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Tamoxifen 'not safe enough for chemoprevention'

Initial results from the International Breast Cancer Intervention Study (IBIS-1) suggest that prophylactic tamoxifen reduces breast cancer incidence by one-third. However, researchers caution that the overall risk to benefit ratio is "still unclear" in the preventive setting (*Lancet* 2002, 360:817-24).

The long-awaited results from IBIS are different but compatible with the outcomes of other trials into chemoprevention of breast cancer. The National Surgical Adjuvant Breast and Bowel Project P-1 study (*J Natl Cancer Inst* 1998; 90:1371-87) in the States found a 50% reduction in breast cancer incidence, where the Italian National trial (*Lancet* 1998; 352:93-97) and the Royal Marsden Hospital trial (*Lancet* 1998; 352:98-101) found little or no reduction. The IBIS researchers write, "Results from all the trials are statistically compatible with a 30–40% decrease in incidence."

However, IBIS-1 found that women on tamoxifen had a significantly higher death rate than those on placebo. The deaths were from a range of cancers, pulmonary embolisms, other vascular causes and cardiac deaths. The authors say the increase in mortality may be partly due to statistical variability, but note that thromboembolism is the most important complication of tamoxifen. "Every effort should be taken to reduce this risk," they write.

They suggest that tamoxifen use should be stopped and appropriate antithrombotic measures used during and after major surgery or periods of immobilisation.

"Although tamoxifen is unquestionably valuable in the adjuvant setting, some of its oestrogen–agonist properties restrict its ultimate usefulness—for both efficacy and side-effects," they say.

Anastrozole may be more effective than tamoxifen in reducing recurrence, may not have the main side-effects of thromboembolic disease and endometrial cancer, according to early results. Other problems such as bone loss may occur but the IBIS researchers write, "The use of an aromatase inhibitor in the preventive setting is attractive and will be considered as an option in the forthcoming IBIS-II trial."

An accompanying editorial (*Lancet* 2002; 360; 813-4) agrees that tamoxifen is effective in reducing oestrogen-receptor-positive breast cancer and ductal carcinoma in situ, but adds, 'None of the trials have the power as yet to determine whether tamoxifen reduces breast cancer mortality.'

The editorial states that newer drugs with a better safety profile need to be developed and that better ways are needed to target the drugs to the women who will benefit most. It concludes, "Until the research agenda is further advanced, chemoprevention of breast cancer will remain a promising idea with an uncertain future."

Consider oopherectomy for subset

Young women with breast cancer, who have a family history of ovarian cancer have a "striking excess risk and substantial absolute risk" of ovarian cancer, say Swedish researchers (*Lancet* 2002; 360:891-94). "In this subgroup, counselling, and perhaps even prophylactic oopherectomy, might be considered."

The population-based study linked data on 30,552 breast cancer patients born after 1931, with information on breast and ovarian cancer diagnosis from 146,117 first-degree relatives. It found that women who were under 40 when diagnosed with breast cancer, and who had a family history of ovarian cancer, had a 17-fold increase in their own risk of ovarian cancer in a follow-up period of 6 years. A family history of breast cancer raised their risk less dramatically. These risks decreased with increasing age at breast-cancer diagnosis.

"Our study lends support to theories of a connection between as yet unknown genes and cancer susceptibility," the researchers wrote. There is currently no effective screening strategy for ovarian cancer but they note that–if their results are confirmed elsewhere– "they seem to allow identification, based on easily obtained clinical information, of a small subgroup of women with breast cancer who are at particularly high risk of ovarian cancer."

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Neuroblastoma screening 'not recommended'

The disadvantages of screening for neuroblastoma easily outweigh any benefits, according to an expert panel from the International Society of Paediatric Oncology (SIOP Annual Update, Oporto, Portugal, 18-21 September 2002). Their discussion followed the presentation of 2 studies (MPO, 2002, p254, 0138 and 0139) reporting data from screening programmes set up in Germany and Japan, respectively.

Neuroblastoma is the second most common childhood malignancy. It was intuitively thought that screening should help reduce mortality from the disease and in the last 10–20 years several pilot screening studies were set up in many European countries. However, some cases of neuroblastoma spontaneously regress and these cases, if detected through screening, could result in an over-diagnosis and inappropriate treatment of patients.

