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Tamoxifen reduces genetic risk

Tamoxifen reduces the risk of contralateral breast cancer in women with genetic mutations; an international group has found (*Lancet* 2000, **356**, 1876–1881). Researchers from Europe, the US and Canada found a 75% reduction in risk of contralateral breast cancer in women who used tamoxifen for 2 to 4 years. The protective effect was independent of oophorectomy.

In the 10 years after diagnosis of breast cancer in carriers of *BRCA1* or *BRCA2* mutations, the risk of a contralateral breast cancer is about 35%. This study included women with these mutations, and compared 209 of those with bilateral breast cancer with 384 matched controls with unilateral breast cancer. The women were questioned an average of 11 years after their initial diagnosis.

The protective effect of tamoxifen increased with duration of use up to 4 years, probably by blocking the activity of endogenous oestrogens. However, tamoxifen was effective in women whether or not they had undergone oophorectomy and the researchers suggest that it might also work via other mechanisms. "The protective effects of oophorectomy and tamoxifen seem to be independent and additive," they said.

Tamoxifen was more protective for women diagnosed in North America than for those diagnosed in Europe.

"THE PROTECTIVE EFFECTS OF OOPHORECTOMY AND TAMOXIFEN SEEM TO BE INDEPENDENT AND ADDITIVE."

The European patients had a higher proportion of *BRCA1* mutations, and a younger age at first diagnosis of cancer, but these differences are insufficient to explain the differences in tamoxifen's effect, the researchers said.

Oophorectomy was especially protective among women whose first breast cancer was diagnosed before they were 50 years old, and much less protective among women diagnosed later. Initial treatment with chemotherapy reduced risk of contralateral breast cancer by 60% and its greatest effect was apparent within 2 years of treatment, though risk rose after 10 years. The researchers suggest it eradicates prevalent, subclinical cancers.

"Tamoxifen can reasonably be offered to women with *BRCA1* or *BRCA2* mutations and breast cancer for the prevention of contralateral breast cancer,'' they concluded. The study did not allow them to recommend the optimum duration of tamoxifen but they noted that use for longer than 4 years was not associated with any further reduction in risk. They were also unable to determine whether tamoxifen slows the growth of existing tumours or reduces the development of new ones.

Improving the PSA test

Measurement of other serum concentrations may improve the sensitivity of the prostate-specific antigen (PSA) test for prostate cancers, suggest Swedish and US researchers (*Lancet* 2000, **356**, 1902–1903). They say that levels of insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) might help identify men at risk.

They collected blood samples from 209 men with newly diagnosed and untreated prostate cancer and matched them for age with 221 healthy men. Men with a normal PSA had a 2.5-fold increase in risk of cancer for every 100 ng/ml increase in IGF-1 concentration. Risk of cancer also increased with reduced levels of IGFBP-3 in this group.

IGFBP-3 normally binds IGF-1, and prevents IGF-1 from binding to receptors at the prostate cell surface. PSA is an IGFBP-3 protease, which greatly lowers the affinity of IGFBP-3 for IGF-1.

The results support suggestions that IGF-1 may be important during the initiation and early progression of prostate cancer. Advanced disease seems independent of IGF-1.

"The additional use of IGF-1 and IGFBP-3 can potentially improve sensitivity of the diagnostic procedures," they write. Furthermore, men with high PSA levels who are cancer-free but at increased risk because of their IGF-1 and IGFBP-3 levels might be given treatment to adjust these levels as a preventive measure. The researchers say that further, well-designed studies are urgently needed to assess the role of these measurements.

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End of life decisions in France

More than half the deaths in intensive care units in a large prospective study in France were preceded by a decision to withhold or withdraw life-support therapies (*Lancet* 2001, **357**, 9–14). This is despite the lack of guidelines from French scientific societies and legislation, which prohibits both active and passive euthanasia.

Researchers surveyed 113 of 220 intensive care units in France for 2 months, during which 7309 patients died. They found that 53% of deaths were preceded by a decision to withhold or withdraw life support therapies. Decision-making processes appeared to be flawed. For example, only 54% of decisions involved nursing staff, and 12% were taken by a single physician, with no consultation. 11% of decisions were taken during the night-shift, suggesting a degree of haste, and less than half of the decisions involved the patient's family.

