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Individual risk assessments in breast cancer

Gene expression profiling of breast tumours can identify patients with a high risk of recurrence, researchers say. Two groups independently suggest that this could act as a first step towards tailoring therapy to individual patients and allow many to forego unnecessary chemotherapy.

In one study (*Nature* 2002, **415,** 530–536), Amsterdam researchers selected 98 primary breast cancers and examined approximately 25 000 genes using micro array. This allowed clusters of the tumours to be recognised on the basis of the similarity of approximately 5000 significant genes. Division of the patients into those with good or poor outcomes within 5 years of follow-up related to the cluster into which they fell. Genes involved in a variety of more biologically aggressive processes (such as control of cell cycle, invasion, angiogenesis) were up regulated in the poor prognosis group.

"PROGNOSTIC PROFILES ARE A POWERFUL TOOL FOR TAILORING TREATMENT"

The prognostic profile is potentially 'a powerful tool' for tailoring adjuvant systemic treatment, reducing the use of chemotherapy and for deciding on adjuvant hormonal therapy. Genes that are over-expressed in poor-prognosis tumours are also potential targets for the rational development of new cancer drugs. 'Identification of such targets may improve the efficiency of developing therapeutics for many tumour types,' they say.

"SUPERIORITY OVER CURRENT METHODS HAS YET TO BE SHOWN"

In the other study, (*Lancet* 2002, **359**, 131–132) samples from 55 consecutive patients in Frankfurt, were grouped according to their expression of 41 marker genes. Hierarchical clustering methods produced two clusters: class A and non-class-A. The class A subgroup had a high proportion of patients with node-positive tumours and distant metastases at the time of diagnosis. Two-year follow-up revealed that 11 of 22 patients in class A progressed to metastatic diseases. When patients with T1-T3 tumours were considered separately, researchers found that 9 of 20 cases in class A had recurrences, compared with only 3 of 27 outside of this group.

The authors conclude that their work is a step towards an individual risk-profile system. 'Future directions should combine these molecular methods with the standard tumour classification system to obtain improved patient-tailored therapies.'

Professor Roger Blamey, EUSOMA Vice-President, was unconvinced by the conclusions. 'The articles were very optimistic that this method would provide prognostic predictions that could be used clinically. However, this suggestion ignored the great amount of work that has already gone into prognostic prediction and already there are very good methods, such as the well-validated Nottingham Prognostic Index, for carrying this out.

'They also ignore the fact that prognosis is determined by both time-dependent factors such as lymph node status and tumour size, which the micro array does not measure, and biological factors, which it does. These two sets of factors are of equal importance and, used synergistically, give a good measure of prognosis.

'This area of looking at ultimate determinants of tumour behaviour, the DNA pattern of each individual cancer, is exciting, but it has yet to be shown that it is superior to methods currently available,' he said.

Thyroid cancers 'require aggressive surgery'

Total thryoidectomy and modified radical neck dissection are essential primary treatment for medullary thyroid carcinomas (MTC), say German researchers. They say that less aggressive surgery will not cure most patients, and that in specialised centres, complication rates are 'acceptably low'.

Their study (*Surgery* 2001, **130**, 1044–1049) included 36 patients at the University of Heidelberg with either sporadic or hereditary MTC. Between 1994 and 2000, patients underwent thyroidectomy and systematic central and lateral lymph node dissection. Histologic examination showed 75% of patients had lymph node involvement.

Postoperative normalisation of serum calcitonin levels, the most important predictor of prognosis, was achieved in 89% of patients with no lymph node metastases, but in only 30% of those with lymph node involvement.

At 5 years, the overall survival rate was 96.4% and the disease-free survival was 71%. The researchers conclude, 'We recommend total thyroidectomy and unilateral modified neck dissection in sporadic MTC and bilateral cervicolateral neck dissection in hereditary MTC.'

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Genetic predictions in colorectal cancer

Chromosomal imbalance is a better predictor of outcome than histopathological stage of colorectal cancer, new research suggests. A joint US/UK/Italian group found that imbalances in chromosomes 8p and 18q gave valuable prognostic information.

The study (*Lancet* 2002, **359**, 219–225) included 180 patients who had no evidence of lymph node or distant metastases at the time of surgery. Each allele in tumour samples was directly counted.

