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The pill, parity and cervical cancer

Long term use of the Pill may be a powerful co-factor in the development of cervical cancer, studies suggest. This could turn out to be more important than any link between the Pill and breast cancer, a commentator says.

A Working Group from the International Agency for Research on Cancer (IARC) found that, among women positive for human papillomavirus (HPV), those who had taken the Pill for more than 10 years had 4 times the risk of developing cervical cancer, compared with never-users. Taking the Pill for between 5 and 9 years more than doubled the risk compared with never-users (*Lancet* 2002, **359**, 1085–1092).

"BOTH MAY PROMOTE PROGRESSION TO INVASIVE CANCER"

Among HPV-negative women, use of the Pill did not appear to raise the risk of cervical cancer.

The study was based on pooled data from case–control studies of invasive carcinoma (IC) or carcinoma *in situ* (CIS). Women were interviewed about their use of oral contraceptives, and HPV status was determined by PCR. Of 1591 women with invasive cancer, 94%, were positive for HPV; of 292 women with carcinoma *in situ*, 72% were positive; this compares with only 13% of the 1916 healthy controls.

HPV has been linked with cervical cancer, but most HPV infections are transient and it is unclear what co-factors may be involved in cases that progress to carcinoma. "Our results lend support to the existence of an association between oral contraceptives and HPV and suggest that studies not restricted to women who were positive for HPV could have underestimated the effect of oral contraceptives," the researchers say.

"STUDIES COULD UNDERESTIMATE THE EFFECT OF THE PILL"

A further study among the same group of HPV-positive women (*Lancet* 2002, **359**, 1093–1101) found a link between parity and squamous cell cancer. Women who had seven or more full term pregnancies were at 3.8 times the risk, compared with those who had none. The authors point out, "Declining multiparity, which has occurred in most developed and developing countries over past decades, might explain part of the worldwide secular decline in cervical cancer mortality and incidence."

Neither high parity nor use of oral contraceptives were associated with HPV prevalence. An accompanying editorial suggested this means "that both of them act not by enhancing the acquisition or persistence of HPV infection, but rather by promoting progression to CIN and invasive cancer" (*Lancet* 2002, **359**, 1080–1081).

The editorial states that there is now a need to bring together all the relevant data, to quantify any effects and to assess how these might shift the balance of benefits and risks of oral contraception. The WHO has commissioned such work, it notes.

"Any causal relation between long-term oral contraception and cervical cancer would be most important in the developing world, where cervical cancer is common," the editorial concludes. "For nearly 2 decades, concerns about oral contraceptives and neoplasia were focused mainly on breast cancer—with the eventual outcome being reassuring. Ironically the relationship with cervical cancer may turn out to be more important."

Emma Cannell

Chemoprevention: debate continues

The picture emerging from the trials of tamoxifen in chemoprevention of breast cancer, is that the drug reduces the incidence of the disease by between 30 and 40%, according to a key investigator. Dr Jack Cuzick (Cancer Research UK), lead investigator of the International Breast Cancer Intervention Study (IBIS) said, "It's looking very clear now."

Presenting results at EBCC (Barcelona March 2002), he said it is too early to judge the ultimate effect on breast cancer deaths among the prevention trials in healthy women. "It is essential to continue to follow the participants to see if a particular high risk group of healthy high-risk women can be identified for whom the benefits of tamoxifen clearly outweigh any risks," he said.

Soon after the conference, a 7-year follow-up from the Italian Tamoxifen Trial was published (*Lancet* 2002, **359**, 1122–1124) showing a non-significant reduction in breast cancer diagnoses among women taking the active drug. Dr Cuzick said the study made an important contribution to overall knowledge, but on its own, was too small to be convincing.

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NHL: Another casualty of SV40?

Simian Virus 40 (SV40) may be a co-factor in the development of some non-Hodgkin lymphomas (NHL), scientists say. The highly potent oncogenic DNA virus, a member of the polyomavirus family, has been associated with the pathogenesis of brain tumours, osteosarcomas and mesotheliomas. Now, two groups have independently linked it with NHL (*Lancet* 2002, **359**, 817–823; *Lancet* 2002, **359**, 851–852).

The incidence of NHL has nearly doubled since 1970 and no obvious risk factors have emerged, although a viral cause has been suspected. Animal models have previously suggested the link with SV40, but so far the evidence in humans has not been convincing.

