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Blood tests for major cancers?

Simple blood tests measuring cell-free circulating nucleic acids could be developed to diagnose each of the 4 major cancers in the Western world, say Swiss and Irish researchers (*International Journal of Cancer* 2003, **103**, 149–152). Existing evidence suggests it could be possible to detect more than 80% of patients with these diseases using a combination of DNA and RNA markers. "The promising data suggest that it would be worthwhile to initiate large-scale clinical trials," they say.

For example, *k-ras* mutations occur in about half of all colorectal cancers and its detection could be coupled with tests on circulating RNA markers, such as the telomerase RNA component hTERT. Normal somatic cells have low or undetectable telomerase levels but cancer cells have detectable activity in 85–100% of cases. The telomerase assay appears to be able to detect early disease.

Microsatellite markers in plasma DNA have been measured in some subtypes of lung cancer and data suggests that quantification and microsatellite characterisation of plasma DNA "may be a valuable non-invasive diagnostic tool for discriminating patients from unaffected individuals and for detecting early recurrence during follow-up". Use of RNA markers could further improve the early detection rate.

A high proportion of breast cancer patients have high plasma DNA levels at diagnosis. Previous work examining microsatellite markers and point mutations in *p53* have found that alternations in tumour DNA are often replicated in plasma DNA before mastectomy. After mastectomy, persistence of mutant plasma DNA was associated with poor prognosis, suggesting that the presence of undetectable micrometastatic disease. Again, coupled with tests for circulating tumour RNA, and telomerase RNA in particular, could improve the detection rate of breast cancer. "Breast cancer is an interesting target for molecular diagnosis since large quantities of money are presently spent on mass screening programs for this disease," the authors say.

"LARGE SCALE CLINICAL TRIALS SHOULD BE INITIATED"

In prostate cancer, PSA tests are in widespread use but result in a high rate of false-positive results. The authors say that the most frequent DNA alteration related to this disease is promoter hypermethylation of the *GSTP1* gene. It can be reliably detected by MSP. This test "appears to be a relatively specific tool for the molecular diagnosis of prostate cancer in body fluids", they say.

"According to the present data, it might be possible to detect over 80% patients with these diseases using a combination of appropriate RNA and DNA markers". Further work is needed to refine PCR assays, identify other tumour markers and improve tests, but the authors conclude that clinical trials comparing molecular assays with conventional tests should be initiated: "Such trials would not only answer questions relating to molecular screening, diagnosis and follow-up but might also provide us with pathophysiologic insights into the genesis and progression of these common cancers."

Fall in lung cancer deaths

Deaths from lung cancer among British women under 70 years old have fallen to their lowest level in 30 years, according to Cancer Research UK. Analysis of data from the Office for National Statistics and the General Registrar's office revealed that, in 2001, there were 4550 deaths from lung cancer in women under 70 years. There were 8500 deaths in the over 70s, because of the boom in women's smoking after World War II.

Deaths from lung cancer among British women peaked in 1988, when there were nearly 6000 deaths in women under 70 years. The current decline in this age group indicates that there will be an overall fall in women's deaths from lung cancer as the population ages.

Levels of smoking in the UK have fallen dramatically. In 1970 around 60% of adults smoked, compared with 27% now. Sir Paul Nurse, Chief Executive of Cancer Research UK said lung cancer is one of the easiest to prevent. "This is really key for a disease where only 5% of people are still alive 5 years after diagnosis."

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Validation of RECIST criteria

The Response Evaluation Criteria in Solid Tumours (RECIST) criteria for evaluation of tumour size modifications in response to treatment has been validated by French researchers (*Br Journal Radiology* 2002, **75**, 903–908). They say the RECIST is a simplified method which gives results in accord with the previous guidelines from the World Health Organisation (WHO).

RECIST uses unidimensional instead of bidimensional measurements, a reduced number of measured lesions, withdrawal of progression criteria on isolated increase of a single lesion, and different shrinkage thresholds for definitions of tumour response and progression.

The group at Centre Hospitalier Lyon Sud studied a prospective series of 91 patients receiving chemotherapy for metastatic colorectal cancer. Data from tomographic measurements were reviewed by an expert panel. Overall response and progression rates according to the WHO criteria were 19 and 58%, respectively. Using the RECIST criteria, 16 patients were reclassified in a more favourable subgroup, giving an overall response rate of 28% and a progression rate of 45%. However, when the criteria of isolated increase of a single measurable lesion was ignored in the WHO criteria, only 7 patients were reclassified.