They found 5 year disease-free survival was 100% among patients with no imbalances. It was 74% among those with imbalances in one of the chromosomes; and 58% among those with imbalances in both. The differences were significant.

'The most reasonable interpretation of these data is that patients whose tumours contained allelic imbalance of the studied chromosomes had micro metastases at the time of surgery that eventually proliferated and became clinically apparent,' the researchers wrote.

They suggest that allelic imbalance of chromosomes in general may indicate a propensity for metastasis, owing to increased instability or increased number of generations of the dominant clone. 'If this explanation is true, assessment of allelic imbalance of any chromosome commonly lost during tumour progression should provide useful prognostic information,' they say. They predict that quantitative methods of assessing allelic imbalance for other types of cancer 'will provide equally useful prognostic information.'

However, caution is urged in an editorial (*Lancet* 2002, 183–184). It points out that some of the markers used in the study are on 18p not 18q, and that another assumption made by the researchers is contradicted by recent findings. However, it agrees that the long-term potential of genome-based markers for cancers 'is tremendous.' It states, 'Those genes in particular whose loss influences the progress and course of the tumour by reducing overall genomic stability may prove most valuable as markers; the relevant genes on 8p and 18q, once identified and confirmed, may fall into this category.'

Keyhole surgery 'not recommended'

Laparoscopic surgery should not be offered to patients with colon cancer outside of randomised controlled trials, US researchers say (*JAMA* 2002, **287**, 321–328). A multicenter trial found only minimal, short-term benefits in quality of life (QOL), compared with standard open colectomy. It concluded that until trials establish that laparoscopic-assisted colectomy (LAC) is as effective in preventing recurrence and death from colon cancer, 'this procedure should not be offered to patients'.

The Clinical Outcomes of Surgical Therapy (COST) is a multicentre, randomised controlled trial, funded by the US National Cancer Institute, and designated high priority. Between 1994 and 1999, 574 patients were enrolled, and data on quality of life was available on 449 of them.

LAC for colon cancer resulted in statistically significant but clinically modest decreases in use of analgesia and length of hospital stay. The researchers said, 'These differences do not translate into statistically significant improvements in symptoms or QOL in the immediate postoperative period or over 2 months of follow-up.'

The primary objective of COST is to test the hypothesis that disease-free and overall survival following LAC and open colectomy are equivalent. Accrual for this part of the trial closed in 2001 but results will not be available for several years.

An accompanying editorial (*JAMA* 2002, **287**, 377–378) agreed that LAC 'should not be recommended in clinical practice' and said that an appropriate message is needed both for professionals, and patients 'who continue to request, and on some cases demand' it. It stated, 'The well-designed COST study is an example of how the perception of the probable benefit and advantages of a surgical procedure in the current era of burgeoning technology can be countered by solid scientific evidence.'

Cancer Research UK launches

Cancer Research UK, the new charity resulting from the merger of Cancer Research Campaign and Imperial Cancer Research Fund, was officially launched on World Cancer Day (4th February 2002). The new charity announced a £75 million programme of new investment.

The programme includes new research institutes in Cambridge, Oxford, Newcastle and Glasgow, in partnership with the Universities, Government and other charities. It also has a new contract with the US' National Cancer Institute 'to exchange resources, share best practice, and facilitate the exchange of ideas and information about cancer research'.

Joint director general, Professor Gordon McVie, said the launch of the new charity 'signals the dawn of a new age for research. Cancer is by far the most complex disease known to man and conquering it will be a challenge to both the intellect and the imagination.'

Baroness Hayman

Baroness Hayman, chairman of Cancer Research UK, said, 'There will be enormous public expectation for us to deliver on new treatments for cancer and we are all excited by that challenge. It will be a privilege to lead Cancer Research UK as it works to make a real difference for the world's cancer patients.'

The charity has an annual scientific budget of £130 million and employs 3000 dedicated research staff.

Asbestos link with lung cancers 'missed'

Many more cases of asbestos-related lung cancers may arise than are reported, say Italian researchers. They estimate 2000 cases per year in Italy, compared with the 281 reported for all occupational causes in the years 1990–1995 (*Am J Clin Pathol* 2002, **117**, 90–95). The finding has implications for legal actions and compensation.