Both groups used the polymerase chain reaction (PCR) to detect SV40 T-antigen DNA sequences in NHL tissue samples. They used Southern blotting and sequencing to confirm the specificity of the PCR products obtained, as SV40 T-antigen sequences lack a 96p insert found in the related JC and BK human polyomaviruses. T-Antigens are multifunctional proteins that are essential for transformation. They act by binding to consensus sequences of key cell cycle regulators such as p53 and pRb and functionally inactivating them. The T-Antigen is also conserved in these polyomaviruses emphasising its importance.

More than 40% of the NHL samples analysed in both studies included SV40

"INCIDENCE HAS NEARLY DOUBLED SINCE 1970"

T-antigen sequences. By contrast, no HHV-8 viral sequences were detected and 27% of the samples were positive for EBV. Only 7% showed co-infection for both SV40 and EBV. It was not found in various control samples or in non-malignant lymphoid samples.

One group sequenced five of the SV40-positive PCRs. They found that one was similar to a strain associated with several human primary brain cancers, one was unknown and three were similar to a strain of virus discovered in contaminated polio vaccines from 1955.

An accompanying commentary (*Lancet* 2002, **359**, 812–813) points out that it is now necessary to look for some indication that these sequences are functional, for example, by examining whether T-antigen is bound to p53 or pRb. The timing of exposure, tissue tropism, p53 status of the cell and coincident molecular alterations are all likely to be important in determining whether transformation occurs. It is also intuitive to expect immunosuppression to play its part. However, in an apparent contradiction of this, a higher percentage of HIV-negative than HIV-positive samples were positive for SV40 in one study. It seems that the T-antigen is necessary, but not sufficient for transformation.

Emma Cannell

BCG in superficial bladder cancer

Bacillus Calmette-Guerin (BCG), widely used to vaccinate against tuberculosis, is now the agent of choice after transurethral resection (TUR) in certain patients with superficial bladder cancer. A meta-analysis has shown that intravesical BCG reduces the risk of progression in patients with papillary tumours and/or carcinoma *in situ*.

Researchers at the European Organization for Research and Treatment of Cancer (EORTC) conducted a meta-ana-

"THE MECHANISM OF ACTION IS UNKNOWN"

lysis of 24 randomised trials in patients with superficial bladder cancer who underwent transurethral resection (TUR). They compared intravesical BCG with intravesical chemotherapy, an immunotherapy other than BCG, or no further treatment after TUR.

A previous meta-analysis from the EORTC concluded that adjuvant intravesical chemotherapy has no impact on preventing progression when viewed over the long term.

The latest results, which were due to be presented at a special session on late-breaking news at the American Urological Association (AUA) meeting

Dr Richard Sylvester

in May 2002, focused on BCG. The study found that adjuvant intravesical BCG reduced risk of progression compared with patients in the control groups. However, only patients in studies where maintenance BCG was given benefited; in these studies the risk of progression was reduced by 37%.

Dr Richard Sylvester (EORTC Data Center, Brussels) said, "BCG elicits a non-specific immune response; the exact anti-tumour mechanism of action of BCG is unknown."

On-going work is looking at ways of reducing the dose of BCG in order to reduce side-effects, and at establishing the optimal induction and maintenance schedules. "The ultimate goal will be to tailor the treatment to the individual patient according to their immune status and how they react to installations," he said.

The results should influence current practice, said Dr Sylvester: "In patients with an intermediate or poor prognosis, BCG is really now indicated." The results were being presented at the AUA and have been submitted to a urological journal in order to convince urologists to use BCG since they are the ones seeing these patients.

NEWS FROM AACR

Aspirin for the bowel...

Low-dose aspirin may reduce risk of cancer in the large bowel, say Dartmouth researchers. They found that 80 mg per day reduced the risk of some recurrent adenomas by up to 40%.

Participants had had at least one adenoma removed within 3 months of the study. They all took 325 mg of aspirin daily for 3 months to exclude those with problems. Afterwards, 1121 patients were randomly allocated to receive either placebo, 80 or 325 mg aspirin per day.

Lower-dose aspirin showed most effect, reducing overall risk of recurrence by 19%; and of the more aggressive tubulovillous or villous adenomas by 40%. The higher dose reduced overall risk by 4% and of the more aggressive tumours by 19%. Longer-term follow-up is ongoing (AACR, 2002, Abstract no. 3319).

... and green tea for the stomach

Green tea may almost halve the risk of stomach and oesophageal cancers among some men, a joint Los Angeles/Shanghai study found.

