anastrozole may have the potential to prevent up to 80% of hormone-sensitive breast tumours (*Lancet* 2005, **365,** 60–62).

Clinical trials registration: full data required!

Every trial participant and every investigator should be asking, ''Is this clinical trial fully registered?'' according to the International Committee of Medical Journal Editors (ICMJE). In a new statement, the ICMJE says it has adopted the World Health Organisation (WHO)'s minimal data set as its requirement for registration.

The ICMJE stated in September, 2004, that trials will be considered for publication only if they have been registered before the enrolment of the first patient. This applies to trials that started recruiting on or after July 1st, 2005. However, debate has continued on what information should be made publicly available at the onset of a trial.

WHO held a meeting (Geneva, 25–27 April, 2005) including representatives of governments, pharmaceutical companies, journal editors, registry owners and independent researchers (*Lancet* 2005, **365,** 1829–1831). Within a wider discussion, the meeting established a minimum data set that is scientifically necessary to be informative about the trial.

The ICMJE says (*Lancet* 2005, **365**, 1827–1829; also *New Eng J Med* 2005, **352**, 2436–2438) that the WHO data set addresses all of its key requirements, and has adopted it. ''We will consider a trial for publication if the authors register it at inception by completing all 20 fields in the WHO minimal data set,'' the statement says.

However, it stresses that each field must contain useful information. ''Many entries in the publicly accessible clinicaltrials.gov database do not provide meaningful information in some key data fields. For example, certain pharmaceutical company entries list a meaningless phrase – such as 'investigational drug' – in place of the actual drug name, even though US law requires trial registrants to provide ''intervention name''.

While the WHO meeting was not fully satisfactory for all groups, lead author Metin Gülmezoglu (WHO, Geneva) says it represents ''an important milestone for setting the standards and encouraging collaboration and dialogue between the industry, governments, journals and academia''.

Previous trial registration efforts have not been terribly successful and compliance has been disappointing. But Dr Gülmezoglu underlines the importance of this attempt: ''Strengthening capacity for trial registration and setting up registers are necessary if we are to maximise access to research information globally and improve the ethical foundation and the efficiency of the research enterprise.''

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Childhood cancer survivors suffer from chronic health problems

Children who received treatment in the 1970s and 1980s, and survived their cancers, are five times more likely to suffer from moderate to severe health problems in adulthood, according to research from CCSS (Childhood Cancer Survivor Study).

''This study provides the first estimate of the frequency of physical health problems in childhood cancer survivors as they become adults'', said lead author, Dr Kevin Oeffinger (University of Texas Southwestern Medical Centre, USA). ''Most survivors will have future health problems related to their previous cancer therapy, which are likely to increase as they reach their 30s and 40s''.

The study, presented at the annual meeting of ASCO (American Society of Clinical Oncology, 13–17 May 2005, Orlando, Florida, USA), compared the incidence of moderate (grade 3) and severe (grade 4) chronic heath problems among 10 397 adult cancer survivors and 3034 controls who were their healthy siblings. The survivors were diagnosed and treated for paediatric cancers between 1970 and 1986. Survivors had a mean age of 9.7 years at diagnosis and 26.7 years (range 18–48) at study evaluation.

Eighty-five percent of survivors had at least one chronic disease. The cumulative incidence of chronic disease in survivors by age 45% was 57% (grade 3) and 37.4% (grade 4). This compares to 18.2% (grade 3) and 4.6% (grade 4) in their healthy siblings. The relative risk of a survivor having grade 3 or 4 chronic disease, adjusted for age at study, and gender, was 5.0.

The severe health problems included: second cancers (usually more aggressive than the patients' original tumours), heart disease, renal transplant or need for dialysis, mental retardation requiring special education, paralysis of an extremity.

''MOST SURVIVORS WILL HAVE FUTURE HEALTH PROBLEMS''

In the discussion following the presentation of the study, ASCO president Dr David Johnson, said that many of these health problems will probably not be replicated in those receiving treatment today due to the extensive changes in clinical practice, especially in radiotherapy, compared to 30 years ago.