Asbestosis is normally considered decisive proof of linkage between a lung cancer and previous exposure to asbestos. It relies on the demonstration of discrete foci of fibrosis associated with asbestos bodies in the walls of respiratory bronchioles. However, the Turin group suggests that a high concentration of asbestos bodies, even in the absence of fibrosis, can indicate occupational levels of exposure.

They studied 924 non-selected surgical cases of lung cancer with no record of occupational history. They found 56 cases which were 'definitely asbestos-related'. However, in 12 of these cases, this diagnosis was made only after a high concentration of asbestos bodies was found by light microscopy. This prompted repeated examination of additional sections. 'The asbestos body concentration should be determined in all cases in addition to an examination for histological asbestosis,' they write.

During the 1990s, there were about 32 000 cases of lung cancer per year. 'The extrapolation of our pathological estimate could suggest that in this country, about 2000 cases per year should be linked with asbestos exposure.' Between 1990 and 1995 281 cases were reported and 91 were eventually compensated.

"A MOLECULAR MARKER UNIQUE TO ASBESTOS IS NEEDED"

In their series, occupational history was not recorded and lung fibrosis was not detected in X-rays. They conclude, 'It might be supposed that the lung cancer cases related to asbestos exposure through the present work were otherwise destined to remain unrecognized while they have now given rise to the proper medico legal actions.'

An accompanying editorial (*Am J Clin Pathol* 2002, **117**, 9–15) points out that the concentration of asbestos bodies used by the Italian group as a cut-off for a level sufficient to produce asbestosis is lower than others have reported. It suggests 'some of the fibrosis in their cases might be from causes other than occult asbestosis'.

The editorial states that it is often difficult to separate the relative contribution of tobacco and asbestos. 'There is no reason that lung cancer in a tobacco-smoking asbestos worker should not be related purely to tobacco smoking.' What is needed is a molecular marker that is unique to asbestos or at least not caused by tobacco smoke, that would allow us to link a lung cancer to asbestos exposure.

It concludes, however, that until such a test becomes available, 'The only consistently reliable marker for an asbestos-related lung cancer is asbestosis, especially in asbestos workers who are also tobacco smokers.'

Young and very young women 'have similar prognoses'

Women with breast cancer who are under 25 years have the same survival rates as those aged between 25 and 35, say UK researchers (*Cancer* 2002, **94**, 606–614). They found no difference in tumour pathology between the 2 groups and said that among women under 36 years, 'There does not appear to be a correlation between age and either severity of disease or outcome.'

The retrospective, case-control study analysed tumour characteristics and disease outcomes of 15 'very young' women treated at Guy's Hospital, London and aged 25 or under. They were each matched with 3 'young' women aged between 26 and 35, and these 2 cohorts were further compared with 2285 'older' patients aged between 36 and 65.

There were no statistical differences in tumour characteristics or in overall survival between the young and very young women. Differences between these groups and the older women were highly significant. Lead researcher Dr Nicolas Beechey-Newman said, 'The absence of well-differentiated cancers and the high mortality rate indicate a need for careful selection of both local treatment and adjuvant systemic therapy to maximise the chance of cure in this very young age group.'

Incubators 'not linked to leukaemia'

High exposure to magnetic fields inside infant incubators was not linked with an increased risk of childhood leukaemia in a Swedish study (*Epidemiology* 2002, **13**, 45–49). Researchers said their work provides 'little evidence' for an association.

Power lines and electrical installations close to children's homes have been extensively studied but results are inconsistent. Magnetic fields inside incubators are often considerably higher than can be measured in residential areas close to transmission lines, but exposure is for a limited time period early in a child's life.

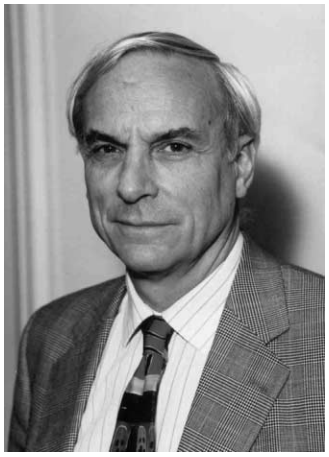
The study included all children with leukaemia born in Sweden between 1973 and 1989. One control per case was chosen, individually matched by sex and time of birth. Information about treatment in infant incubators was retrieved from medical records.