Of 18 244 middle aged and older Chinese men included in the study, 190 went on to develop gastric cancer and 42 oesophageal cancer. Researchers analysed urine samples collected before the diagnoses, and compared levels of markers for two tea polyphenols, epigallocatechin (EGC) and epicatechin (EC), with those among 772 matched control subjects within the cohort. The polyphenols are anti-oxidants which have been shown to have chemoprotective benefits for some cancers.

The presence of EGC in baseline urine significantly reduced the risk of both cancers, but no association was found with EC. EGC reduced relative risk by 50%, but only among subjects who had low serum levels of carotene, another anti-oxidant. Dr Can-Lan Sun (Norris Comprehensive Cancer Center, Los Angeles) said, "It appears that tea polyphenols may play an important protective role in people who have low levels of other antioxidants" (AACR, 2002, Abstract no. 2354).

- A phase II study of green tea as treatment for advanced prostrate cancer had disappointing results. Researchers at the Mayo Clinic, Rochester, found that only one patient in a group of 42 had a 50% drop in prostrate-specific antigen (PSA) levels, and his response was brief. 'We tested high doses of green tea, but we did not see the favourable effects for which we had hoped,' said lead investigator, Dr Aminah Jatoi. (AACR, 2002. Abstract no: 2444).

St John's Wort "reduces activity of cancer drugs"

St John's wort, a popular over-the-counter herbal remedy, may compromise the activity of anticancer agents, a Dutch researcher told members of American Association for Cancer Research (93rd Annual Meeting, San Francisco, 6–10 April 2002).

Dr Ron Mathijssen (Rotterdam Cancer Institute, The Netherlands) presented preliminary data from a study examining the combined effects of irinotecan and St John's wort. Complete pharmacological data, available from 3 patients, showed that systemic exposure to a measurable metabolite of irinotecan (SN-38) decreased by 40% when treatment was combined with St John's wort. The effect lasted for more than 3 weeks after the combined treatment.

Studies in the literature report that two ingredients in St John's wort, hypericin and hyperforin, stimulate an enzyme involved in drug metabolism, known as cytochrome P450 (CYP 344). Around half of all drugs, including irinotecan, are metabolised, at least partly, by the same enzyme.

"The combination effect we found with St John's wort and irinotecan might occur with many other anticancer agents," said Dr Mathijssen. "The problem is potentially more widespread than this single study shows" (AACR, 2002, Abstract no. 2443).

Patient-tailored therapies

Protein profiles may give clinicians early warning that treatments are not working, US scientists say. A joint Food and Drug Administration (FDA)/National Cancer Institute (NCI) study analysed the protein profiles of patients with breast and ovarian cancer. The patients received trastuzumab (Herceptin), followed 1 month later by paclitaxol (Taxol).

Analysis of samples from 20 patients so far indicates that, among those who respond to trastuzumab, the drug reduces activation of the Akt protein, involved in programmed cell death. In non-responders, trastuzumab has no effect on Akt. "We think that in the responders, Herceptin is reducing activation of Akt, which destroys the signalling pathway that tells cancer cells to survive," said Dr Emanuel Petricoin, co-director of the Clinical Proteomics Program (FDA/NCI). "When the patients receive Taxol, that drug throws the cells into apoptosis. But in the non-responders, the pro-survival signals remain intact and the cancer cells refuse to die even when Taxol is given."

This information should allow clinicians to select the best therapy initially, monitor the patient's response, and, after recurrences, chose another therapy or combination of therapies to target the abnormal protein pathway (AACR, 2002, Abstract no. 681).

A novel test may be able to predict after a single-dose of chemotherapy whether an individual patient is likely to respond, said Dr Neil Steinmetz, from developers North American Scientific, Inc. Based on a radiopharmaceutical called Apomate, the test measures changes related to cell death and provides an indication of whether the tumour is responding to treatment in the first 3 days. (AACR, 2002, Abstract no. 4136).

Drugs round-up

FURTHER RESULTS FROM ATAC (Arimidex, Tamoxifen, Alone or in Combination) study suggest that anastrozole may halve the risk of contralateral breast cancer, compared with tamoxifen. The study, among 9366 postmenopausal women with early breast cancer, has already suggested that anastrozole is more effective in terms of disease-free survival and patients' tolerance of the drug. Dr Jeffrey Tobias (University College Hospitals, London) presented the new data at EBCC-3, and said, "It's clear that in many respects anastrozole is a superior agent to tamoxifen."

