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Expert statement on reproduction and breast cancer

A US National Cancer Institute workshop on Early Reproductive Events and Breast Cancer (24–26 February 2003) reviewed information on the risk of breast cancer associated with pregnancy. It defined what is known, identified gaps in knowledge and established areas which would warrant further study.

Well-established epidemiological findings included:

- Early age at first term birth is related to lifetime decrease in breast cancer risk
- Increased parity is associated with a long-term risk reduction, even when controlling for age at first birth
- Additional long-term protective effect of young age at subsequent pregnancies is not as strong as for the first term pregnancy
- A nulliparous woman has approximately the same risk as a woman with a first term birth around age 30 years
- Breast cancer risk is transiently increased after a term pregnancy
- Neither induced abortion nor spontaneous abortion are associated with an increase in risk
- Long duration of lactation provides a small additional reduction in breast cancer risk after consideration of age at, and number of, term pregnancies

Epidemiological gaps included:

- By what mechanism does pregnancy at an early age protect against breast cancer?
- What are the effects of age at pregnancy on subgroups of women such as those with *BRCA1* and *BRCA2* mutations?
- What is the mechanism by which lactation affects breast cancer risk?
- Does gender of offspring have an effect?

Future research directions included:

- Integrate the methodology of genomics and proteomics into the study of pregnancy in relation to risk of breast cancer
- Pursue international studies to develop hypothesis for observed international differences in breast cancer risk
- Develop surrogate markers to identify risk of breast cancer following pregnancy
- Translate knowledge about protective effects of pregnancy into intervention trials with human populations
- Support the collecting, archiving and sharing of relevant biospecimens

NCI Director Dr Andrew von Eschenbach said, "I convened the Workshop to provide a comprehensive and integrated scientific assessment of the important association between reproductive events and the devastating problem of breast cancer." He said the outcomes will help "to provide the public with accurate information about pregnancy-associated factors that may influence breast cancer risk, and to define a research agenda for the Institute through which to better define the risk factors that can lead to more effective strategies of prevention."

The Workshop report was reviewed by NCI's Board of Scientific Advisors and Board of Scientific Counselors. Comments from scientific, medical and lay communities are being solicited through the NCI Web site (www.cancer.gov). The report will be used to guide the Institute's future research agenda and the development of public communication materials about the impact of factors associated with pregnancy that affect a woman's risk of subsequently developing breast cancer.

Pregnancy and ovarian cancer

Pregnancy may induce the shedding of premalignant ovarian cells, according to researchers from Copenhagen (*Epidemiology* 2003, **14**, 168–173). Cell clearance during pregnancy could explain the link between high parity and a reduced risk of ovarian cancer, they say.

A mathematical model was built around the assumption that similar cell clearance would take place during first and second pregnancies, but clearance would be decreased with later age at pregnancy. It was then tested using data on reproductive history from a cohort of 1.5 million Danish women born between 1935 and 1978, and followed for 28.7 million person-years. There were 2035 cases of invasive ovarian cancer during follow-up.

Despite the very few parameters in the model, it has a "satisfactory fit" with the data, the researchers say. "A cell clearance mechanism exhibiting the observed age dependence could be the main cause for the association between pregnancies and ovarian cancer risk," they conclude. The hypothesis "theoretically offers a possibility of preventing cancer by mimicking natural mechanisms that remove precancerous cells," they say.

An accompanying editorial (*Epidemiology* 2003, **14**, 139–140) says the observations suggest new directions of study: "Future epidemiologic studies of pregnancy should include careful measurements of steroid and peptide hormones." A better understanding of the mechanism by which pregnancy protects "will lead to new insights into aetiology, prevention and therapy of these tumours in women," it states.

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Aspirin "reduces recurrence of polyps"

Daily aspirin significantly reduces the risk of colorectal adenoma in patients with previous colorectal cancer, US researchers say (*New England Journal of Medicine*, 2003, **348**, 883–890; and *New England Journal of Medicine*, 2003, **348**, 891–899). The studies found that aspirin has a "moderate chemopreventive effect" among high-risk patients.