The main reasons given were futility and poor expected quality of life and the researchers concluded that the context and characteristics of the decisions were not dissimilar from those made in the United States, where clinical studies and guidelines have been published. However, they said, the decision-making processes "differ greatly" between France and North America and that the lack of official statements from French scientific bodies could explain the "several limitations" to the process recorded in the survey.

'Prophylactic mastectomy 'may reduce anxiety''

Bilateral prospective mastectomy may provide psychological benefits, UK researchers say (*BMJ* 2001, **322**, 76–79). The first prospective psychosexual study of bilateral mastectomy found that women at high genetic risk of breast cancer who chose surgery had reduced anxiety afterwards. Women who declined surgery had no reduction in psychological symptoms.

Researchers interviewed 143 women with increased risk of breast cancer who were offered bilateral prophylactic mastectomy. The 79 women

Professor Ian Fentiman

who accepted surgery showed a significant reduction in psychological morbidity 6 and 18 months after surgery. The 64 who declined surgery showed no such reduction. The latter group were more likely to be prone to anxiety, less likely to believe they would develop breast cancer and more likely to believe that screening could help. Neither body image nor sexual functioning changed significantly among women in either group.

The researchers call for further research into methods of ensuring that risk perception is accurate.

"WE URGENTLY NEED A NATIONAL REGISTER."

Almost one third of women who had surgery believed it inevitable that they would develop breast cancer. "If women are making decisions based on inaccurate perceptions they might regret these decisions later," they say.

Commenting on the research, surgical oncologist Professor Ian Fentiman (Guy's Hospital, London) agreed that many women overestimate their risk, based on their family history. ''In terms of the benefits of prophylactic mastectomy,

"DECISIONS BASED ON INACCURATE PERCEPTIONS MAY BE REGRETTED."

there will be some decrease in risk, but the magnitude of this is not known. For this reason we urgently need a national register of women who have had prophylactic mastectomies so that the long-term effects can be determined and women with concerns given accurate information.''

A related review (*BMJ* 2001, **322**, 116) directs doctors to the website *www.facingourrisk.org*, which includes personal accounts of women who have made the decision to have surgery.

Micrometastases in cervical cancer

Molecular assessment of micrometastases may help identify the women with cervical cancer which is likely to progress, according to UK and Hungarian researchers (*Lancet* 2001, **357**, 15–20). They found that 50% of women with early-stage cervical cancer shed tumour cells in the lymphatic system. The amount is significantly associated with poor clinicopathological prognosis.

The researchers analysed samples from 32 women with cervical cancer at various stages. They used a reverse-transcriptase PCR technique to identify cytokeratin 19 in pelvic lymph nodes.

They found high transcription of cytokeratin 19 in all 32 primary cervical cancers, and in only one of 32 nodes from patients with benign disease. They found significant differences in transcription according to differentiation, stage and the presence or absence of lymphovascular space involvement — all of which are associated with clinical outcome in cervical cancer. Further, 15 of 16 patients with evidence of micrometastases had the highest transcription in a first lymph-node drainage system.

Only a very small fraction of micrometastases continue to grow to form tumours and the researchers say, "Quantification, characterisation and assessment of the potential of distant tumour growth of micrometastases is, therefore, essential in further studies". Ultimately, they say, a panel of markers including others such as angiogenic factors may provide optimal information. "Such a panel may enable clinicians to identify the small group of patients who are destined to develop recurrent disease," they conclude.

Potential for lung cancer screening?

Technological advances are making screening for lung cancer increasingly viable, say two UK doctors (*J R Soc Med* 2001, **94**, 2–5). Malcolm Dalyrumple-Hay and Nigel Drury (Southampton General Hospital, UK) say that smoking cessation alone is insufficient to combat lung cancer. A successful test could reduce mortality in a short period of time, they say.