Lekshmy Balakrishnan
Orlando

Minimum clinical recommendations

The European Society of Medical Oncology (ESMO) has produced a collection of 35 sets of Minimum Clinical Recommendations for the treatment of cancer (*Annals of Oncology* 2005, **16,** S1 or see http://annonc.oup.org/content/vol16/ suppl_1/index.shtml?etoc).

The recommendations are intended to provide the user with a set of requirements for a basic standard of care that ESMO would consider necessary in all countries of Europe. They are not designed to replace extensive clinical practice guidelines or review articles, but to describe minimum common standards. Because of the rapid changes in the field of medical oncology, each guideline undergoes a yearly update.

Professor Rolf A Stahel, chair of the ESMO Guidelines Task Force, said the guidelines are intended to help clinicians offer the best care to the patients on a daily basis. ''They also help support negotiations with politicians, administrators and insurance companies regarding what level of care should be made available. Clinical practice guidelines are important for the future development of medical oncology as a specialty and serve to achieve a high common standard of care for patients with cancer in Europe.''

New Maggie's Centre Opens

The fourth Maggie's Centre – Maggie's Highlands – has opened in Inverness, Scotland. The Centres provide emotional and psychological support, information, stress management and relaxation techniques for anyone affected by any type of cancer, including carers.

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Maggie's Highlands, Inverness

Maggie's Centres are renowned for their innovative architecture: the unifying concept underlying the design of the centre and garden at Maggie's Inverness is mitosis, or the division of cells in a healthy body.

The centres aim to be a welcoming and informal environment where visitors can share their experiences with others in similar situations and, with professional help, inform themselves about the realities of the disease. All are close to the major cancer hospital treatment centres, inviting people to take time out and giving them a non-institutional place to call their own. Use of facilities and classes is free of charge.

Maggie's Edinburgh was the first to be established, in 1996, and other Centres now exist in Dundee and Glasgow. Building of a Centre in Fife is due to start this year, and a campaign for Maggie's London is underway.

EPIC results

The latest results from the European Prospective Investigation into Cancer and Nutrition (EPIC) confirm that high levels of consumption of red and processed meat are associated with an increased risk of colorectal cancer (*J Nat Cancer Inst* 2005, **97,** 906–916). High fish intake may be associated with a decreased risk, but the evidence is less convincing.

EPIC prospectively followed 478,040 men and women from 10 European countries, who were free of cancer at enrolment between 1992 and 1998. Information on diet and lifestyle was collected at baseline. After a mean follow-up of 4.8 years, 1329 colorectal cancers had been diagnosed.

The absolute risk of developing colorectal cancer within 10 years for a study subject aged 50 years was 1.28% for those who ate less than 20 g of red and processed meat per day. It was 1.71% for those who ate more than 160 g per day – a 35% increased risk. Those with the lowest fish consumption had a risk of 1.86%; compared to 1.28% among those who ate most fish. There was no association between poultry consumption and risk.

The reduction in risk associated with fish consumption and the increase in risk associated with increased red meat consumption were independent of each other.

Dr. Elio Riboli (International Agency for Research on Cancer, Lyons, France) co-ordinated the study and added, ''The association of meat and fish consumption with colorectal cancer risk was independent from the reduction in risk associated with dietary fibre consumption that was observed in the same study population.''

Iodine deficiency and thyroid cancer risk

Provocative new information on the risk of thyroid cancer following the Chernobyl disaster suggests a powerful role for diet and iodine supplementation. Researchers found that children exposed to radioactive iodine had a 3-fold risk of developing thyroid cancer if they lived in an iodine-deficient area. Conversely, taking potassium iodide as a dietary supplement reduced the risk of thyroid cancer by a factor of 3.

A team led by Dr. Elisabeth Cardis (International Agency for Research on Cancer, Lyons, France) studied 276 patients with a confirmed diagnosis of thyroid cancer following the nuclear reactor accident in 1986 (*JNCI* 2005, **97,** 724–732). They were case matched with 1300 healthy controls. All were younger than 15 years at the time of the accident.