The first study compared daily aspirin with placebo among 635 patients with previous colorectal cancer. Patients were examined by colonoscopy a year after randomisation. Adenomas were found in 17% of patients in the aspirin group, and in 27% of those receiving placebo. The study was halted early by an independent data and safety monitoring board because of the statistical significance of the results.

In the second study, 1121 patients with a recent history of adenoma received either placebo, low-dose or high-dose aspirin. Follow-up colonoscopy at 1 year found a relative risk of any recurrent adenoma of 0.65 among the aspirin group, compared with placebo.

The results confirm numerous earlier observational studies that suggested that people who regularly take aspirin have lower rates of colorectal adenomas. Both studies were supported by the US National Cancer Institute (NCI) and Dr Ernest Hawk, chief of the Gastrointestinal Cancers Research Group in the NCI Division of Cancer Prevention, said, "These trials are very encouraging because they prove that we can disrupt the development of colorectal cancer by preventing the polyps that can become cancer. If we can prevent adenomas from forming, we believe we ultimately can reduce colorectal cancers and colorectal cancer deaths."

A statement from the NCI said the data suggests that "daily aspirin may be an appropriate supplement to regular surveillance procedures in individuals at an increased risk of colorectal cancer similar to the level of risk in the people in these trials." The participants were all adults with a history of colorectal adenoma or early-stage cancer. "Long-term aspirin therapy is not appropriate for everyone," it warned.

IARC report on fruit and veg

A diet rich in fruit and vegetables is likely to lower the risk of gastrointestinal cancers, according to a review by the World Health Organization (WHO)'s International Agency of Research on Cancer (IARC). It found the clearest evidence for a cancer protective effect in stomach, lung, oesophageal and colorectal cancers.

The IARC Working Group was comprised of 22 scientists from 10 countries. After a week-long meeting in Lyons, France, the Group concluded that findings from both human studies and animal experiments "indicate that a higher intake of fruits and vegetables is associated with a lower risk of various types of cancer".

"1 IN 10 CANCERS IN THE WEST ARE DUE TO AN INSUFFICIENT INTAKE"

The clearest evidence of protection from a fruit-rich diet was found in stomach, lung and oesophageal cancers. Similarly, a higher intake of vegetables "probably reduces the incidence of cancers of the oesophagus and colon-rectum," the group found.

The Working Group estimated that approximately one in 10 cancers in Western populations are due to an insufficient intake of fruits and vegetables. Similar, although variable, fractions apply to other populations around the world, and may be higher in regions where the intake of fruits and vegetables is lower.

The group was chaired by Professor Tony McMichael (Australian National University). He said the evidence for any particular type of cancer in relation to fruit and vegetable intake lacks certainty. However, the pattern of findings for cancers overall is persuasive, he said. "Individual dietary habits are complex and they are accompanied by various other personal behaviours such as smoking and alcohol consumption, that can also affect cancer risk. So it is not easy to get conclusive evidence on diet–cancer relationships. However, long term follow-up studies of many thousands of people in the general population are now providing higher quality information about these relationships", he said.

Professor Paul Kleihues, IARC Director, said there is "a fairly consistent association" between higher levels of fruit and vegetable intake and some reduction in cancer risk. "This, plus the evidence of beneficial effects of fruits and vegetables on other major diseases such as heart disease, indicates that individuals and communities should increase their intake of these foods. This is an important message for governments, the food industry and consumers," he said.

"Ultimate irony" in gastric cancer

White males in affluent societies appear to have traded the risk of one type of gastric cancer for another, Australian researchers say (*Journal of Clinical Epidemiology* 2003, **56**, 1–9). The incidence of gastric carcinoma has fallen in most societies, but they note that, among white men, there has been a more recent steady rise in the incidence of adenocarcinoma of the cardia and lower oesophagus.

The Australian group reviewed literature published in English and said that the evidence for a major role for *Helicobacter pylori* in the aetiology of gastric corpus cancer "is compelling". However, it probably accounts for fewer than half the cases in Western societies.

