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An 'explosion' of cancer expected by 2030

The International Agency for Research on Cancer (IARC) is predicting an explosion of cancer. A statement released on World Cancer Day (4th February, 2008) predicted: 'By 2030, it could be expected that there will be 20 to 25 million incident cases of cancer, and 13 to 16 million cancer deaths annually.'

This is compared to various estimates that suggest that in 2000, there were 10.4 million new cases of cancer diagnosed worldwide and 6.5 million deaths from cancer.

Furthermore, the burden of cancer has now shifted from westernised, developed countries several decades ago, to medium- and low-resource countries today. 'WHO (World Health Organization) regions with a large proportion of countries of low- or medium-resource are hardest hit and the impact in such countries, still faced with the burden of infectious disease and a low budget for health, will be considerable in terms of the treatment needs and the costs of treatment,' IARC's 2007 Annual World Cancer Data Update states.

'The great problems facing low- and medium-resource countries into this century are the growth and ageing of the population and the westernisation of their lifestyle, and tobacco. Changes in lifestyle habits, increase in sedentary lifestyle, weight gain and obesity and sociological changes notably increasing age at first birth and decreasing parity in women, are leading to large increases in breast and colorectal cancer in particular,' according to the Update.

''THE BURDEN HAS SHIFTED FROM THE WEST TO MEDIUM– AND LOW-RESOURCE COUNTRIES''

It is accompanied by a set of 2008 cancer challenges. The specific priorities include taking action against tobacco worldwide, implementing what is known to reduce cancer risk, and developing concerted action against breast and cervical cancer.

One initiative, also launched on World Cancer Day, aims to protect children from second-hand smoke. The International Union Against Cancer (UICC) said that 700 million children – almost half of the world's children – breathe air polluted by tobacco smoke.

UICC is leading an initiative to promote smoke-free environments for children, under the slogan 'I love my smoke-free childhood'.

Messages for parents include refraining from smoking at home or in the car, teaching children there is no safe level of second-hand smoke, not smoking while pregnant or near someone who is pregnant.

'Tobacco-related cancers lead the list of preventable deaths and hundreds of thousands of people who have never smoked die each year from diseases caused by second-hand smoke. That's why this initiative is so important,' says Isabel Mortara, UICC's executive director.

The Pill 'halves the risk of ovarian cancer'

Oral contraception confers long term protection against ovarian cancer, according to a meta-analysis including 45 epidemiological studies. The Collaborative Group on Epidemiological Studies of Ovarian Cancer found that taking the Pill for 15 years halves the risk of ovarian cancer, with a significant reduction in risk continuing for more than 30 years after use has stopped (*Lancet 2008*;**371**:303–14).

In high income countries, the study found that taking the Pill for 10 years reduces the risk of developing the disease before the age of 75 from 12 down to 8 per 1000 women. Risk of death before age 75 was reduced from 7 to 5 per 1000 women.

Lead author Professor Valerie Beral (Cancer Research UK Epidemiology Unit, University of Oxford, UK) said, 'Worldwide, the Pill has already prevented 200,000 women from developing cancer of the ovary and has prevented 100,000 deaths from the disease. More than 100 million women are now taking the Pill, so the number of ovarian cancers prevented will rise over the next few decades to about 30,000 per year.'

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San Antonio Breast Cancer Symposium

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Tamoxifen: '10 years is better than 5'

The recommendation to limit adjuvant tamoxifen treatment to 5 years may have been premature, researchers say (Abstract #48). They found that 10 years of treatment gave a small but statistically significant advantage over 5 years'.

The ATLAS trial (Adjuvant Tamoxifen: Longer Against Shorter), included 11,500 women, and found that the additional 5 years of tamoxifen conferred a 12% reduction in the risk of breast cancer recurrence, compared with stopping treatment (p =0.005.)

Presenting the data, Professor Sir Richard Peto (University of Oxford, UK), pointed out its limitations. Only 59% of the patients were definitely ER+, the remaining 41% were untested. Of the untested women around one quarter are likely to have been ER-, and hence unlikely to experience any benefits from tamoxifen. In addition there were site to site differences in compliance rates. 'The upshot is that ATLAS only shows around 72% of the true effect of tamoxifen,' he said.

