PERGAMON

European Journal of Cancer 39 (2003) 1331–1335

European Journal of Cancer

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New studies support mammography

Two new studies have provided further evidence that mammographic screening can reduce deaths from breast cancer. The first (*Lancet* 2003, **361**, 1405–1410), in two Swedish counties, found a 40% reduction in deaths. The second (*Lancet* 2003, **361**, 1411–1417), in The Netherlands, found a 20% reduction. The Swedish study compared deaths from breast cancer in the 20 years before screening was introduced (1958–1977) with those from breast cancer diagnosed in the 20 years afterwards (1978–1997). It included 210 000 women aged between 20 and 69 years in the counties of Östergötland and Dalarna. Deaths among women aged 40–69 years were more than 20% lower in the second period. There was no such decline among younger women. Further, after reduction for age, changes in incidence and self-selection bias, there was a 44% reduction in breast cancer deaths among women aged 40–69 years who were screened. There was a much lower reduction in deaths in the same group of women who were not screened. The authors concluded that the reduction among screened 40–69-year-old women "can probably be accounted for by treatment being given earlier in the tumour's natural history, which is made possible by screening". This study also found that the reduction in deaths among women in their 40s was similar to that in the 40–69-year age-group as a whole. The authors suggest that this is because the screening interval is 18 months among younger women compared with 2 years in the older age group. They concluded that routine screening in these two counties "is associated with a breast cancer mortality reduction of about 40–50%, which is greater that the benefits observed in randomised screening trials." Professor Stephen Duffy (Cancer Research UK, London), an author on the paper, said it produced "very strong evidence" that screening and other improvements in breast cancer care "can almost halve the number of women who might otherwise die from the disease". "While mammography is largely accepted by the scientific and medical community as a benefit to women, there are still some who express doubts as to its value. This study goes a long way towards silencing the dissenting voices. It also suggests there is a good case for offering younger women the chance to be screened if they have any additional risk of getting breast cancer such as a strong family history of the disease."

The Dutch study examined data on 27 948 women who died of breast cancer aged between 55 and 74 years between 1980 and 1999. Individuals were grouped into clusters, depending on where they lived, and the data was analysed using national population statistics. Mortality rates had been increasing by an annual 0.3% until screening was introduced, but declined by 1.7% per year subsequently. The turning point arose at around the time in which screening began for each municipality. The researchers concluded that adjuvant systemic therapy is unlikely to be the cause of the turning point. "If this therapy had had a large effect on mortality rates, the estimated point at which breast-cancer mortality became a downward trend in the clusters of municipalities would be unlikely to coincide with the year screening was introduced," they said. The study was not able to link data on deaths with that from screening organisations, which meant that the analysis was based on total breast-cancer mortality, including that from breast cancers diagnosed before the start of screening. "Hence, the actual reduction associated with the start of screening in the Dutch screening programme. . .could well be higher than the observed 20%" they said.

"EARLIER TREATMENT MAY ACCOUNT FOR THE REDUCTION IN DEATHS"

Iressa approved in US and Australia

Iressa (gefitinib, ZD1839) has been approved by the US Food and Drug Administration and the Australian Therapeutic Goods Administration for the treatment of patients with advanced non-small cell lung cancer (NSCLC). The Epidermal Growth Factor Receptor (EGFR) inhibitor, Iressa, is now the only FDA-approved option for third-line patients who have previously received both platinum-based and docetaxel chemotherapies. It fulfilled FDA criteria for the accelerated approval process (for life-threatening conditions where a new drug provides meaningful therapeutic benefit over available treatments, or where no approved therapies exist). This means that manufacturer AstraZeneca has to complete a programme of clinical studies in order to gain full FDA approval. Iressa was approved in Australia in May 2003, and previously in Japan (July 2002). A marketing application was submitted in the European Union in February 2003.