Given the evidence for an increase in reflux symptoms on eradication of *H. pylori*, and the links between long-standing reflux symptoms and obesity with lower oesophageal adenocarcinoma, they say "We may be seeing the ultimate irony".

"As society grows more affluent and hygienic, it diminishes its risk of gastric adenocarcinoma, but, in males at least, it simultaneously increases its risk of adenocarcinoma around the cardia."

Leonardo da Vinci: an update

The 3-year Leonardo da Vinci project (December 2000–December 2003) initiated by the Federation of European Cancer Societies (FECS) and supported by the European Commission Education Directorate is now entering its second phase. The interim report to the European Commission outlining the activities and results of the first phase was submitted in October 2002 and subsequently approved by the Commission. In the first phase, the needs and wishes of health professionals in continuing medical education (CME) in oncology in Europe were identified.

In response to the identification of these needs, the Leonardo Steering group, which met at the end of January 2003, decided to focus on the following activities for the remaining part of the project:

As regards web-based educational materials, three multidisciplinary case studies will be developed and posted on the FECS educational website as part of a pilot project to assess feasibility and use of this type of CME programme. Multiple-choice questionnaires will be included as part of the learning method. Representatives from ESMO, ESSO, ESTRO and EONS, all partners in the Leonardo project, will work together to develop the cases, which will address different tumour types, different tumour stages and different clinical environments. A preliminary evaluation of this e-learning activity with recommendations will be made at the end of the year for inclusion in the final report to the European Commission.

In addition, three educational sessions at ECCO 12 will be captured and posted on the FECS educational website and on CD-Rom. Multiple-choice questions will be inserted after each presentation for self-evaluation of the learning outcome. Again, the feasibility, use and value of this programme will be evaluated in view of the possible development of an accreditation policy for enduring materials by the Accreditation Council of Oncology in Europe (ACOE).

However, the Leonardo Steering group decided not to pursue the idea of linking the educational websites of member societies enabling users to perform searches on the basis of selection criteria. Indeed, the feasibility study demonstrated that the existing quantity of educational materials available on the societies' websites is currently insufficient to launch such an initiative. The idea will be revisited at a later stage.

Activities directed towards the mutual recognition of CME credits in Europe will be pursued. Collaboration with the European Union of Medical Specialists (UEMS) will continue to follow a common strategy. An audit of national situations on accreditation of CME credits and mutual recognition will allow evaluation of remaining disparities and potential obstacles. Further contacts will be established with relevant national accreditation authorities as appropriate.

The Leonardo da Vinci Steering group is finalising its suggestions on the evaluation of the quality of CME events. They should improve evaluation of the learning outcomes of an event. Amended application and evaluation forms for CME organisers who wish to have their events accredited will be submitted to the ACOE at their meeting in April 2003 for approval.

Françoise Van Hemelryck
FECS

New virtual tumour bank in the UK

A national virtual tumour bank is being set up in the UK by the National Cancer Research Institute (NCRI). The NCRI says the National Cancer Tissue Resource "has been designed to provide the infrastructure, co-ordination and ethical framework required to meet both current and future cancer research needs."

Several hospitals and research centres currently run their own tissue collection banks, but to date there has been no national infrastructure for standardisation of tumour sample and data collection and storage across the country. The new managed distributed network was designed by the National Translational Cancer Research Network, a network of 10 cancer centres, which works in partnership with the NCRI, which co-ordinates the UK Government, Medical Research Council (MRC), Cancer Research UK and other cancer charities.

Dr Liam O'Toole, NCRI Director, said that a lack of tissue samples could severely slow down the rate of progress in genomics and proteomics. "Up until now we have had a fragmented approach to collecting and using tumour samples for research. This initiative. . .gives us an opportunity to do things properly on a much bigger scale for the benefit of cancer patients."

The tumour bank will receive a total of £1 million per year for 5 years from the Department of Health, Cancer Research UK and the MRC. The Welsh Assembly has provided funding for a Welsh Tumour Bank that will be developed alongside the National Cancer Tissue Resource.