'This interim analysis does make it very likely that continuation of tamoxifen would produce clinical benefits,' said Sir Richard, adding that the current recommendation to limit tamoxifen treatment to 5 years, which was based on data from NSABP B 14, is likely to have been premature.

'The numbers in NSABP B 14 were too small to justify dismissing the important question of whether continuing tamoxifen beyond 5 years could, in the long run, moderately reduce the recurrence rate,' said Sir Richard. 'The new ATLAS data suggests that longer term use is likely to produce benefits.' The finding is likely also to be relevant to treatment durations of the newer aromatase inhibitors (AI) for breast cancer.

Janet Fricker

ATAC: the first 100 months

The 100 month data from the ATAC trial shows that, 4 years after stopping adjuvant treatment, the absolute reduction for the risk of breast cancer recurrence continues to increase for anastrozole (Arimidex) over tamoxifen. The study demonstrated for the first time a carry over effect for an aromatase inhibitor (Abstract # 41).

"The study shows us that the protective effect of anastrozole is present well beyond completion of treatment, providing an undisputable reason for starting treatment with anastrozole to give women the best chance of staying cancer-free," said Professor John Forbes (Newcastle Mater Misericordiae Hospital, Australia), presenting the data.

The ATAC (Arimidex, Tamoxifen, Alone or in Combination) study, which started in July 1996, recruited 9,366 patients from 381 cancer centres. Treatment advantages of anastrozole over tamoxifen had already been established in hormone sensitive advanced breast cancer. ATAC was designed to establish whether the benefit would also be seen in postmenopausal women with early stage, hormone receptor-positive, breast cancer.

Women were randomised to receive adjuvant hormonal treatment with either anastrozole, tamoxifen, or both agents in combination. The first major analysis at 33 months led to discontinuation of the combination arm since it showed no benefit compared with tamoxifen alone.

Results at a median follow-up of 100 months showed that, among the hormone receptor positive subgroup, anastrozole reduced the risk of all recurrences by 24 % (p=0.0001), improved the disease free survival by 15% (p=0.003), and reduced the risk of distant metastases by 16% (p=0.022). The absolute difference in recurrence at 5 years was 2.8%, increasing to 4.6 % at 8 years.

The carry over effect, say the investigators, is likely to be due to the elimination of micrometastases in the first five years.

Most strikingly, the incidence of

(*continued at the bottom of page 633*)

Trastuzumab after progression

Continuing treatment with Herceptin (trastuzumab) is associated with improved progression free survival in women whose advanced HER2-positive breast cancer has progressed after initial treatment with the drug, according to results from 2 studies.

The international GBG26/BIG 3-05 study included 482 women with HER2-positive, locally advanced or metastatic breast cancer who had been treated with trastuzumab as first-line treatment, with or without chemotherapy. They were randomised to continue with the trastuzumab plus capecitabine or with capecitabine alone.

Interim results for 152 patients (Abstract # 4056) showed that progression free survival was a median of 8.5 months among those who continued treatment with trastuzumab, compared to 5.6 months among those receiving capecitabine alone. The overall response rate was 49% with the Herceptin combination compared to 24.6% for capecitabine alone.

The lead investigator, Professor Gunter von Minckwitz (University of Frankfurt, Germany), said: 'These interim results demonstrate that continued use of trastuzumab leads to shrinkage of the tumour and symptom control in women with HER2-positive metastatic breast cancer for whom other treatments have failed.'

A second study retrospectively evaluated routine clinical use of Herceptin in patients with advanced breast cancer in Germany between 2001 and 2006 (Abstract # 4059). Results for 910 women showed that continuing treatment with trastuzumab after disease progression was associated with a median overall survival of 20.1 months since first progression, compared to 13.4 months among those who stopped the drug (p=0.0014).

Susan Mayor

San Antonio Breast Cancer Symposium

Mitch Dowsett wins William L McGuire Award

Left to right: Dr. C Kent Osborne, co-director of the San Antonio Breast Cancer Symposium; Professor Mitchell Dowsett (The Royal Marsden Hospital, London, UK); Dr. Stephen Stein (GlaxoSmithKline); Dr. Charles A Coltman, co-director of the San Antonio Breast Cancer Symposium.