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0959-8049/03/$ - see front matter
doi:10.1016/S0959-8049(03)00436-2

BRCA status and chemoresistance

Ovarian cancers associated with *BRCA* mutations may be more sensitive to chemotherapy than sporadic tumours, according to a US/Canadian group (*Cancer* 2003, **97**, 2187–2195). They found that women carrying *BRCA* mutations had a better response to platinum chemotherapy than those with sporadic disease and, possibly as a consequence, better survival.

"WOMEN CARRYING BRCA MUTATIONS HAD A BETTER RESPONSE TO PLATINUM CHEMOTHERAPY"

The study included 71 Ashkenazi Jewish women with epithelial ovarian cancer, 34 of whom had germline *BRCA* mutations. Those with the mutations were younger than those with sporadic disease, and were less likely to have tumours with a low malignant potential. However, they also had higher response rates to primary therapy and significantly improved survival.

The survival advantage of those with *BRCA*-associated disease could not be attributed to less aggressive disease. The authors suggest that it may be a result of an enhanced response to combination platinum-based chemotherapy: *in-vitro* chemoresistance predicted tumour response to platinum chemotherapy correctly in the BRCA-associated tumours, but not in the sporadic tumours.

In the discussion, the authors say that preclinical studies have shown that *BRCA1* affects chemosensitivity in both breast and ovarian cell lines. Further, recent clinical data implies that enhanced chemosensitivity in *BRCA*-associated ovarian cancers may be a result of the higher tumour growth fraction, compared with samples from sporadic ovarian tumours. More larger studies are necessary to confirm the improved survival in BRCA ovarian cancers, and to better elucidate the biological bases of the survival advantage, they say.

However, they conclude that, if their supposition is correct, "this information may be useful for the clinician in planning the patient's treatment and in the selection of patients for clinical trials".

An accompanying editorial (*Cancer* 2003, **97**, 2127–2129) says the study hints at how knowledge of *BRCA* mutation status can be used to improve the care of women with ovarian cancer. "Although it is far from the total picture, it certainly could be an interesting piece of the puzzle," the editorial states.

Folate intake and genotype

An interaction between plasma folate and a key regulatory enzyme may be a key factor in the development of colorectal adenomas, Japanese researchers say (*International Journal of Epidemiology* 2003 **32**: 64–66). They found that the *MTHFR* (methylenetetrahydrofolate reductase) genotype appeared to influence whether high folate levels protected against development of the disease.

The study compared 177 middle-aged Japanese men with colorectal adenoma, with 192 controls with normal colonoscopy. Plasma folate levels were slightly lower in adenoma cases than in controls. In men with the *TT* genotype, but not those with the *CC* or *CT* genotype, plasma folate levels appeared to be protective.

"These findings are consistent with results from previous studies in Western populations," the researchers said.

Burnham Institute receives unrestricted grant

The Burnham Institute, La Jolla, CA, has received a 5-year US $500 000 unrestricted cancer research grant from Bristol-Myers Squibb. The grant provides seed funding for the Institute's cancer drug discovery programmes to accelerate the translation of results from basic cancer biology research into new therapies for the clinic.

It will be supervised by Dr John C. Reed, President of the Burnham Institute, who is credited with the discovery of numerous proteins that regulate the programmed cell death pathway in cancer. He demonstrated that resistance to anti-cancer drugs is linked to anti-death genes in cancer cells, which prevent them being killed by chemotherapy.

Breast density in chemoprevention

Changes in breast density may be an early indicator of the efficacy of chemoprevention, researchers say. The UK International Breast Cancer Intervention Study (IBIS) team say that breast density is a sensitive marker of hormonal and reproductive-induced risk among women without breast cancer, but at increased risk of developing the disease (*Breast* 2003, **12**, 10–16). Despite the subjective nature of determination of breast density, it has been repeatedly shown to be predictive of breast-cancer risk. It would be useful to know, the authors say, whether density is more closely related to hormonal risk factors, whose effects are at least potentially alterable by hormonal chemoprevention, than to unalterable factors such as family history.