The French group concluded that, overall, their work provides evidence for the accuracy and usefulness of RECIST criteria and validates the use of unidimensional measurement, the simplification of the definition of progressing tumours, and the selection of the biggest five lesions per organ.

However, they say the consequent variations in assessment of efficacy should be kept in mind in various clinical situations. "Any comparison between non-randomized trials performed before and after publication of the RECIST criteria should be performed with caution. Data analysis on investigational new drugs might slightly overestimate efficacy based on the response rate when compared with previous phase I trials."

Most lesions in colorectal cancer are confined to lung and/or liver, detectable on CT scans and usually assessable. The authors note that RECIST criteria should be validated in more complex situations such as clinically measurable masses, bone metastases or central nervous system tumours. Use of CA125 has recently been integrated into RECIST criteria for ovarian tumours, and prostate-specific antigen for prostate cancers. These changes "might soon be validated and added to clinical and radiological tumour measurement," they say.

Screening interval in hereditary colorectal cancer

Surveillance for hereditary nonpolyposis colorectal cancer (HNPCC) should be conducted at least every 2 years, say researchers from the Netherlands (*Diseases of Colon and Rectum* 2002, **45**, 1588–1594). Cancers detected were more likely to be local and resectable than when surveillance was conducted less frequently.

A total of 114 families were identified from the Dutch HNPCC registry. They either had a mismatch repair gene or met clinical criteria for HNPCC. The surveillance group included initially healthy family members who underwent at least one examination without showing evidence of colorectal cancer. Other family members who had previously undergone partial or subtotal colorectal cancer were also studied.

Over a 10 year period, 35 cancers were detected: 16 among those screened at least every two years and 19 among those screened less often. All but one of those in the former group were local and resectable; 6 of those in the latter group were more advanced.

Family members were at substantial risk of developing colorectal cancer. Proven mutation carriers had a 10.5% 10-year cumulative risk; compared with 15.7% after partial colectomy. "We recommend surveillance for hereditary nonpolyposis colorectal cancer with an interval of two years or less," they conclude.

A good death?

Too many patients die an undignified death with uncontrolled symptoms, say UK physicians (*BMJ* 2003, **326**, 30-34). Transfer of best practice from hospices to other care settings is a major challenge, they say.

Diagnosing dying—the last hours or days of life—is a major challenge, especially in a hospital setting where the culture is often focused on cure. Invasive procedures, investigations and treatment may be pursued at the expense of the comfort of the patient. "There is sometimes a reluctance to make the diagnosis of dying if any hope of improvement exists," they say.

In cancer patients, although the dying phase can be precipitous and involve a massive haemorrhage, for example, they say it is usually preceded by a gradual deterioration in functional status. Patients may become bedbound, semicomatose, only able to take sips of fluid and no longer able to take oral drugs.

"The most important element in diagnosing dying is that the members of the multiprofessional team caring for the patient agree that the patient is likely to die," they say. Hope that the patient may get better, failure to recognise key signs and symptoms and a fear of shortening life are among the barriers to diagnosing dying. However, disagreement among healthcare staff can lead to poor patient management and confused communication.

Once dying has been diagnosed, the patient and relatives can be told. Healthcare professionals often feel helpless in the face of death, and in many hospitals, they transfer patients to a side room and withdraw from patient and family. "However, this is the very moment when the hospice model of intensive palliative care should come into action, providing physical, psychological, social and spiritual care for the patient and relatives."

The hospice movement has challenged the prevailing death-denying attitude of our healthcare system and championed a positive attitude to caring for dying patients. "To disseminate this model of care a greater focus needs to be given to the educational issues related to diagnosing dying," the authors say.

EUROFILE

The Renaissance of ESO

The European School of Oncology (ESO) has agreed a new five year plan which will mean a huge expansion to its activities. The plan, which will take it from 2003 to 2007 was agreed by ESO's Scientific Committee in Rome, 26 October 2002, at a meeting chaired by ESO's founder, Professor Umberto Veronesi.