Dr Freimut Schilling reported the German experience. A screening programme identified 2 581 188 children (at the age of 1 year) in 6 German states from 1995–2000. They were compared with 2 117 600 children who were not screened. Screening involved high performance liquid chromatography analysis of urine samples for vanillylmandelic acid and homovanillic acid. Both groups had similar levels of stage 4 neuroblastoma (3.7/100 000 compared with 3.8/100 000). Mortality rates were also similar: 1.3/100 000, and 1.2/100 000, respectively. Of those identified through screening, 7 per 100 000 were estimated not to have benefited from earlier diagnosis and treatment. The authors—in agreement with the discussion panel—state, "The findings provide no support for screening". The Japanese study examined screening at 6 and 18 months and concluded that screening at 18 months was useful to identify type II, but not the higher risk neuroblastomas.

In the discussion, Professor Alan Craft, President of SIOP, compared screening for neuroblastoma to screening for adult cancers such as breast and prostate where it is not clear that screening reduces mortality. Nevertheless, these programmes had "helped us to understand more about the biology of the diseases", he said. Dr Louise Parker concurred that we need to know what can be learned from this. "You cannot trust your gut feeling that screening is going to benefit. In the case of neuroblastoma screening, the vast majority have undergone chemotherapy and surgery, perhaps unnecessarily, and could have acute long-term effects. A lot of money is spent on such programmes and they are not good value for money", she said. Representatives on the discussion panel from France, Germany, Austria and Quebec all stated that such programmes had been stopped or were not recommended.

Emma Cannell
Oporto

For more details, see the forthcoming EJC editorial by Professor Craft and Dr Jon Pritchard; and EJC Current Perspective by Dr Schilling.

Smouldering neuroblastoma in children

Indolent or smouldering metastatic neuroblastoma (NB), as previously described in adolescents and adults, is possible among children, researchers say (*Cancer* 2002: 95: 1366-75). They found that recurrence of stage 4 neuroblastoma in children can be arrested for long periods of time, often using therapies of modest toxicity. Complete eradication of this stage of disease is uncommon, they say.

The study was based on a series of 38 children who were under 10 when diagnosed with NB and had metastases 5 years or more from diagnosis. The researchers, at Memorial Sloan-Kettering (New York) report that, though 26 died of disease or toxicity, 12 patients are surviving between 5 and 19 years from diagnosis.

Through the 1980s, less than 5% of deaths from NB occurred more than 3 years after diagnosis. Now, new chemotherapy regimes, emerging biological therapeutic agents and anti-idiotype vaccines "may lead to an increased incidence of chronic NB", the researchers say.

New agent for malignant glioma?

An apoptotic peptide is showing promise in the treatment of malignant glioma, a cancer refractory to most treatments. German scientists have reported that smac peptides can work to promote apoptosis and eradicate the cancer.

Anti-cancer drugs often work by inducing apoptosis but resistance can develop when defects occur in the pathway. Dr Simone Fulda (University Children's Hospital, Ulm, Germany), whose paper was nominated the best submitted by a young researcher, presented the data at the Schweisguth lecture (SIOP Annual Update, Oporto, Portugal, 18–21 September 2002). She has shown that smac peptides can synergise *in vivo* with activators of TNF (Tumour Necrosis Factor)-related apoptosis. TRAIL or TNF-Related Apoptosis-Inducing Ligand is one of these activators. The synergy leads to the destruction of malignant glioma.

Smac is a mitochondrial protein that inhibits XIAP (Inhibitor of Apoptotic Proteins), itself an inhibitor of apoptosis. XIAP proteins are highly expressed in tumours and have been linked with resistance to therapy. Overexpression of smac sensitises cells for TRAIL-induced apoptosis and can overcome the resistance of cells induced by apoptotic protective proteins such as Bcl-2.

Dr. Fulder and colleagues expressed the cytosolic form of smac by deleting the mitochondrial targeting sequence and, using this form of smac, were able to sensitise tumour cells to both TRAIL- and Doxorubicin-induced apoptosis. They developed peptides of smac and tested these in primary tumour cells where co-treatment with TRAIL was found to sensitise cells to TRAIL-induced apoptosis.