Individual doses were estimated for each subject, based on their whereabouts and dietary habits at the time of the accident and in following days, weeks and years; their likely stable iodine status at the time of the accident was also evaluated.

A strong dose–response relationship was seen between radiation dose to the thyroid received in childhood and thyroid cancer risk. Furthermore, the risk of radiation-related thyroid cancer was three times higher in iodine-deficient areas. Taking potassium iodide as a dietary supplement reduced this risk by a factor of 3, even if taken many months or years after the exposure occurred.

The results have important public health implications, the researchers say. ''Stable iodine supplementation in iodine deficient populations may substantially reduce the risk of thyroid cancer related to radioactive iodines in case of exposure to radioactive iodines in childhood that may occur after radiation accidents or during medical diagnostic and therapeutic procedures''.

An accompanying editorial (*JNCI* 2005, **97,** 703–705) states further that the observation cautions against generalising the Chernobyl findings to other exposed populations of children whose diets are not deficient in iodine. ''Conceivably, the elevated radiation risk [in iodine-deficient areas] reflects an interaction with a dysfunctional thyroid gland; this result tempers conclusions with regard to similarities or dissimilarities in risk observed in other studies of children with normal glands.''

New guidelines for marker studies

New recommendations for reporting tumour marker prognostic studies are published in this issue of *EJC* (*see pages* 1690–1696). Produced by a US' National Cancer Institute (NCI) and EORTC working group on cancer diagnostics, the guidelines aim to encourage transparent and complete reporting.

The REporting recommendations for tumour MARKer prognostic studies (REMARK) have been produced in response to the ''pitifully small'' number of markers to have emerged as clinically useful. The authors say that often, great promise in initial studies fails to be backed up in later research. ''It is imperative that we attempt to understand the reasons that multiple studies of the same marker lead to differing conclusions,'' they say.

A variety of methodological problems have been cited to explain the discrepancies, and the guidelines stress the need for relevant information about the study design, pre-planned hypotheses, patient and specimen characteristics, assay methods and statistical analysis methods.

The authors – a collaboration of statisticians, clinicians and laboratory scientists – acknowledge that it may not be possible to report every detail for every study. ''The key point is that there must be a clear statement of what is and is not known,'' they say.

''Poorly designed or inappropriately analysed studies can attract undeserved attention when they produce very dramatic, but unfortunately incorrect results. In contrast, some carefully designed and analysed studies have been overlooked because they produced less dramatic, but perhaps more accurate and realistic results. The poor quality of reporting of prognostic marker studies may have contributed to the relative scarcity of markers whose prognostic influence is well-supported,'' they write.

They refute claims that guidelines pose yet another burden in trying to publish or obtain funding. ''What greater reduction in burden could there be that to eliminate some of the false leads generated by poorly designed, analysed or reported studies which send researchers down unproductive paths, wasting years of time and money?''

UK clinicians to screen embryos for BRCA mutations

Researchers from the Institute for Women's Health, University College London (UCL), UK, are paving the way for embryo screening for the presence of *BRCA1* and *BRCA2* mutations by sending out a questionnaire to ask women with these mutations their opinion of preimplantation genetic diagnosis (PGD). However, in doing so Ian Jacobs and co-workers have reopened the debate on whether PGD for hereditary cancer, especially late-onset disorders, should be offered.

PGD, the identification of a mutant gene at the eight-cell stage of an embryo produced by *in vitro* fertilisation (IVF), is regarded as the main screening alternative to prenatal diagnosis, in which chorionic villous sampling at 11 weeks' gestation can identify a mutation. ''The patients that come to us wanting PGD really do not want to go down the route of terminating a pregnancy'', explains co-worker Sioban Sengupta (Centre for Preimplantation Diagnosis, UCL, UK).

The questionnaire, being prepared by Usha Menon (Department of Gynaecological Oncology, UCL, UK) and Joyce Harper (UCL Centre for PGD, UK), will aim to assess: the effect of an inherited mutation on reproductive choices; whether carriers perceive PGD differently to prenatal diagnosis; and the number of carriers who would consider PGD. On approval by the UCL ethics committee, the questionnaire will be posted to at least 100 women with a *BRCA* mutation. ''PGD is only relevant to a small number of families where the inherited mutation has been identified'', says Sengupta. Moreover, only a small proportion of such families will opt for PGD because of the diculty of the procedure. According to Sue Meyer (GeneWatch UK), screening for late-onset predisposition genes should ''be bounded to situations where women are having proper counselling and choices made available to them''.