Professor Mitch Dowsett (London, UK) received the 2007 William L McGuire Award in recognition of his contributions in the field of breast cancer.

Professor Dowsett is widely recognised for his research on aromatase inhibitors and biomarkers of response and resistance to treatment. 'Mitch Dowsett is one of the real giants of research on hormonal treatment in breast cancer and a leader in translational research. He is extremely deserving of this award,' said Dr. C Kent Osborne (Baylor College of Medicine Cancer Center, Houston, Texas), co-director of the San Antonio Breast Cancer Symposium.

The award was established in 1992 to commemorate Dr. William L McGuire, whose research played a major role in introducing oestrogen receptor assays on breast tumour tissue as a guide to treatment decisions for women with breast cancer. It is sponsored by GlaxoSmithKline.

Dr. McGuire, along with Dr Charles A Coltman, the current co-director, founded the San Antonio Breast Cancer Symposium in 1977.

Professor Dowsett is Head of Biochemistry at the Royal Marsden Hospital, Professor of Biochemical Endocrinology at the Institute of Cancer Research, and Professor of Translational Research in the Breakthrough Breast Cancer Research Centre, London, UK.

ATAC: the first 100 months (*continued*)

contra-lateral breast cancer, which showed only a negligible difference (0.8%) at 5 years, showed a significant absolute difference of 1.7% (p= 0.004) at 100 months.

Some patients have been reluctant to begin treatment with an aromatase inhibitor because of the potential for increased bone loss. The new data provides reassurance, showing that although the incidence of fractures was nearly 30% higher in the anastrozole arm during treatment, post treatment the fracture rates were nearly identical in the 2 arms.

No difference has yet been seen in overall survival. To put this in context, said Forbes, the survival advantage associated with tamoxifen took 10 years to show up. 'We have to accept that breast cancer is a chronic problem and that if strategies are directed at stopping it coming back then survival will look after itself. To put it simply – if a woman doesn't have breast cancer she won't die of it,' he said.

Janet Fricker

Capecitabine plus trastuzumab 'improves outcomes'

Adding the oral chemotherapy agent capecitabine (Xeloda) to trastuzumab (Herceptin) and docetaxel increases the time to progression among women with advanced HER2-positive breast cancer, researchers say.

The international CHAT study (Capecitabine, Herceptin and Taxotere) randomised 222 women with HER2-positive locally advanced or metastatic breast cancer, to receive trastuzumab plus docetaxel, with or without capecitabine (Abstract # 309).

The median time to progression was 18.6 months in women receiving capecitabine, trastuzumab and docetaxel, compared to 13.6 months among those given only trastuzumab plus docetaxel (p=0.0295). Median progression free survival also increased, from 12.8 months with the two-drug combination to 17.9 months when capecitabine was added (p=0.0402).

'Trastuzumab's ability to increase survival changed the treatment landscape for patients with advanced breast cancer. Adding capecitabine to the most commonly used first-line regimen of trastuzumab plus a taxane enables patients to live even longer without their disease progressing,' said lead investigator Andrew Wardley (Christie Hospital NHS Foundation Trust, Manchester, UK).

The results translated into longer one- and two-year survival rates with capecitabine plus trastuzumab/docetaxel, he said, although the median overall survival had not yet been reached after 18 months of follow-up. The one-year survival rate was 0.91 with triple therapy, compared to 0.85 with two drugs, while the two-year survival rates were 0.75 and 0.66, respectively.

Both regimens were generally well tolerated and cardiac safety was consistent with other trastuzumab-based trials, he said.

Susan Mayor

Janet Fricker was sponsored to attend the meeting by Astra Zeneca; Susan Mayor by Roche.

Low cancer risk in Down's syndrome linked to *Ets2* gene

Cancer risk is decreased in patients with Down's syndrome, shows a new study done in mouse models. Trisomy of the Ets2 gene represses APC^{min}-mediated intestinal tumours in Down's syndrome (*Nature 2008;***451**:*73–76*).

Ts65Dn (the most commonly used mouse model of Down's syndrome), and Ts1Rhr and Ms1Rhr (mouse models with partial trisomy of chromosome 21) were used to assess the incidence of APC^{min}-mediated intestinal tumours in Down's syndrome.