Several trials in the 1970s used plain chest X-rays and gave disappointing results; the American Cancer Society then withdrew its support for screening in 1980. This research has since been criticised — the Mayo Lung Project in the US was the only large randomised trial in which the control group received no additional routine screening and it lacked sufficient power to detect a 20% decrease in mortality. However, chests X-rays are unlikely to feature in any future screening programme, say Drs Dalyrumple-Hay and Drury.

New molecular biomarkers have renewed interest in sputum collection. Previous studies have found sputum cytology too insensitive to be effective, but research into individual protein and DNA markers could establish their role in early detection, monitoring and risk assessment for lung cancer in conjunction with radiological techniques, they say.

Computed tomography (CT) has been seen as too expensive and demanding for use in widespread screening but modern CT is becoming faster and more acceptable. Improvements in computer-aided diagnosis technology may reduce the need for specialists' time. Further, the development of ultra-low-dose (CT) "could constitute a considerable breakthrough," they say, as it will reduce the screened population's exposure to radiation. Currently, even low-dose helical scanners deliver 10 times more radiation than a chest X-ray.

"THERE HAS BEEN A WALL OF SILENCE SURROUNDING LUNG CANCER."

CT has already been introduced for screening high-risk groups in the US and Japan, but, "Despite its potential there seems little prospect of such a UK national screening programme in the foreseeable future," the authors note. "The resources required are far beyond the scope of an overloaded National Health Service."

There is little public pressure for such a screening programme; lung cancer has a low public profile in Britain. A recent MORI opinion poll for the Cancer Research Campaign (CRC) found that 7 out of 10 people in Britain believe that smokers who develop lung cancer have brought the disease on themselves. Dr Richard Sullivan, CRC head of clinical programmes said, "This poll shows most people feel that, for smokers, it's a self-inflicted disease which, we believe, helps explain its lack of profile".

However, the majority of those questioned — 84% — did not want lung cancer patients to be discriminated against. They felt that lung cancer sufferers were as deserving of NHS treatment as other cancer patients. Dr Sullivan said that lung cancer is almost invisible to the public eye: "There has been a wall of silence surrounding lung cancer for far too long. We need to break this down and show that we do care for patients with the disease — regardless of whether or not they developed it because of smoking".

A pervasive influence

Efforts to reduce tobacco use face the "pervasive, countervailing influence of tobacco promotion by the tobacco industry" according to a US Surgeon General's report (*MMWR* 2000, **49**, no. RR-16). Promotion ''takes place despite overwhelming evidence of adverse health effects from tobacco use,'' it states.

The report finds evidence of effectiveness for different approaches to tobacco control including educational strategies; pharmacological treatment of addiction; regulation of advertising and promotion; clean air regulations and restriction of minors' access to tobacco products; taxation on tobacco products. "The impact of these various efforts as measured with a variety of techniques, is likely to be underestimated because of the synergistic effect of these modalities," it states.

State tobacco control programmes, funded by excise taxes on tobacco products and settlements with the tobacco industry, were applauded. They have generated "early, encouraging evidence of the efficacy of the comprehensive approach to reducing tobacco use," it states.

The report states that in the 1990s, it became increasingly apparent that a public health success in reducing tobacco use requires activity on all fronts. "A comprehensive approach — one that optimises synergy from a mix of strategies — has emerged as the guiding principle for future efforts to reduce tobacco use."

Smoking in US films

A voluntary ban by the tobacco industry has failed to reduce the prominence of cigarettes in box-office hits, researchers report (*Lancet* 2001, **357**, 29–32). Tobacco companies publicly ended direct financial payments for tobacco brand placement in films in 1989. However, the researchers found no reduction in brand appearances following this ban.

They analysed the top 25 box-office films produced between 1988 and 1997 and found brand appearances were as common in films suitable for adolescents as for adults. They appeared in 20% of films rated for children. There was a striking increase in actor endorsement of cigarettes over the period, which rose from 1% of films before the ban to 11% afterwards. "Whether or not a financial exchange takes place between the industries, the result is the same: US cigarettes are being marketed to a global audience through cinema films," the researchers note.