The long-term aim is to establish a network of tissue acquisition centres linked to a range of processing centres that will extract DNA, RNA and related bio products. Tissue micro arrays will be produced for samples associated with key clinical trials. The networks will be linked and managed through a co-ordinating centre that will work with the research community to develop standard protocols for collection and storage of tumour samples. A central information system will track samples through the system and provide a bio informatics hub to link histopathological data with clinical/outcome data and research results.

The NCRI partners recognise that a coherent and ethical national framework is needed, and the Department of Health and patient representatives will be involved in overseeing the tumour bank. Sir Paul Nurse (Cancer Research UK) said, "This initiative is key to restoring public confidence in the research community and rebuilding bridges between doctors and their patients. It sets out clear boundaries for the collection of tumour samples which are essential for us to better understand cancer and help us improve treatments for people with the disease."

New marker for tamoxifen resistance?

The oestrogen receptor (ER) co-activator A1B1 may be an important predictive marker for tamoxifen resistance in clinical breast cancer, US researchers say (*Journal of the National Cancer Institute* 2003, **95**, 353–361). They say it "deserves additional investigation as both a diagnostic and a therapeutic agent."

Researchers from the Baylor College of Medicine, Houston, TX, USA, determined A1B1 and HER-2 protein levels in 316 breast cancer patients. They found that high A1B1 expression among patients not receiving adjuvant tamoxifen was associated with better prognosis and longer disease-free survival. By contrast, among patients not receiving tamoxifen, high A1B1 expression was associated with worse disease-free survival, which is indicative of tamoxifen resistance.

A1B1 expression was also necessary for the resistance associated with higher HER-2 expression to be clinically manifest. Patients whose tumours expressed high levels of both A1B1 and HER-2 had worse outcomes with tamoxifen than all other patients combined.

They concluded, "The antitumour activity of tamoxifen in patients with breast cancer may be determined, in part, by tumour levels of A1B1 and HER-2." HER-2HER

In an accompanying editorial (*Journal of the National Cancer Institute* 2003, **95**, 338–340), Dr V Craig Jordan (Northwestern University Medical School, Chicago, IL, USA) suggests that tamoxifen may be both "a pioneering life-saving medicine and an agent to decipher the molecular perturbations of the breast cancer cell." It is "a reasonable goal" to develop a predictive test for tamoxifen resistance, he says, but it may be more useful to use the extensive literature on its molecular pharmacology to examine individual associations in clinical studies: "In this way, the predictable changes that tamoxifen can induce in the breast cancer cell could provide a rational road map for patient care."

"The triumvirate of ER, HER-2/neu expression, and coactivators, clearly needs to be coordinated to work in harmony, and it would be valuable to learn whether there is an innate mechanism that accelerates resistance to tamoxifen. Arguably the most important component of this resistance is the ER itself," says Dr Jordan.

"The activation of the tamoxifen–ER complex, either directly (through phosphorylation cascades) or indirectly (through phosphorylation of the coactivator) is an elegant solution to the problem of tamoxifen-resistant disease. Nevertheless, the question must be asked whether the physician can already subvert the power of the triumvirate by the judicious use of new approaches to endocrine therapy in select patients?" he says.

Life events "increase risk"

Death of a husband, divorce or separation may double a woman's risk of breast cancer, Finnish researchers found (*American Journal of Epidemiology* 2003, **157**, 415–423). The findings suggest life events have a role in breast cancer aetiology "through hormonal or other mechanisms", they say.

The prospective study included 10 808 women included in the population-based Finnish Twin Cohort. All were same-sex twins born before 1958, of whom both were alive in 1975. They completed a baseline health questionnaire in 1975 and a follow-up questionnaire, including questions on life events, in 1981. Data on the incidence of breast cancer from 1982 was obtained from the Finnish Cancer Registry.

The results were adjusted for known risk factors such as later age at first full-term pregnancy, but this did not explain the link with life events. Divorce or separation, death of a husband and death of a close relative or friend were each associated with increased risk of breast cancer.

The relationship is biologically plausible, the researchers say, since stressful life events have been seen to alter immunological function. Stress-induced disruption of the neuroendocrine axes, such as that relating the hypothalamus and pituitary to the gonads, could also be involved. It can increase or decrease the secretion of various hormones, such as oestrogens.