Trisomy for orthologues of about half of the genes on chromosome 21 in Ts65Dn showed a 44% decrease in the total number of tumours compared with euploid mice (p=0.008). There was a 26% reduction in the average number of intestinal tumours when compared with Ts1Rhr mice, which has segmental trisomy for 33 of the genes that are triplicated in Ts65Dn. In Ms1Rhr, segmental monosomy for the same 33 genes resulted in an increased number of tumours. Of the 33 genes triplicated, Ets2 gene was noted to contribute most to the tumour-repressing effect seen with trisomy. When only the Ets2 gene was returned to the normal two-copy level with the remaining the 32 genes still kept trisomic, the average tumour number increasedto 81-2% (p=0.012).

Senior author Roger Reeves (Johns Hopkins University, Baltimore, MD, USA) explains, 'Ets2 gene..regulates expression of 200 known downstream targets and probably many more. We think that Ets2 and/or some subset of those downstream targets could be drug targets for cancer prophylaxis'.

Clara Moore (Franklin and Marshall College, Lancaster, PA, USA) says, 'the potential for overexpression of genes at [a] modest level to repress tumorigenesis, while reduced expression of [the] same genes increases cancer risk, presents a new model for dosage-sensitive genes'. She adds, 'assumptions of cancer prevention based on oncogene expression levels should be reassessed in light of these new findings'.

Sharan Prakash Sharma

*This story originally appeared in Lancet Oncol 2008;***9**:*99.*

Drugs approvals in metastatic colorectal cancer

The European Commission has approved the use of capecitabine (Xeloda) in metastatic colorectal cancer in combination with any chemotherapy in all lines of treatment, with or without bevacizumab (Avastin). It has also granted a label extension to bevacizumab so that it may now be used in combination with any standard chemotherapy at any stage of a patient's treatment for metastatic colorectal cancer.

The approvals mean that many more patients with the disease will be eligible for treatment with these new drugs.

Capecitabine was licensed as a first-line monotherapy in metastatic colorectal cancer in countries including the EU and USA in 2001. It was further approved by the European Medicines Agency (EMEA) and US' Food and Drug Administration (FDA) for adjuvant treatment of colon cancer in March and June, 2005, respectively.

For bevacizumab, the extended label allows its use in combination with every standard fluoropyrimidine-based chemotherapy, or with capecitabine (Xeloda) or oxaliplatin. Previously, it could only be used in combination with intravenous 5-FU or 5-FU/irinotecan-based chemotherapy.

The NO16966 phase III study played a part in both new approvals. This study included 2034 patients and found that the chemotherapy combination XELOX is as effective in terms of progression-free survival (PFS) as FOLFOX. The addition of bevacizumab to chemotherapy (the XELOX regimen or FOLFOX-4) improved PFS by 20% compared with chemotherapy alone. In patients who received treatment until disease progression, the benefit was greater, and the addition of bevacizumab improved PFS by 58%.

Language mapping in glioma surgery

The extent of brain exposure necessary for safe removal of gliomas may be less than previously thought, say US researchers. A new approach to language mapping may minimise lasting side effects following surgery to remove tumours within or near language pathways (*N Engl J Med 2008;***358**:18–27).

Neurosurgeons typically perform a large craniotomy in order to identify positive sites associated with language. The tumour is then resected within the boundaries of these points. The technique means that much of the brain is exposed and patients subjected to lengthy stimulations and tests.

Researchers at University of California, San Francisco, USA, designed a 'negative mapping' study in which resection decisions were guided by identifying stimulation points near to the tumour that did not affect language. It eliminated the neurosurgeon's dependence on the positive sites as controls 'allowing minimal cortical exposure, less extensive intra-operative mapping, and a more rapidly performed neurosurgical procedure', the authors say.

The study included 250 patients who underwent surgery between 1997 and 2005. The 'tailored craniotomy' exposed the tumour and up to 3 cm of surrounding brain tissue. A grid electrode was used for language mapping.

At presentation, 159 of the 250 patients had no speech problems; 91 had some language deficit. A week after surgery, language function was the same or improved in 77.6 patients, was worse in 8.4% and new speech deficits had developed in 14%. However, by 3 months, only 6 of the 245 surviving patients (2.4%) had decreased language function. At 6 months, only 4 of the 243 surviving patients (1.6%) had a permanent postoperative language deficit.