Regardless of the exposure, there was no increase in either acute lymphoblastic leukaemia or all leukaemia combined. There was a slightly elevated risk of acute myeloid leukaemia, but the researchers said this was probably an effect of random variation. They concluded that high levels of magnetic field exposure experienced over a short time period early in life 'are unlikely to affect childhood leukaemia risk.

'These results, however, cannot be used to draw conclusions about the association between exposure to magnetic fields and the risk of childhood leukaemia in general, because of the differences in the nature of the exposure.'

New guidelines from EUSOMA

New guidelines on the use of hormonal therapy in breast cancer have been issued by EUSOMA (*EJC*, **38**(5), 2002, 615). Hormonal therapy has been brought into prominence by the results of several key clinical trials that have reported in the last two years. The introduction of the guidelines is therefore timely, according to Professor Roger Blamey, EUSOMA Vice-President, who chaired the writing committee.



Professor Roger Blamey

Trials in pre-menopausal women have shown that in oestrogen-receptor positive tumours, goserelin (Zolodex) given as adjuvant therapy is as effective as chemotherapy (ZEBRA, the Austrian ABCSG-5 trial and GROCTA-2 from Italy). In light of these results, for advanced disease, a main recommendation in the Guidelines is that ovarian suppressive therapy should be the adjuvant treatment of choice for oestrogen receptor (ER) positive patients.

In postmenopausal women, early results from the ATAC adjuvant trial recently reported at San Antonio (December 2001) show that anastrozole (Arimidex) gives a better result in terms of disease-free survival than tamoxifen; quality of life was also better.

In advanced disease in pre-menopausal women, a recent meta-analysis of four trials showed advantage in the use of a combination of LHRH agonist plus tamoxifen.

The guidelines stress the importance of ER in predicting response to hormone therapy and therefore ER should be measured in all primary tumours. Quality assurance of these measurements is essential.

Situations in which hormonal therapy should not yet be considered outside of clinical trials include cancer-in-situ and chemoprevention for women at high risk, as determined by family history. The guidelines also consider the advantage of using hormonal therapy as primary medical therapy in invasive cancer and the means of combating side effects.

Klausner moves on

Dr Richard Klausner, former director of US' National Cancer Institute, has resigned his post as head of the new Case Institute of Health, Science and Technology (CIHST). He is to be a special advisor on counter terrorism to the President.

Dr Richard Klausner

According to the Blue Sheet (2nd January 2002), CHIST may fold in the wake of his departure. It was intended to focus on projects in molecular technology, bio informatics, translational science, public health service technology, and increased access to digital services.

Klausner is to be the link between the National Academy of Sciences' counter terrorism efforts and the White House Office of Science and Technology.

Faecal occult blood tests 'reduce mortality'

Regular use of faecal occult blood tests (FOBT) reduces mortality from colorectal cancer (CRC), according to two separate studies. Researchers say their work supports attempts to introduce population screening.

In the first study (*Gut* 2002, **50**, 29–32), Danish researchers invited 30 000 subjects for screening, and compared them with 30 000 controls who were not informed about the study. They found that 7 rounds of biennial screening over 13 years reduced relative risk of CRC mortality to 0.7, compared with controls. There was no difference in deaths from other causes.

Reduction in risk of death from CRC in sigmoid colon and rectum was much less than elsewhere in the colon. The researchers say this provides support for a screening programme using a combination of FOBT and flexible sigmoidoscopy. The study is on going.

The second study, from Israel, (*Gut* 2002, **50**, 33–37) compared a group of 2538 who agreed to testing, 1010 who refused, and 1376 controls who were never offered it. They found a significant reduction in CRC deaths among those who agreed to testing compared with either of the other groups. Annual screening was carried out for 3 years and follow-up continued for a further 8 years.