AWARDS AND APPOINTMENTS

New department head at St Radboud

Professor Peiter de Mulder was recently appointed head of internal medicine at St Radboud University Hospital in Nijmegen, The Netherlands. He has been deputy head of the department since 1984.

Professor de Mulder was trained at Nijmegen University and wrote his PhD thesis on 'Monocyte function in Hodgkin's disease'. His current research interests are in the field of immunotherapy in cancer, especially renal cell carcinoma and head and neck cancer. He has a particular interest in malignancies of the genito-urinary tract and specific expertise in antiemetic research.

He is a member of several EORTC groups, such as the biotherapeutic development group, the head and neck group and the genito-urinary group. He is a past chairman of the Quality Assurance Committee of the EORTC and a Board member. He is currently study co-ordinator of five ongoing EORTC phase II and phase III trials of various compounds (16997, 30868, 30885, 30932, 30955) in patients with advanced bladder or kidney cancer.

Professor de Mulder currently chairs the Nijmegen working party for head–neck tumours, co-founder and chairman of the managerial committee of the Dutch Immunotherapy working party and secretary of the faculty focus for innovations, Nijmegen.

Brad Timms

Outsider joins ONS Board

Dr Gregory Crow has been named as the first non-member director of the Oncology Nursing Society (ONS) Board of Directors. The membership voted in 2000 to designate a seat for a non-ONS member who brings specialised skills and expertise. Dr Crow will serve until May 2002.

He is currently professor, graduate co-ordinator and programme director of nursing leadership and case management programmes at Sonoma State University, CA. Dr Crow has a doctorate in education, an MSc and a BSc in nursing from the University of California, San Francisco. He has worked at the school of nursing and the college of professional studies at the University of San Francisco.

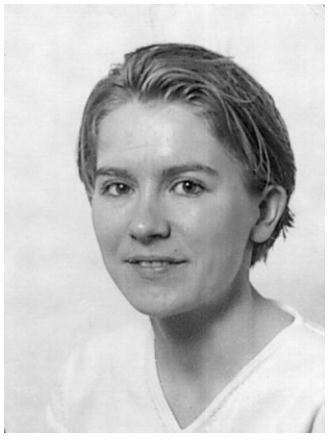
Dr Crow has been a consultant on an ONS nursing leadership initiative and has published extensively in nursing and management publications.

Assessing the skill of the surgeon

Surgical skill varies so widely that it could lead to unjustified rejection or approval of adjuvant therapies on trial, according to Dr Marlies Landheer, research fellow at EORTC Data Center. The quality of surgery is obviously important for the patient, and in surgical trials, but she says, "It may be absolutely crucial in trials of post-operative chemotherapy and radiotherapy. This type of research is particularly important within the EORTC."

Dr Landheer is devoting a year to devising ways of assessing the quality of surgery in cooperation with the EORTC Quality Assurance Committee. "It is difficult to define guidelines for quality assurance in surgery. There are no quantifiable parameters available fopr routine quality assurance measures as compared to radio and chemo-based therapy. It is a challenge."

Local control was for a long time thought to depend on the biological behaviour of the tumour rather than of the quality of surgery. She says that it has been difficult to pin down the influence of the individual surgeon, especially since medics have been reluctant to categorise the quality of their colleagues' work. "It has taken a long time to convince surgeons and other medical professionals of the relationship between their skills and the outcome in terms of local control and survival. Although there is now strong evidence of the importance of surgical skill, for example in the treatment of rectal and breast cancer, it is still crucial to provide evidence of similar relationships in other tumours."



Dr Marlies Landheer

Dr Landheer began her research fellowship at the EORTC in June 2000 as a medical research fellow in surgical oncology. Her fellowship, financed by the "Nederlandse Kankerbestrijding/ Koningin Wilhelmina Fonds", is part of her Ph.D. studies. She graduated in medicine from the Katholieke Universiteit, Nijmegen, Holland in 1999 and before joining the EORTC, she worked at the department of surgery, Rijnstate Ziekenhuis, Arnhem. When she leaves the EORTC, she will train in surgery at Rijnstate Ziekenhuis, Arnhelm and at the University Hospital, Nijmegen.