The peptides enhanced the anti-tumour activity of TRAIL when tested *in vivo* in a human malignant glioma mouse model. TRAIL alone was also effective at delaying growth, but all of the mice died. Only the combination treatment resulted in increased survival. The combined treatment had no toxic effects on normal cells and has not yet been tested systemically. Dr Fulder described the smac peptides as promising new agents to potentiate the efficacy of cytotoxic therapies.

Emma Cannell

Human growth hormone: the risks

Human growth hormone treatment may be associated with an increased risk of death from Hodgkin's disease and colorectal cancer, London researchers say (*Lancet* 2002, 360, 273-77).

A cohort study used data from 1848 patients (1209 males, 639 females) treated in the UK with human pituitary growth hormone between 1959 and 1985. Data on incidence were collected until December 1995 and on mortality until December 2000. It was compared with rates in the general population. 241 of the patients died.

Overall mortality from cancer among the patients was almost 3

"100,000 PATIENTS HAVE RECEIVED HGH"

times that among the general population. Mortality from colorectal cancer was 10 times the base rate, and from Hodgkin's disease, it was 11 times. After exclusion of patients considered at high risk due to their initial diagnoses (n=496), significant increases in mortality rates were still observed for these cancers. All cancers occurred after the cessation of growth hormone treatment and there were no leukaemias in the cohort.

To date, there has only been limited direct evidence linking growth hormone treatment with cancer. The increased risk for leukaemias previously observed could be due to the patient cohorts that have been studied. Growth hormone raises the serum levels of the insulin-like growth factor-1 (IGF-1), which has both mitogenic and anti-apoptotic effects— and raised IGF1 levels have been observed in high risk CRC adenomas. Several cohort studies have also reported an increase risk of colon cancer with increased serum IGF-1 concentrations.

Due to the small numbers of cases, the authors are cautious in their interpretation and state, "Further investigation in other cohorts is needed". It is also unclear how their results will apply to those treated since 1985 with recombinant growth hormone. An accompanying commentary (*Lancet* 2002; 360, 268-9) concurs "continued follow-up is imperative" given this "provocative and somewhat worrisome" data. It points out that the incidence of most cancers increases with age and the cohort are just reaching ages where this will start to rise precipitously.

Furthermore, a recent report (*J Natl Cancer Inst* 2002; 94:454-60) showed that a common polymorphism in the human growth hormone gene results in decreased concentrations of growth hormone and IGF-1 and is inversely related to the risk of colorectal cancer. The commentators

"THE DATA IS PROVOCATIVE AND WORRISOME"

suggest that doses should be individualised so that normal IGF1 levels are reached in each patient and should not be based on the patient's weight or growth rate. Given that the number of patients who have been treated with growth hormone worldwide has been conservatively estimated to be 100 000, this study should provoke a reassessment of the risks and benefits of growth hormone therapy to ensure it is prescribed appropriately, they say.

Emma Cannell

Discussing quality of life

Quality of life profiles are a starting point, rather than a substitute, for patient–doctor discussions, say German researchers (*Journal of the Royal Society of Medicine* 2002: 95: 481-488). They suggest structured conversations and say, "There is no contradiction between this empirical approach, and doing something 'humanistic' for the patient."

Using the EORTC-C30 quality of life questionnaire, they examined correlates of quality of life from doctors and patients' viewpoints. Symptom distress was strongly linked with psychological scores but neither somatic symptoms nor global quality of life were related to objective clinical criteria, such as tumour growth. "Clearly quality of life is a domain outside the biochemical/molecular paradigm," they said.

Doctors' and patients' expectations of treatment were very different. Among patients receiving mostly palliative therapy for advanced cancer, 58% of patients expected a cure, where doctors believed this was realistic for only 7%. "A remarkable observation was that those who expected healing had a significantly better quality of life," they noted.

Therapeutic priorities were another source of difference. Among patients having cholecystectomy, a return to physical fitness was sometimes ranked more important than death or hospital stay. Yet, the researchers say, in more than 60 studies this was never a primary endpoint. "These studies seem to have assessed outcomes that were of more interest to doctors than to patients."