At the time of data cut-off, women had been treated for 30 months and followed for 33 months on average. Dr Tobias acknowledged, "It is very early days," but said that the numbers involved in the trial meant that the data was solid. "It is the largest randomised trial of a cancer drug ever undertaken," he said.

The curves for disease-free survival started to diverge at 2 years and the difference in the drugs' performance was "clear and progressive," he said. There was a "dramatic reduction" in contralateral breast cancer. Among 3125 women on anastrozole, there were 9 invasive and 5 DCIS stage contralateral breast cancer. This compared with 30 invasive cancers and 3 DCIS in the 3116 tamoxifen patients.

The only area where tamoxifen outperformed anastrozole was in preservation of bone density, he said. Women on anastrozole were significantly more likely to fracture a bone (180 compared with 113 for those on tamoxifen). Dr Tobias said this could be dealt with relatively easily, by giving bisphosphonates to women with low bone density.

Dr Tobias suggested that anastrozole should be included in the IBIS II trial in chemoprevention of breast cancer among healthy women. "This agent clearly has a very bright future in breast cancer, both in treatment of the patient who has developed breast cancer, in adjuvant therapy and also, in due course, in chemoprevention," he said.

Anastrozole is licensed in Europe for the treatment of advanced and recurrent breast cancer in postmenopausal women. AstraZeneca has filed for a licence extension in Europe to include treatment of postmenopausal women with early-stage breast cancer. Anastrozole is licensed in Japan for adjuvant use in postmenopausal women.

TREATMENT WITH FULVESTRANT (Faslodex) may leave patients sensitive to other forms of endocrine therapy, according to a presentation (EBCC, Barcelona, March 2002). Its use reduces oestrogen receptors on breast cancer cells and new data suggests that endocrine therapy is still effective after treatment with fulvestrant. Another study presented at EBCC suggested that fulvestrant is more effective than anastrozole in patients with visceral metastases.

HERCEPTIN IS TO BE MADE AVAILABLE throughout the UK, following a recommendation by the National Institute for Clinical Excellence (NICE). It is estimated that 2000 women with advanced breast cancer will benefit from the drug each year. Until the decision, in March 2002, only a small number of hospitals were using the drug.

NICE ALSO ADVISED THAT NICOTINE replacement therapy and buproprion, aids to smoking cessation, are not only clinically effective, but are "among the most cost effective of all health care interventions."

RITUXIMAB HAS BEEN APPROVED in Europe for the treatment of aggressive non-Hodgkin's lymphoma (NHL). The authorities based approval of the novel treatment, MabThera, on the results of the GELA study (*N Eng J Med* 2002, **346**, 235–242). It found that after 2 years, 70% of patients given rituximab plus standard chemotherapy (CHOP) survive. This compares with 57% of those given CHOP alone.

'Once in a lifetime' sigmoidoscopy

Flexible sigmoidoscopy, offered on a single occasion to screen for colorectal cancer "is acceptable, feasible and safe", say researchers. The UK Flexible Sigmoidoscopy Trial Investigators report that this screening regime, directed at 60 year olds, gives a "high yield of neoplasia" (*Lancet* 2002, **359,** 1291–1300).

Men and women aged between 55 and 64 years were sent a questionnaire asking if they would attend for flexible sigmoidoscopy if invited. Of the 194 726, or 55%, who said they would, 170 432 were randomised to screening or control groups. Attendance among those assigned to screening was 71%.

Early results show that distal adenomas were found in 12% and distal cancer in 0.3%. Around 5% of the sample was referred for colonoscopy. There was one perforation after flexible sigmoidoscopy and four after colonoscopy.

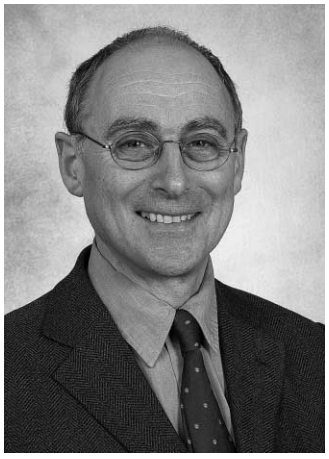
> *"PHYSICIANS SHOULD BE ENCOURAGED TO RECOMMEND SIGMOIDOSCOPY"*

The study group will be followed for 15 years and the first analyses on incidence and mortality are expected in 3 years' time. However, early results are encouraging. The proportion of localised cancers detected with this regime is higher than reported with faecal-occult blood testing, suggesting it may detect cancer earlier. "The high yield suggests that we will see substantial reductions in the incidence of colorectal cancer," the investigators report.