Quality assurance is a hot topic and will become more important in the near future, she says. "I hope to play not only a significant role in the development of useful tools and criteria but also in convincing the medical world and enabling quality assurance to take place in surgery. Quality assurance might even necessitate renewed trials into the efficacy of adjuvant therapies," she says.

She adds, "As I hope to become a good surgeon, it is good to know the consequences of your individual skills. And as I'm now reading so much about varying quality, I'm sometimes frightened by the existing differences."

Samantha Christey
EORTC Communications Officer

INTERVIEW

Dr Martine Piccart is head of chemotherapy at the Jules Bordet Institute in Brussels, Belgium, and a member of ASCO, AACR, ESMO and EORTC's gynaecological cancer study group, breast cancer cooperative group and early clinical trials group. She chairs the Breast International Group (BIG).

Dr Martine Piccart

Where did you train?

I trained in medicine and internal medicine in Brussels. I took a 2-year fellowship in medical oncology at the New York University Medical Centre, before returning to the Jules Bordet Institute in Brussels in 1985. I have been here ever since.

Who inspired you?

Professor Henri Tagnon was a visionary, exciting to talk with and he enthused all around him. Dr Rozencweig, a medical oncologist at the Institute here, was also tremendously enthusiastic. Dr Franco Muggia in New York was fantastic to work with and I learned a lot from him.

Why did you choose to work in the field of cancer?

My father was a gynaecologist and I had made the decision to study medicine by the time I was 7 years old. In my early teens, my great uncle had colon cancer and I visited him here, at the Jules Bordet Institute. Something happened then, something impressed me, and when I started my medical training I already had it in mind to study oncology.

Did any other branch of medicine appeal?

I was tempted by paediatrics.

Might you have done something else altogether?

I studied the piano intensively between the ages of 7 and 18 and took a diploma in the theory of music. Once at University, I did not have the time to complete my piano examinations, but I still play and have given concerts to raise money for charities, the EORTC and the Institute here.

What has been the highlight of your career to date?

The first was when I was invited by the board of ASCO to give an educational lecture at the annual meeting. It was something I would never have dreamed of. The second was when I received the ESMO award, given "to recognise the exceptional contribution of an individual to advance medical oncology in Europe," in my case in the field of breast and ovarian cancer. I did not know that my colleagues appreciated my work to that extent.

….and your greatest regret?

I have been, and remain, extremely enthusiastic about the EORTC, and for 3 years was closely involved with the people trying to help it adapt to what is happening in medical oncology, with the faster development of new drugs, and so on. A year ago, my involvement came to an end and I was disappointed.

If you could complete only one more task before you retire, what would it be?

To set up an ongoing, live meta-analysis of existing large trials. The Oxford Group updates meta-analyses every 5 years, but there is an exponential growth in clinical trials and we need this done every year. It would be difficult to persuade researchers to part with data, but it is feasible.

What is your greatest fear for the profession?

That we will fail to remain independent of the pharmaceutical industry. It is important that we collaborate because the industry comes up with interesting new compounds, but it is increasingly difficult for independent groups to attract investigators.

What impact has the Internet had on your working life?

More negative than positive! It is nice to be able to communicate easily with colleagues, but I receive too much e-mail to deal with. Also, more and more patients use the Internet and it can take me a long time in clinic to explain why their information is not correct.

How do you relax?

With music. When I play the piano I forget everything. My children and whole family are musical, we play music together at home and it is lovely.

Who is your favourite author?

I do not read as much as I would like, but for light holiday reading, I choose Christian Jacq, who writes about Egypt. For serious reading, I enjoy Albert Camus.

What do you wish you had known before you embarked on your career?

That a career in clinical research can be rather like running a small enterprise! I supervise 25 researchers of different disciplines and I never expected to need management skills.

What piece of advice would you give someone starting out now?

Learn English and, most importantly, try to train abroad. It is an enriching experience and gives you a different perspective.

What is your favourite carcinogen?

The stress of a new challenge. I love it when a new drug arrives. We know what it does in the laboratory, but we have to develop it into a successful treatment for cancer. It can be tremendously exciting.