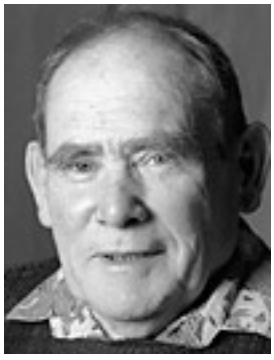
Quality of life profiles allow doctors to recognise deficits in particular areas, the researchers say, but they stress that the reasons why a particular deficit exists is not always evident from the profile. "The patient has to explain," they say. The benefit of any action taken can then be assessed by a further profile, they say.

Commenting on the study, Professor Peter Fayers, (University of Aberdeen, UK), chairman of EORTC Quality of Life Group said that he welcomed the return of interest to the subject of patients' expectations. It was raised about 20 ago when it was suggested that quality of life is a measure of the difference between the hopes and expectations of an individual and the individual's present experience, but has been largely ignored since. However, he said expectations can seriously impact on perceived quality of life.

"It is important for doctors to be aware of patients' expectations. If they sense that a patient is way off course in terms of negative expectations, they do need to explain more and address it. There is not sufficient attention paid to the idea of expectations" he said.

Nobel Prizes for Cell Death research

Dr John Sulston (Cambridge UK), Dr Sydney Brenner (Berkeley, California, USA) and Dr Robert Horvitz (Cambridge, Massachusetts, USA) have been jointly awarded the Nobel Prize in Physiology or Medicine for their work on "genetic regulation of organ development and programmed cell death".



Dr Sydney Brenner

The Nobel Assembly at Karolinska Institutet said the laureates have made "seminal discoveries". Establishing and using the nematode *Caenorhabditis elegans* as an experimental model system, they identified key genes and showed that corresponding genes exist in higher species, including man. "The discoveries are important for medical research and have shed new light on the pathogenesis of many diseases."

Dr Brenner worked in Cambridge, UK, with *C. elegans* because of its short generation time and its transparency, which made it possible to follow cell division directly under the microscope. In 1974, Brenner demonstrated that specific gene mutations could be induced in the genome by the chemical compound ethyl methane sulphonate. Different mutations could be linked to specific genes and to specific effects on organ development. He received his Prize for this combination of genetic analysis and visualisation of cell divisions observed under the microscope.

Dr John Sulston extended this work and, in 1976, described the cell lineage for a part of the developing nervous system. He showed that every nematode undergoes exactly the same program of cell division and differentiation. Dr Sulston's "seminal discovery" is that specific cells in the

Dr John Sulston

cell lineage always die through programmed cell death. He demonstrated the first mutations of genes participating in programmed cell death, including the nuc-1 gene.

Dr Horovitz conducted a series of elegant experiments in which he used *C. elegans* to identify, in 1986, the first

Dr Robert Horvitz

2 "death genes", ced-3 and ced-4. He showed that functional ced-3 and ced-4 genes are a prerequisite for cell death to be executed. Later, he showed that another gene, ced-9 protects against cell death by interacting with ced-3 and ced-4. He also identified a number of genes that direct how the dead cell is eliminated.

The Nobel Assembly said that research on programmed cell death is intense in cancer. "Many treatment strategies are based on stimulation of the cellular suicide program. This is, for the future, a most interesting and challenging task to further explore in order to reach a more refined manner to induce cell death in cancer cells."

Sir Paul Nurse, Chief Executive of Cancer Research UK, said the work "has provided a better understanding of how cells change their fate to make different tissues and organs and has also revealed that cells can undergo programmed cell suicide. These processes are very important for understanding the development of cancer."

New insight into repair enzyme

The protein MBD4, previously shown to repair genetic mismatches in vitro, has been shown to have the same effect in mice (*Science* 2002, 297: 403-5). Researchers say their findings suggest "that human MBD4 plays a similarly important role in reducing inherited disease and cancer."

MBD4 is mutated in up to 43% of human colorectal tumours with microsatellite instability, which suggests that the mutation contributes to genetic instability. *In vitro* work has shown that the protein is involved in the repair of an important mismatch—the deamination of 5-methylcytosine—itself responsible for more than 20% of all base substitutions giving rise to genetic diseases such as cancer.