Analysis of data on a subset of 102 women in the IBIS trial (aged between 35 and 70 years and with at least twice the normal risk of developing breast cancer) revealed that smoking, increased body-mass index, parity and increased age were all associated with a lower breast density. For example, each unit change in body mass index reduces a woman's relative risk of having extremely dense breasts by 15% and being parous reduces it by 82%. Breast density varies with ethnic group, but the authors note that the association of increased density with breast-cancer risk appears to prevail in various ethnic groups.

They conclude that breast density is a sensitive marker of hormonal and reproductive-induced risk in a population without breast cancer, but at an elevated risk of developing the disease. Further, it appeared that breast density was reduced with tamoxifen.

"Breast density would appear to be a potential criterion for the selection of subjects for hormonal chemoprevention studies. These results also suggest that sub-group analysis of chemoprevention trials, by changes in density, should be performed so that the sensitivity of reduction in breast density as an early indicator of changes in breast cancer might be assessed," the authors conclude.

Fuel for the fibre debate

The importance of dietary fibre in the prevention of colorectal cancer has been re-emphasised in two key studies. The European Prospective Investigation into Cancer and Nutrition (EPIC) and the US-based Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial have both announced results which suggest that a high intake of dietary fibre provides substantial protection. The EPIC Study (*Lancet* 2003, **361**, 1496–1501) found that in populations with a low average intake of dietary fibre, an approximate doubling of dietary fibre intake could reduce the risk of colorectal cancer by 40 percent. The PLCO trial (*Lancet* 2003, **361**, 1491–1495) found that high intakes of fibre, especially from grains, cereals and fruits, was associated with a lower risk of colon adenoma. The studies took different approaches to the question. EPIC included 519 000 people from 10 European countries, who completed a dietary questionnaire and were then followed-up for cancer incidence. PCLO was a randomised controlled trial, comparing the fibre intake of 33 971 people who on sigmoidoscopy showed no polyps, with 3591 who had at least one histologically-verified adenoma in the distal large bowel. The study involved 10 US centres, with very different dietary practices. The findings contrast with other studies published in the past 4 years, such as the US Nurses Study, which found that dietary fibre had no protective effect on the development of either colonic adenomas or colorectal cancer. The reason for the discrepancy is unclear. An accompanying editorial (*Lancet* 2003 **361**: 1487–88) points out that dietary fibre varies enormously in structure and composition and is difficult to measure. "Contrasting preferences in food in different population groups may lead to apparently similar intakes of dietary fibre, but these intakes are of very different plant cell-walls, with different implications for cancer," the editorial states. Both EPIC and PLCO span several different population groups, with different sources of dietary fibre being preferentially consumed. It is also possible that in the US Nurses study, the population group only had low intakes of dietary fibre. Around 30% of the EPIC cohort were consuming substantially more dietary fibre than the mean of the highest quintile of the US Nurses' study. Dietary fibre may need to be increased to 30 g a day before protection can be demonstrated.

EPIC Study co-ordinator, Dr Elio Riboli (International Agency for Research on Cancer, IARC, Lyons, France) said that after an average follow-up of 4.5 years, 1065 cases of colorectal cancer had been identified. People in the top quintile for fibre intake, who ate 35 g of fibre per day on average, saw their risk of colorectal cancer reduced by 40% compared with others consuming 15 g per day on average. The study "shows that it is possible to significantly reduce bowel cancer risk by moderately increasing consumption of whole cereals, fruit and vegetables, which are the main sources of dietary fibre." Lead author, Dr Sheila Bingham warned that fibre supplements or special foods with added fibre were not studied, and that it should not be assumed that they have the same protective effect as foods that are naturally rich in fibres. "The people who had the most protection were eating about seven portions of fruit and vegetables per day, similar to the amounts eaten by Southern Mediterranean populations, and equivalent to six slices of wholemeal bread each day, whereas those at most risk were only eating about two portions of fruit and vegetables per day.