"FOBT MAY BE MORE EFFECTIVE THAN IS RECOGNISED"

'The prolonged beneficial effect of FOBT suggests that this type of screening programme may be more effective than previously recognised,' they wrote. They found that their refuser group included more men of Asian-African origin. This group had higher rates of smoking and coffee drinking and ate more fried food than those who accepted. They also ate less fibre and dairy products and drank less tea. 'A special effort should be made to convince them to participate in screening programmes for CRC,' the researchers concluded.

INTERVIEW

Giel Vaessen manages postgraduate courses for nurses at Limburg University of Professional Education, the Netherlands. He is president of the European Oncology Nursing Society (EONS), Chair of FECS' Accreditation Council of Oncology in Europe, and will chair the Nursing Programme at ECCO12 in Copenhagen, 2003.

Giel Vaessen

Where did you train?
At the nursing school at Sittard Hospital, in the South of the Netherlands. After my diploma I worked for 2 years on a haemodialysis ward.

Who inspired you?
Jos Bergh, Director of the School of Nursing in Heerlen. He offered me my first job as a lecturer. He always said, 'You have create your own future'. He asked me to lead the postgraduate oncology nursing course even when I knew nothing about oncology nursing but he supported me as I learned.

Why did you choose to work in the field of cancer?
Because I was offered this job. Once I had started I knew that it was right for me. It is broad in scope, so many different diseases and patients of all ages.

Did any other branch of nursing appeal?
While I was teaching in Heerlen, I studied the science of touch for 10 years. I set up my own practice to help people with physical and mental problems, usually pain and fatigue. Most of my clients are patients with cancer or survivors.

Might you have done something else altogether?
My dream was to travel round the world as a guide, taking people through mountains. Or perhaps to have my own travel agency.

What has been the highlight of your career to date?
Being given the opportunity and the facilities to set up nursing courses in cancer care and palliative care at Limburg. Also, becoming a board member of EONS, and feeling that people all over Europe trusted me to do a good job!

. . . **and your greatest regret?**
That I didn't go into the travel business after all! I'm only half-joking. My employer is good to me and I plan my own week, but we're always really busy, we have many teaching sessions and tight deadlines. Sometimes I regret that I'm not in the Bahamas right now!

If you could complete only one more task before you retire, what would it be?
To establish pan-European education in cancer care and palliative care, a kind of European school for nursing in oncology. Later this year, I'm starting a 2-year course in Dutch, French and German but I'd like to run a course for the whole of Europe. I'd also like to ensure I leave EONS in good shape when my presidency ends, and to have increased collaborative efforts across Europe.

What is your greatest fear?
That in some countries it will take 20 or 30 years before nurses have their own respected position in cancer care, without being dictated by doctors. I've run courses in palliative care in Budapest and Cyprus, standards are very different even low. The nurses want to learn but there's no time, no money and no encouragement for them to study further.
Another fear is the continuity of EONS work and activities. It relies on a few volunteers and is so busy that this is not realistic. We need many more nurses to take on the work actively, to succeed in our strategy and plans.

What impact has the Internet had on your working life?
The downside is that I get too many emails, and they have got to be answered. If I don't check the mailbox every day I think it would explode! But the up side is the wonderful access to knowledge.

How do you relax?
From the end of November until April I go skiing as much as possible in Austria, Switzerland and Germany and it is beautiful, being outside in the snow. In the summer, I play tennis every Sunday, which stops me working 24 hours a day. When I travel to conferences abroad, I try to stay on and visit the city, go to museums and concerts. And sometimes I love to watch TV and do nothing.

Who is your favourite author?
John Grisham for the action and unexpected outcomes. Simone de Beauvoir for her philosophy. I read her books carefully and compare the Dutch version with the original French, because words can lose their meaning in translation.

What do you wish you had known before you embarked on your career?
How to manage time, and how to make decisions rather than just jumping into things with great enthusiasm. I teach students to think about the consequences of saying yes to requests; what it means for their career, their work and their personal life.

What piece of advice would you give someone starting out now?
You are responsible for your own career. Do not blame an employer for lack of opportunities, only you can build your own career. You are your own person and should go for what you want.

What is your greatest vice?
I take no notice of my own advice and am always saying yes to things without thinking. My colleagues duck when they see me coming in case I want them to take a lecture for me because, yet again, I have double-booked!