UK centres that offer PGD for families with a history of inherited disease must concur with UK Human Fertilisation and Embryology Authority (HFEA) guidelines, and PGD licence applications to test for disease that has not yet been licensed are assessed by HFEA on a case-by-case basis. Although PGD for *BRCA1* or *BRCA2* mutations has been done in Belgium and the USA, whether HFEA will approve screening for mutations associated with this disorder, which has late onset and does not affect all with the mutation, is unclear. ''For breast cancer'', notes Semra Kahraman (Assisted Reproductive Techniques and Genetic Diagnosis Centre, Istanbul Memorial Hospital, Turkey), ''although these genes are highly penetrant, we cannot rule out the possibility of the future child experiencing the disease, even if he [or] she does not carry the mutation''. However, families with a history of hereditary cancer are faced with a lifelong risk of, and screening for, various cancers that can affect many organs.

''Many women with an inherited cancer-risk gene would be pleased to be able to take steps to avoid passing that gene on to their children'', says John Toy (Medical Director, Cancer Research UK). ''Patients have several options'', comments Harper, ''some will decide to remain childless, some will adopt, some will go for gamete donation, and some for prenatal diagnosis . . . but in the middle we have PGD, and as far as I'm concerned couples should be aware of their options and then they decide what is right for them.'' Toy adds, ''asking such women for their views forms part of an essential public debate to gauge how acceptable this type of intervention could be to society.'' HFEA says that the survey will be of particular interest because it might give insight into demands on PGD services.

However, with the increasing potential applications of PGD come concerns about resource allocation for a service being offered for less-severe diseases and, moreover, of the potential burden of responsibility on women, to ask them to weigh the option of PGD against having to undergo IVF, the variable success of implantation, and of ways of coping with breast cancer. Furthermore, ''Long-term effects are a serious issue'', adds Jacobs. At present, little is known about the effects of PGD on an embryo and follow-up data for PGD children is sparse.

In the future, the cost of PGD in public healthcare will be offset by future costs of treating hereditary cancer. In the meantime, use of PGD remains open to debate. But professionals who treat or counsel patients with a family history of cancer are faced with answering tough ethical questions while trying to give patients the best choice. ''I understand all the ethical objections and concerns, but there is also potential to make sure that the burden of an incredible family history of trauma – psychological and physical – is ended'', concludes Jacobs.

Claire Tilstone

This story originally appeared in Lancet Oncol 2005, **6,** 358.

New NICE guidelines on ovarian cancer

The UK's National Institute for Health and Clinical Excellence (NICE) has issued updated guidance on treatments for advanced ovarian cancer. The guidance makes recommendations for the treatment of four types of ovarian cancer, based on how quickly the cancer responds to first-line platinum-based therapy and how quickly it relapses. NICE has updated three separate pieces of guidance on topotecan, pegylated liposomal doxorubicin hydrochloride (Caelyx), and paclitaxel.

Andrea Sutcliffe, Executive Lead for the NICE appraisal said, ''Even if (ovarian cancer) is detected early, between 55% and 75% of women will suffer a relapse after their initial chemotherapy and at this stage of their disease the women and their doctors will consider the risks and benefits of further treatment. Our guidance reflects the latest evidence and will help to inform their consideration of the treatment options for advanced ovarian cancer.''

For more details, see www.nice.org.uk/TA091.

PODIUM

Chemoprevention comes of age

Andreas Gescher is Professor of Biochemical Toxicity, University of Leicester, UK. He trained in pharmacy in Germany and the UK, and his research focuses on the development of novel tumour-suppressing chemopreventive agents. He is a former chairman of the EORTC's Pharmacology and Molecular Mechanisms Subgroup and the Guest Editor of EJC's forthcoming Special Issue on Cancer Chemoprevention.