Controversial therapy finds its place

High-dose therapy with autologous stem-cell rescue is effective in the treatment of multiple myeloma, UK researchers say (*New Engl J. Med.*, 2003, **348**, 1875–1883). It "may be considered as an effective standard first-line treatment approach for younger patients," they say. The therapy was widely used in the US for the treatment of breast cancer before the scandal in 2001, in which South African researcher Dr Bezwoda admitted falsifying results. When his work was disqualified, there was no longer any proof that the treatment was better than standard therapy. In multiple myeloma, first-line treatment with high-dose therapy yields higher remission rates that conventional-dose treatments, but evidence of improved survival has been limited. Randomised trials are "difficult and slow" to conduct, the UK researchers say, "because of technical complexity and, often, strong beliefs among clinicians and patients." The new research was a Medical Research Council multicentre study. It was a randomised, prospective study including 407 previously untreated patients under 65 years old. The 'Standard group' received doxorubicin/carmustine/cyclophosphamide/melphalan; the 'Intensive group' received cyclophosphamide/vincristine/doxorubicin/methylprednisolone, along with stem cell harvesting. Response rates were 5 times higher in the Intensive than in the Standard group (44.3% compared with 8.5%), and median survival was increased by a year (from 42.3 to 54.1 months). A meta-analysis of this data, along with that from two published smaller trials of similar design, found that the survival benefit was "clinically-relevant". They conclude that first-line treatment incorporating high-dose therapy is effective in younger patients with symptomatic myeloma. Lead researcher Professor Peter Selby (Cancer Research UK, St James Hospital, Leeds) said, "This treatment certainly has a controversial past, especially for treating breast cancer. However, our large-scale study proves that high-dose therapy is effective for patients with multiple myeloma."

The *NEJM* report concludes, "This is one of the relatively few examples in oncology of a dose-intensive chemotherapy approach being firmly grounded on randomised prospective trial data."

Commemoration of Russian cancer surgeon

The Russian cancer community commemorated the 75th anniversary of the birth of their late colleague, Professor Nicolai Trapeznikov. Professor Trapeznikov, who died in September 2001, was a leading cancer surgeon for almost 30 years. Professor Trapeznikov, a member of *EJC*'s Editorial Board, was well-known nationally and internationally. He was a member of UICC's Governing Council for many years, area co-ordinator for European School of Oncology (ESO), and actively involved in research projects in collaboration with the World Health Organization (WHO) and IARC.

He studied medicine at Kirov State Medical University and completed a WHO fellowship at the Royal Marsden Cancer Hospital, London. Later, he received an American Cancer Society fellowship and trained in US comprehensive cancer centres. At home, he established the first bone tumour department, immediately after completing his PhD. He later founded the Russian Bone Tumours Management School. He was instrumental in setting up the largest Cancer Research Centre in the country, in Moscow, and he received an academic degree and membership of the Academy of Medical Sciences of the former USSR, the highest professional and scientific recognition. Professor Trapeznikov co-founded the WHO Melanoma Group and for 25 years was a Principal Coordinator in Russia for numerous trials. He successfully distributed results of the trials and changed previous treatment concepts within Russia. At the Moscow Cancer Research Centre, he headed many projects in cooperation with UICC and IARC, and was the Russian representative on the General Motors Cancer Research Foundation.

When dramatic political changes disrupted links within the cancer services in the late 1980s, Professor Trapeznikov did his best to overcome separation among the newly-independent countries of the former USSR. He was appointed ESO Area coordinator for Russia and the CIS countries, and ran 20 training courses for more than 1100 delegates from Russia, CIS and Baltic countries. In 1996, he organised the First Cancer Congress in Russian and CIS countries, which attracted 1000 participants.

His former colleagues Professor M. Davydov, Professor M. Aliev and Professor L. Demidov said, "Professor Nikolai Trapeznikov's life symbolised sincere movement towards reasonable cooperation between CIS countries in fighting cancer. In addition, for Western countries, he was able to construct a bridge between Russian and Western Oncology." The commemoration took place in May 2003.