The UK group generated mice bearing a mutated *Mbd4* gene and confirmed the lack of MBD4 expression. When $Mbd4^{-/-}$ mice were compared with wild-type mice, there were significantly more mutations in the former. In particular, the authors found that C to T transitions at the CpG sites were increased 3-fold in the $Mbd4^{-/-}$ mice whereas these transitions were not increased at non-CpG sites. When $Mbd4^{-/-}$ mice were transferred to the cancer susceptible $Apc^{Min/+}$ background, tumour formation was accelerated and there were CpG to TpG mutations in the *Apc* gene. This suggests that MBD4 may be a suppressor of CpG mutability and tumorigenesis *in vivo*.

Emma Cannell

INTERVIEW

Dr Agnes Glaus is co-chair of the Center for Tumor Detection and Prevention, St Gallen, Switzerland. She is Past-President of the European Oncology Nursing Society (EONS), co-chair of the German section of European School of Oncology (ESO), and a former President of the Swiss Oncology Nursing Society. She has won EONS' Distinguished Merit Award and the Swiss Cancer League's medal.

Dr Agnes Glaus

Where did you train?
I trained in nursing at St Gallen, in public health nursing at Berne, in management at Zurich and took my masters and doctorate in cancer nursing at the European Institute of Health and Medical Sciences, University of Guildford, UK.

Who inspired you?
I was impressed and inspired by Professor Rosemary Crow at Guildford. She understood what nursing should be and linked her vision with science; always thinking and arguing scientifically.

Why did you choose to work in the field of cancer?
Actually, I was sent to work on a cancer ward without being asked! In the late 1970s, nobody really wanted to work in cancer and head nurses had a problem finding staff. But it was a period of major development and I was working alongside internationally-acknowledged experts Professors Hans-Jörg Senn and Walter-Felix Jungi. I felt it was a privilege to meet cancer patients and learn from them what it means to have cancer, to live with the treatments and with impending death.

Did any other branch of nursing appeal?
Initially, I wanted to work in surgery but I found the ethical and psychosocial challenges in oncology appealed to me more than nursing patients for a short time and never seeing them again. I am interested in nursing chronically ill people and geriatric patients—they are a challenge within cancer nursing. In such difficult fields we can only succeed on a long-term basis if we link nursing with science and research as well as with continuing education.

Might you have done something else altogether?
No. I always wanted to be a nurse.

What has been the highlight of your career to date?
Studying for my diploma in nursing, I learned that nursing is not only about illness, but also about health, and this prompted me to study public health, and to strive to find out what cancer nurses need to care for their patients and families. I went on to set up post-graduate education for cancer nurses. Such education is now routine but it was new and had to be developed in the 1980s. Later, I enjoyed entering the scientific world at University.

..and your greatest regret?
Nursing has been wonderful and opened a whole world up to me but it has taken over almost my whole life and left me little time for myself. I have not had the chance to enjoy the fun side of just being a student—I always was a nurse and student at the same time. I don't have children and I would have liked to. On the other hand, I have almost cared for my profession as if it were a child and I have enjoyed putting my time and energy into it.

If you could complete only one more task before you retire, what would it be?
To help and be involved in the growth of cancer nursing as a scientific community in Europe.

What is your greatest fear?
That nursing does not get the recognition it deserves and that as a profession, it is losing ground. I fear that this will lead to such a shortage of nurses that nursing will cease to exist. Personally, the challenge I face is to have the strength to deal with changes that will occur. It's been said that ageing is a balance between gains and losses and dealing with this is a major challenge in my near future.

What impact has the Internet had on your working life?
It's had a great impact for communicating with people throughout the world and for the scientific resources.

How do you relax?
I like to sleep in! Also to go walking in the hills and observe nature. I like listening to music, reading poetry, and writing.

Who is your favourite author?
I like many German poets and often read them when I am preparing a talk; it often gives me deeper insight. Theodore Storm's "The beginning of the end" is a favourite and I read the Psalms for their poetry and comfort.

What do you wish you had known before you embarked on your career?
I'm not sure there's anything that I would have changed, but it has been very hard work! Especially studying and taking exams in a foreign language. Of course I enjoyed it very much but it would have been easier to study here, in German. It's possible now, but wasn't then.

What piece of advice would you give someone starting out now?
To be successful you have to deal daily with the balance between being close to someone and keeping a distance. You must remain your own person, a skilled companion, and not become the patient.

What is your greatest vice?
I often spend too much energy on things. I would like to have a bit more lightness of being.