Since July 2001, ESO has already started to broaden its scope, with the 'Learning to Care' programme. It comprises an annual Masterclass, with scholarships for 60 participants; the magazine CancerFutures; and a series of courses and seminas to celebrate the School's 20th anniversary. 'Learning to Care' was funded by 8 pharmaceutical companies (Amgen, Astra Zeneca, Aventis, Bristol-Myers, Eli Lilly, Novartis, Ortho Biotech, Pharmacia Oncology), which each donated US $100,000 per year, giving a total of US $2.4 million from July 2001 to June 2004. The companies do not have their names linked to specific events.

ESO's Director, Dr Alberto Costa says the money opened up new possibilities for the School. "We had never previously had the opportunity to plan ahead in this way."

Following on from this, ESO has now received support from a group of private donors which will allow it to develop over the next five years. Dr Costa says the donors recognised the importance of ESO's mission, which is to transfer existing knowledge into everyday practice. "Of course, we all acknowledge the importance of research, and there are a lot of charities supporting it. But there are not many funds dedicated to the transfer of knowledge generated by research into clinical practice. Basically, only industry funds this, and it is inherently biased. Some cancers, like rare paediatric cancers or brain tumours will never receive the attention they deserve from industry," he said.

ESO's five year plan encompasses training, including e-learning, and expansion into new cultural, geographic and professional areas. Current teaching modules such as the Masterclasses, courses and seminas in English and local languages are to be improved and developed to include assessment tests, discussions including patients and courses in oncology centres which include practical training. Joint ventures with well-known competent partners will form an increasing part of ESO's activities.

The development of e-learning, led by Professor Matti Aapro, is one of ESO's goals since it allows remote teaching, anywhere in the world, using up-to-date, personalised material at relatively low cost. Technologies such as CD Rom and DVD have eclipsed older methods including videos of surgery because they integrate text and images much more effectively. The website (at www.cancerworld.org) has been well-received.

New cultural areas include involvement with advocacy groups such as Europa Donna, initially, and more recently, Europa Uomo. The Challenge Fund, devoted to the fight against cancer in the developing world, continues to develop. ESO's support for oncology nursing will include a joint symposium at ECCO from 2003. It has launched a 'Cancer on the Internet' conference (New York, June 2003) which aims to set standards for information on cancer sites; and it is strengthening links with the Karolinska Institute, Stockholm, in order to set up specific initiatives in palliative care.

Geographically, ESO will concentrate on the development of courses in Eastern Europe, the Balkans, former Soviet Union, the Middle East and Latin America. Professionally, ESO is looking at courses involving nurses, and courses for advocates, family doctors, medical students and military doctors. Editorially, it retains its links with *EJC*, having also established the scientific magazine, CancerFutures, which carries interviews and reports rather than traditional scientific articles. A regular column explores connections between medicine and art.

The ESO Clinical Fellowship Fund will absorb much of the new money, and will be used to set up scholarships to allow ESO students to study and work at a European centre of excellence. Scholarships will be assigned to various fields of oncology and this programme of clinical training is of "extraordinary strategic importance", the five year plan states. In order to keep alive the memory of great figures in European oncology, the scholarships will be named after former dedicated ESO teachers such as the late Emmanuel van der Schueren or the late Jerzj Einhorn. "There is no other place where the leaders and founders of European oncology are specifically remembered," Dr Costa says.

Collaboration is to be at the heart of the ESO expansion. ESO has always been actively linked to the European Institute of Oncology in Milan. The other partners are the Oncological Institute of Italian Switzerland (IOSI) in Bellinzona and Lugano, directed by Franco Cavalli; the Spanish National Cancer Institute (CNIO), Madrid, recently set up and directed by Professor Mariano Barbacid; the Center for Tumor Prevention (Zetup) in St Gallen; the Princess Grace Hospital, Monte Carlo; and the Southern Europe New Drug Organisation, Milan. The partners will be the first centres of excellence to accommodate the new ESO clinical fellows.

Dr Costa stresses the importance of the network. "ESO is a group of partners and this is its basic strength," he says. The expansion of activities will demand increased numbers of staff, but rather than enlarging the Milan office, another is to be set up in Bellinzona, Switzerland. Dr Costa insisted that ESO's core values will be maintained in all of the new activities. "ESO's mission statement states that events are clinically-oriented; interdisciplinary; multiprofessional; evidence-based and open to advocacy. This will not change," he said.