Peptide receptor radiotherapy

Patients with aggressive fibromatosis (AF) may benefit from peptide receptor radiotherapy, Italian researchers say (*Br J Cancer* 2003, **88**, 645–647). They report on two patients with fast-growing recurrences, who obtained protracted clinical benefits from the relatively new technique.

Few options are available for patients with aggressive fibromatosis if they are unsuitable for surgery and resistant to external-beam radiation therapy (EBRT). Peptide receptor radiotherapy may be a possibility. It uses radiolabelled peptides that recognise tumour cell-surface receptors and allow the delivery of large quantities of radioactivity to the tumour site.

A somatostatin analogue, Y-DOTATOC, can be seen before treatment. The Italian group used the technique on a 30-year-old woman having a local relapse, and a 22-year-old man who had four relapses in 4 years. The woman showed a partial response which had lasted for more than 3 years at the time of publication; the man's condition had been stable for 19 months.

"To our knowledge, this is the first report showing that Y-DOTATOC can provide clinical benefits in patients with AF, and the benefit obtained supports further investigation in this setting," they conclude. Where adequate tumour uptake is observed, it "could be considered as a further treatment option to increase the chance of obtaining disease control."

Glioma cells and low radiation doses

Repeated low-dose irradiation could greatly improve the effectiveness of radiotherapy of gliomas, French and US researchers say. This ultrafractionation "could allow safe treatment of patients with cumulative doses greater than 60 Gy" (*Int J Cancer* 2003, **105**, 33–40). Malignant glioma is one of the most radioresistant tumour types and accounts for approximately 60% of all primary brain tumours in adults. The prognosis remains dismal. Standard care has essentially remained unchanged for decades: surgical resection of as much of the tumour as is safe, followed by radiation therapy and chemotherapy. However, even in the best cases, this only improves mean survival from 2–3 months to 1 year.

In the French/US study, four of five human glioma cell lines exhibited significant X-ray sensitivity at doses below 1 Gy. Irradiation with low doses was markedly more effective than irradiation with single, biologically equivalent doses, in terms of how far the surviving fractions were decreased. Using the same overall dose as conventional radiotherapy, repeated low-dose irradiation was twice as effective at killing glioma cells and gliomas tumour xenografts, the authors say.

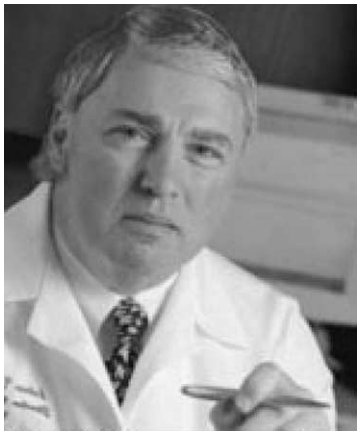
They point out that that the radiation survival response of mammalian cells is more complicated than once believed, and some human cell lines are sensitive to killing by low radiation doses (termed low-dose hyperradiosensitivity (HPS)). This could be because low doses, unlike high doses, do not induce the repair mechanisms which can lead to radioresistance.

They propose a new regimen, ultrafractionation, that may exploit a radiosensitivity commonly observed in otherwise radioresistant human gliomas cells. It warrants clinical investigation into the treatment of gliomas, they say. Ultrafractionation with doses <1 Gy "could greatly improve the efficiency of radiotherapy in human gliomas," they conclude.

PODIUM

Collaboration and cooperation!

Dr. Andrew C. von Eschenbach is Director of the US' National Cancer Institute, part of the US Department of Health and Human Services. He formerly directed the Genitourinary Cancer Center at the University of Texas MD Anderson Cancer Center where he was also the founding director of the Prostate Cancer Research Program. Prior to accepting his position at NCI, he was President-elect of the American Cancer Society.