Traditional, extensive positive mapping 'is no longer needed', the authors state. 'Nearly half of our patients had no positive language sites in their field of exposure, and more than 94% of the cortical stimulations in these patients were negative, yet their functional outcomes remained acceptable.

PODIUM

Cancer trends in Europe

Henrike Karim-Kos took a first degree in human nutrition and epidemiology at Wageningen University, the Netherlands. She worked as an epidemiologist in cancer centres elsewhere in the Netherlands before embarking on a PhD at Erasmus MC Medical Centre, Rotterdam. She is joint first author on a forthcoming EJC paper, 'Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s' (doi: 10.1016/j.ejca.2007.12.015).

How important is it to consider incidence, mortality and survival statistics together?
Many studies consider only survival – and they receive a lot of press attention. But you don't get a complete picture of cancer trends by looking at survival alone. For example, in prostate cancer, survival rates are improving dramatically, which implies that things are going in the right direction. But incidence rates are also soaring, because of the availability of PSA testing. The case-mix now includes a lot of low stage tumours with good prognosis, and the increase in survival tells you nothing about whether treatment has improved. You have to combine the incidence and survival with mortality data. If incidence and survival are increasing and mortality hasn't changed, you can't assume that treatments have improved: other things like over-diagnosis might be involved. If mortality is going down, then new treatments may be having an effect. It is important to look at all 3 sets of data to get a complete overview.

What real trends did you find?
Obesity-related cancers are increasing, especially in north-western Europe, and are probably spreading to central Europe. The incidence of colorectal cancer, for example, increased slightly in most countries except those in central Europe. In a lot of countries, colorectal cancer survival increased, mortality decreased and the incidence was unchanged or slightly increased: this suggests improvements in management or treatment.

What about smoking-related cancers?
In northern and western Europe, we see declining trends in smoking-related cancers, indicating the success of anti-tobacco measures. There was a clear decrease in the incidence and mortality among men in these countries, but rates are now also dropping in central Europe. Among women, the incidence and mortality of smoking-related cancers is still increasing, but encouragingly, we are seeing the first signs of stability in the north and west Europe. In the UK, for example, rates are levelling off. We hope this trend will spread throughout Europe.

Why were cancer trends in the UK and Denmark markedly worse than in neighbouring countries?
These countries still lag behind their neighbours, but they are improving and the trends are going in the right direction. The UK's National Cancer Plan was drawn up in 2000 and it will take about 10 years to have an effect at population level; the data included in our study does not go beyond 2004. Incidence and mortality figures in the UK were similar to those in other parts of northern Europe. Survival was lower, but it is improving and the gap is closing. In both of these countries, governments have kept tight control of health care spending since the 1960s and thus there have been more limited resources. Further, Denmark had high rates of smoking among women; incidence and mortality rates from lung cancer were higher among women in Denmark than anywhere else in Europe.

Were there any unexpected results?
In cervical cancer, survival decreased. It was surprising, but in fact quite logical. Many countries have screening programmes which detect pre-malignancies (which therefore never become malignant) and slow-growing tumours which can be treated quite well. Removing pre-malignancies reduces the incidence but also means that the resulting case-mix includes proportionately more aggressive tumours with a worse prognosis. These tumours may not be detected by screening (if they appear in the screening interval). Overall, survival deteriorates, but incidence and mortality rates are decreasing! It's another example of why it's important to consider the 3 sets of data together.

What is happening in Central Europe?
Survival rates in central Europe have lagged behind those in the rest of Europe, but survival is definitely increasing in these countries now, and mortality is going down. The figures are becoming more like those in other parts of Europe. It's really good news and is partly down to improvements in treatment, but also to earlier diagnosis.

What is the take-home message?
Cancer trends are going in the right direction, and survival is increasing for most cancers. Differences between countries have decreased over time. We need to keep focussing on primary prevention campaigns, such as anti-smoking (already shown to be effective) and anti-obesity campaigns. But secondary prevention such as screening and further research into better diagnostics, treatment and health care management also needs our attention to continue this positive trend.