Helen Saul

"Limited prognostic value" of genetic markers

The prognostic and predictive value of c-erbB-2, p53, bcl-2 and bax genes is limited in breast cancer, Greek researchers say (*The Breast* 2002, **11**, 279–285). None "proved to be independent prognostic factors for patients with breast carcinoma," they concluded.

The researchers examined 121 paraffin-embedded specimens of stage I, II and III breast cancer patients diagnosed and treated in Hippokration Hospital, Athens. Immunostaining revealed that the primary tumour was positive for c-erbB-2, p53, bcl-2 and bax gene expression in 24, 59, 15 and 53% patients respectively. Significant correlations were found between bax overexpression and age, tumour size and disease stage but "no other significant associations were found between other molecular markers and clinical or histological parameters," they said.

Several correlations were found between the molecular molecules. For example tumours overexpressing p53 were significantly more likely to overexpress the other 3 oncogenes in the study "suggesting related genetic mechanisms," they said.

Conventional prognostic factors such as the number of disease-involved lymph nodes and tumour size were independent predictors of five-year survival and disease-free survival. In addition, the lack of oestrogen receptors was associated with a shorter disease-free survival. But they found no statistical relation between the single or multiple gene expression and either five-year survival or disease-free survival.

However, they conclude that, as improved screening procedures make tumour size less important, immunohistochemical proliferation markers may become major determinants of treatment protocols. These molecular markers "might merit consideration if individual genetic alterations can be targeted by means of specific therapies."

Italian researchers came to a similar conclusion in the same issue of the journal (*The Breast* 2002, **11**, 286–294). They assessed 265 postmenopausal with hormonally-treated advanced breast cancer and found the prognostic effect of c-erbB-2 was "relatively limited".

High levels of c-erbB-2 had an unfavourable prognostic effect, but the impact on the response rate was unclear. Further, there was only a weak separation between survival curves for patients with high and low levels. "Other and possibly better prognostic factors for advanced breast cancer should be sought," they said.

For progression-free and overall survival, the effect of c-erbB-2 tended to disappear in the presence of high CA 15.3 levels. They suggest this could mean that, while CA 15.3 is an indicator of tumour burden, c-erbB-2 may be a biological marker of tumour aggressiveness, independent of tumour burden and clinical response to treatment. Its prognostic relevance tends to vanish when the disease is so widespread that a poor outcome is predictable regardless of marker levels.

"Further investigations need to be undertaken to better characterise the shape of the relationship between c-erbB-2 levels and the clinical course of the disease, and possibly to detect new markers to be used jointly, in an effort to improve the predictive capacity of prognostic models in advanced

Individual strategies

Chemoprevention strategies in breast cancer must be individualised to improve effectiveness, writes Professor Kefah Mokbel (St George's Hospital, London). Tamoxifen is only effective in reducing the risk of ER– positive breast cancers. "Its use in subjects who are at risk of developing oestrogen receptor-negative breast cancer can be harmful", he says. This includes *BRCA1* carriers.

"Identifying those at risk of developing oestrogen receptor-positive breast cancer is likely to enhance the effectiveness of this prevention strategy. Research must also be initiated to identify other agents that may be effective for patients at risk of developing oestrogen receptor-negative breast cancer", he says (*Br Journal of General Practice*, 2002, Editorial 972–973).

Two-view screening in UK

The UK Breast Screening Programme is to introduce two-view screening and extend the upper age limit from 64 to 70 years. Researchers have welcomed the change (*Br Journal of Radiology* 2002, **75**, 889–894).

The programme, run by the UK National Health System (NHS), currently offers two-view screening only on the first round. Based on previous work, the researchers say two-view screening should increase detection rate by 24%. The increased detection rate for cancers less than 15 mm in diameter may be as high as 45%, but the overall increase in benefit cannot be easily quantified, they say.

Radiation doses received by women in the programme increase by approximately 80% on each screening round, thus increasing numbers of radiation-induced cancers, but the benefit/risk ratio for two-view screening is still large, they say.

The extension of the upper age from 64 to 70 years "is to be welcomed", because cancer is more prevalent and radiation less likely to induce it among older women. The predicted ratios of cancer detection to induction are therefore greater for this age band than for any other. "If they are satisfactory at ages 50–64 years, they are even more so at this older age band," the researchers write.