Professor Andreas Gescher

Is it fair to say that cancer chemoprevention is still in its infancy?

Possibly it is, when compared to chemotherapy, but it has been around for decades: the term was coined in the late 1970s. Chemoprevention is still considered novel in some quarters, but cancer research funding bodies are now stressing the importance of prevention. Until recently, they have been reluctant to fund long term studies which may not give a clear answer even after 10 years, but that is changing with the realisation that we have to get to grips with cancer prevention.

There have been successes to date?

The first US trial to suggest that tamoxifen might prevent cancer had a tremendous impact. However, there are always downsides to drugs. With tamoxifen, because of our long experience with the drug, we already knew what percentage of women taking it would develop endometrial cancer, and so on. It was always a question of weighing up the risks and benefits, and was relatively straightforward. More recently, trials examining the effects of the COX-2 inhibitors on the development of colorectal adenomas were halted because the drugs doubled or trebled the risk of cardiovascular events such as stroke. I believe these drugs will be found to be effective chemopreventive agents but because we did not know about the adverse events, the finding came as a shock. We will have to weigh up the kind of risk that is reasonable in someone with a high propensity to develop this cancer – and it will be difficult.

Won't it always be difficult to make the case for giving drugs to healthy people?

Our attitudes to risk are fascinating. A few years ago, finasteride was shown to interfere with the development of prostate cancer but this caused no avalanche of people wanting to take the drug. It's probably a good thing, because it is possible that finasteride, while preventing many cases of prostate cancer, may in fact make cancers worse in men unfortunate enough to develop it despite taking the drug. The general public is reluctant to take drugs to prevent diseases, though much keener on eating foods that may contain chemopreventive chemicals, or taking agents which have come from natural sources.

Many chemopreventive agents are found in foods, aren't they?

Yes, but if you look at agents which are found in natural dietary sources, they often have to be taken in enormous amounts to interfere with carcinogenesis. Even if they're a regular part of the diet, once they're separated out and taken in high doses, they may have risks we are unaware of and should be considered novel chemopreventive agents.

Is this widely recognised?

Not really. High doses of curcumin (from turmeric) or genistein (from soy) seem to be necessary to cause the biochemical effects which may prevent cancer. Similarly, resveratrol in red wine has been implicated in the French paradox (of a high fat diet but relatively low incidence of cardiovascular disease) and may also prevent cancer. However, resveratrol's biochemical effect on the cells would not be achieved by drinking three glasses of wine. There is a tremendous gap, which cannot be explained away.

The combination in red wine of resveratrol, alcohol, and other chemicals may be required to get the desired effect: resveratrol alone may act differently from resveratrol in a mixture. Or perhaps we're not looking at it in the right way.

How important is it to know the mechanism of action?

We have to be as ruthlessly scientific as in chemotherapy, where the recent advances have come out of a good understanding of mechanisms. A good understanding of a drug's biochemistry enables us to optimise treatment, and suggest appropriate doses. In chemoprevention, analytical chemistry – which relates work in animal experiments to efficacy in humans – has been neglected. You need to know that drugs actually reach the target organ, where they work in the cancer cascade, and what happens when they are taken in drinking water, or food.

Is molecular medicine being used in the development of chemoprevention agents?

Targets such as overexpressed genes are being identified, and agents developed to interfere. Agents which work *in vitro* are tested *in vivo* and pilot studies planned in human volunteers or cancer patients to test the hypothesis that the mechanism operates in humans. Interpretation is complex because dietary-derived agents operate through so many mechanisms it is conceivable that the most prominent mechanism in cells is not the most important in tissues in humans.

What do you want the *EJC* Special Issue to achieve?

EJC readers who work in this field may be made aware of certain scientific developments which could benefit from their input. But the many more readers who work in the clinic will, I hope, appreciate the opportunity to learn more about the strategies and experiments taking place in the area of prevention. I hope they'll be convinced of the importance of cancer chemoprevention. It's an exciting time, momentum is growing, and if the issue helps persuade people either to contribute or to follow developments in chemoprevention more closely, it will have been worthwhile.