An accompanying editorial (*Lancet* 2002, **359**, 1266–1267) points out that flexible sigmoidoscopy seems to be more readily accepted by patients than many doctors had anticipated. One in 5 experienced more than mild pain, but almost all were glad, 3 months later, that they had had the test and would encourage friends to have it. This "should encourage physicians who have hesitated to recommend sigmoidoscopy because of anticipated reluctance by the patient," it states.

INTERVIEW

Professor Robert Souhami is the Director of Clinical Research Development and Training at Cancer Research UK. He was previously Dean of Clinical Sciences, and Professor of Cancer Medicine at University College London Medical School. He has chaired the Protocol Review Committee at EORTC and he edited the recently-published Oxford Textbook of Oncology *(2nd edition).*



Professor Robert Souhami

Where did you train?
First, at what was then University College Hospital Medical School, London (now the Royal Free and University College Medical School). Then, as a postgraduate, at Johns Hopkins University, USA, and St Mary's Hospital, London.

Who inspired you?
The physician Lord Rosenheim, who was a brilliant diagnostician and a good clinical scientist, with a marvellous manner with patients. Also, Professor Tom Prankerd, Professor of Haematology at University College Hospital Medical School, who was a particularly rigorous clinical scientist.

Why did you choose to work in the field of cancer?
I qualified before medical oncology was thought of. But in the 1960s, Tom Prankerd interested me in the treatment of lymphoma and leukaemias with cytotoxic drugs. Later, I started to use the few drugs we had available to treat small cell lung cancer and other solid tumours. I remained a general physician as well as medical oncologist until 1991.

Did any other branch of medicine appeal?
General internal medicine has always been my passion, and I still believe you have to be a good general physician before you can excel at any branch. It's a point of view that is falling by the wayside in an era of specialisation.

Might you have done something else altogether?
As a teenager my decision to study medicine was neither passionate nor heartfelt. I was just moderately good at science and interested in biology and medicine seemed a reasonable choice.

What has been the highlight of your career to date?
Becoming Professor of Cancer Medicine at my old Medical School, University College, in 1987. My chair was endowed in the name of the wonderful singer, Kathleen Ferrier, with funds that were collected when she died of breast cancer in 1953. I got to know her older sister, Winifred, and I came to know Kathleen through her.

In 1988, I established the first teenage cancer unit in the UK at University College Hospital. It helped to change the pattern of care for teenagers with cancer in the UK.

... and your greatest regret?
Only that I'm not starting out now because it is the most exciting time in cancer medicine. I'd like to start again knowing what I know now. I agree with Oscar Wilde when he said that youth is wasted on the young.

If you could complete only one more task before you retire, what would it be?
I want the new charity, Cancer Research UK, to be a major success. Its formation is the most significant move in cancer research in my lifetime. We now have the opportunity to make UK cancer research, which has always been excellent, absolutely outstanding. We now have enough resources to invest heavily in the equipment and facilities we need, and to train a small number of talented clinical scientists.

What is your greatest fear?
That the pressures of delivering health care in hospitals, and of research assessment exercises and financial cut backs in universities, mean that talented young people no longer see a future for themselves in clinical cancer research. Young people are pulled in all directions and this is a real danger. The new charity must fight their corner, protect and encourage them.

What impact has the Internet had on your working life?
Very little. It's useful as a repository of information, rather than books, but so much of the medical information on it is utter rubbish. The advice to patients often makes your flesh creep.

How do you relax?
I don't, or at least I try not to. I have a woodworking workshop at home and I make furniture. I also have a house in France, which I converted from a barn myself. In London I spend my spare time at films, theatre and with family and friends.

Who is your favourite author?
Saul Bellow. He's a brilliant chronicler of modern American life and has a sense of humanity with all its imperfections. He observes life, presents his characters and their predicaments and illuminates their choices.

What do you wish you had known before you embarked on your career?
I wish I'd known where biological sciences would go. It's true of all my generation; we should have been better trained in basic science.

What piece of advice would you give someone starting out now?
To be a good clinical scientist you need to do a PhD and then take the equivalent of at least 2 post docs. Your job, when you are working alongside basic scientists, is to understand how to apply first class science in clinical practice.

What is your greatest vice?
I keep planning to work less, but can't seem to do anything about it. But I'm still full of energy and there's so much to do at Cancer Research UK.