For younger women with or without a family history of breast cancer, detections exceed inductions by more than a factor of 5 at all ages considered, for a three yearly screening interval. For annual screening, this is only true above age 35 years.

For women with a family history of breast cancer, detections in annual two-view screening are predicted to exceed inductions with sufficient margin only above age 30 years. "Even greater caution may be advisable" for those below 30 years, the paper states.

Women obtaining screening for themselves outside of the NHS programme should be wary, they say. Even where standards in the private sector are as high "it would seem best to avoid annual screening below age 30 years for those with family history and below age 35 years for those without," they say.

PODIUM

The patient's viewpoint

Ms Stella Kyriakides is Vice President of Europa Donna, and its national representative in Cyprus. She is a child psychologist working in the Cyprus Ministry of Health's Mental Health Service. She was diagnosed and treated for breast cancer in 1996.

Ms Stella Kyriakides

Why do we need advocacy groups like Europa Donna?
We bring a different voice to the table where decisions about patients are being made. Europa Donna works to raise public awareness of breast cancer throughout Europe and to mobilise support in pressing for better care, diagnosis and treatment. There are vast differences in the level and quality of breast cancer care between and within European countries. We advocate change, to ensure that all women have access to optimum care in breast cancer.

Where there is good quality screening, early diagnosis and optimum treatment, mortality is falling. We owe it to all European women to make sure they receive the best, no matter where they live.

Does the existence of Europa Donna reflect a failure on the part of health professionals?
It reflects the need for different perspectives. Patient rights are moving to the forefront in health, which is part of an evolution process in many aspects of society. Many health professionals want to work with patient advocacy groups, which shows how confident they feel that we can help them be more effective in their work. It's not a failure, rather recognition of the need for partnership.

What is Europa Donna's perspective?
Advocates see things differently. It is practical rather than emotional. For example, at the time of diagnosis, very few women in this part of the world are aware of what they should be doing. They have to make important life decisions but they are flooded by so much information, often by doctors trying to be helpful, that their lives are thrown into chaos.

From our different perspective, we can give doctors an inside view of what it is like, and suggest what information is needed and how it could be given. Women want to be involved in decision-making. We need to have clinical trials explained to us so we can take part in them because they may sound frightening but they are necessary for change. We can give health professionals a perspective on what patients need because we have been there.

How important are advocates in shaping policy?
Very. Europa Donna now has 29 member countries, each with its own Forum. We have 10 pan-European goals which each country adopts according to its own needs. In Cyprus, we have been advocating appropriate screening and early detection for three years. The national screening programme will be implemented here early in 2003 and I am convinced it is largely due to Europa Donna's activities.

You change policy by making people aware of the issue and that gives you a voice. We are a grass roots organisation, not only patients but well women who lobby Parliament and ministers.

Is it easier to be an advocate in breast cancer than in other cancers?
Society throughout the world seems to be sensitive to breast cancer; there are groups in the States, Australia and the Far East. But this was not the situation 10 to 15 years ago when there was a stigma attached to the disease. It was thought to be contagious as recently as 50 years ago. We have been fighting against this stigma and the lack of information to get to where we are now. Advocacy changes beliefs. It is not easier because it is breast cancer, but because it has been going on for longer.

What sort of reactions do you get from health professionals?
We believe in, and need, positive and excellent interaction with professionals, but this is not the everyday situation. We often come up against very set views, for example from doctors who find it difficult to accept that we have a voice. We strive for partnership and good cooperation, but if we come across such difficulties we have to push on, carefully and always ensuring that our information is correct.

What are Europa Donna's main achievements?
That we have promoted breast cancer awareness in more than 29 European countries, and brought forward European advances in breast cancer through appropriate training of women. We have achieved recognition from many scientific and clinical bodies in Europe and have promoted training in many health professional organisations. This interview with *EJC* embodies our vision of getting the European Breast Cancer Advocacy voice heard.

We have encouraged the formation of All Party Parliamentary Groups for breast cancer in European countries. When breast cancer was discussed at the European Parliament on 1st October, 2002, Europa Donna was asked to put forward the advocacy position.

Where is the organisation going over the next few years?
We need to increase collaboration with different health professionals so that we all work together in implementing European guidelines on breast cancer care. We'd like to see the guidelines implemented in every member country.

Can you envisage a time when there will be no need for advocacy groups?
Advocacy will be important as long as there is breast cancer.