Dr. Andrew C. von Eschenbach

How important is US/European collaboration?
Very. Cancer is a global problem, so we must work globally to pre-empt cancer. To aid collaboration, the NCI established a Liaison Office in Brussels, Belgium in 1972, which facilitates the interchange of information, experimental drugs, research, and scientists between Europe and the United States.

Is there sufficient collaboration at present?
NCI's interest in excellent collaboration may appear insatiable at times, but the level of exchange between Europe and our country is sufficient at present.

Where has collaboration been most successful?
Exchange has been most impressive in preclinical and clinical evaluation of new cancer treatments. Temozolamide, for example, which is of great interest for the treatment of brain tumours and melanoma, originated in UK research laboratories, was studied in NCI's drug screening system, and later developed worldwide by an industrial partner. Flavopiridol, which targets the cell-cycle regulating machinery, and perfosine, which targets signal transduction, both originated from German companies which later worked with NCI. Topotecan originated from NCI's National Cooperative Drug Discovery Program and was developed by a US corporate partner with critical input from European clinical pharmacologists.

A big boost to US/European collaborations in cancer treatments has come from the US Food and Drug Administration (FDA) which now accepts European clinical trials data without requiring that additional studies be done in the US

Another area of success is in our fellowship exchange programmes, which permit many European scientists to train at NCI. Many who have participated are now key European scientists. Finally, the US/European partnership has even had an influence on the American Association for Cancer Research (AACR). Begun in Europe, the NCI-EORTC Symposium has evolved into the NCI-EORTC-AACR Symposium on Molecular Targets and Cancer Therapeutics.

NCI strives to pursue the best agents as candidates for clinical trials through collaborations that transcend borders.

And least successful?
Our US/European partnerships still suffer from suboptimal coordination and communication. And an earlier attempt, in the 1970s, to establish a nursing exchange was not successful.

What obstacles need to be overcome for collaborative efforts to become more productive?
Culture and language continue to be obstacles to optimum productivity. And proprietary rights have grown as an issue that often impedes US/European collaboration, although this latter barrier is faced by partnerships at home as well as abroad.

Do some areas of research lend themselves to collaboration (or need it) more than others?
The need for global clinical trials networks for rare types of cancer is obvious. A good example occurred in the development of Glivec as a treatment for gastrointestinal stromal tumours (GIST). Prognosis tends to be poor, even for early tumours that can be removed by surgery. Treatment with standard chemotherapy and radiation has little effect.

Exciting phase II results in European and US trials, led the NCI and EORTC to form an international partnership to further evaluate Glivec in GIST. The collaboration involved Novartis as well as sarcoma experts within the US and Europe and resulted in the development and rapid completion of two large parallel phase III studies. The FDA approved Glivec for the treatment of GIST on Feb 1, 2002.

Is there a lingering parochialism among researchers?
Parochialism is not restricted to nations and continents. It exists even among various scientific and medical disciplines. Our constant challenge is to create synergies across perceived borders.

What do you see as the different strengths and weaknesses of US and European researchers?
Academic researchers in Europe perhaps place less emphasis on 'publish or perish', that is, being first author in a peer-reviewed journal. Recently, in our country, a movement has begun in academia to have patents count as publications, so patents held by scientists may also begin to play a role in tenure-track careers in the US.

Are there any specific plans in place to boost collaboration across the Atlantic?
Recent cooperative agreements between NCI and various European groups include: Cancer Research UK, EORTC, Southern Europe New Drug Organization, Biotherapy Development Organization, and European Drug Development Network (MOU). Also, an All-Island Cooperative Group just formed that includes both Northern Ireland and Ireland.

NCI representatives are active in all these European groups, and European members in turn are invited to participate in Operating Committee meetings held by NCI's Division of Cancer Treatment and Diagnosis.

Can we expect any results in the near future which might underline the importance of collaboration?
Yes. As NCI goes forth with its challenge goal to eliminate the suffering and death due to cancer by 2015, US/European pre-clinical and clinical evaluation of potential new agents for better cancer treatment will increase, as will collaborations in the areas of diagnostics and imaging.