Psychological reactions to life events can also lead to behavioural changes. However, the researchers say their work suggests an increase in risk independent of body mass index, weight change, alcohol use, smoking or physical activity.

More work is necessary to confirm this finding, the researchers conclude, "to further explore the potential role of an individual's behavioural and psychological coping styles in mediating or modifying the effects of life events."

The aftermath of Hodgkin's lymphoma

Modern therapeutic strategies for Hodgkin's lymphoma must fully account for the late effects of treatment, UK researchers say. Hodgkin's lymphoma is now one of the most curable of all non-cutaneous malignancies, making treatment-induced late effects particularly relevant (*Lancet* 2003, **361**, 943–945).

Treatment-related mortality exceeds that from Hodgkin's lymphoma by 12–15 years after initial therapy. The most common causes of excess deaths are second malignancies, especially lung cancer, and ischaemic heart disease.

"It is imperative that all patients who have had thoracic radiation are strongly encouraged never to smoke," the researchers say. Risk of secondary breast cancer after irradiation of mediastinum or axillae in young women is 20–50% and these patients should be offered a screening programme. The dose–response relation underscores the necessity of using the minimum radiation dose to obtain tumour control.

A 3-fold increase in cardiac deaths has been noted, endocrine disorders and infertility are common and the psychological trauma associated with contracting a malignant disease is great. "Present treatment strategies must therefore aim to give minimum therapy without jeopardising the high rates of cure that are now possible with front-line therapy," researchers say. Choice of approach is dependent on an appreciation of short- and long-term side-effects. "Increasingly the patient must be involved in an informed decision-making process," they conclude.

PODIUM

Cancer research "faces severe threats"

Dr Martine Piccart is head of chemotherapy at the Jules Bordet Institute, Brussels, and founder and chair of the Breast International Group, which is a network of more than 30 clinical trials groups from around the world. She is a member of numerous European and American societies, and a former chair of the EORTC's Breast Cancer Group and Treatment Branch.

Dr Martine Piccart

What's the problem?
I am alarmed because young oncologists are no longer motivated to carry out cancer research. We are facing tremendous difficulties in finding enthusiastic people. Our field has changed in 20 years. When I started, studies could be initiated relatively quickly and the administrative burden linked to trials was small. We collected only essential data and studies were fun; you could do them on top of clinical duties.

Nowadays, it is completely different, partly because of the Good Clinical Practice (GCP) guidelines. It takes months to activate clinical research projects and there are all sorts of administrative barriers to be overcome. The report forms are huge; lots of data are collected, a great deal of which is not essential. This is the way things are evolving. I am really worried.

Are there other repercussions from the increased administrative burden?
It is also affecting patients. The informed consent procedure is becoming so complicated that it is discouraging them from entering clinical trials. The consent form is too big and too detailed for a sick patient to read. It is too heavy and sometimes shows no humanity.

We are becoming more like the States, where only 1% of patients enter trials. It is still higher than that in Europe but it is going to get worse.

Is it affecting current studies?
I had a problem recently in a trial which should not have been too difficult for patients to accept—an effective classical drug on top of a new agent which may or may not add something. But the informed consent form made it difficult for patients to understand that both arms of the trial received the classical drug. The important details of the trial were buried among the details of 30 potential side-effects, some of which are extremely rare. Imagine a patient, sick and under so much stress, looking at this!

Are there cost implications?
If the amount of data collected, and the paperwork, increases too much, it will kill academic research; institutes will not be able to cope with these requirements. It is becoming so expensive to carry out a trial that only pharmaceutical companies can afford to do it. And even they are concerned about the extra work. This is a disaster. We need both the pharmaceutical industry, with its innovative agents; and academic researchers who will always be important in answering questions in radiotherapy and surgery and who also give key input in drug studies and translational research. Already pharmaceutical companies are moving their headquarters to the States, and, increasingly, European protocols are being examined at US headquarters. In the States, there are no barriers of language or national guidelines. If we want to facilitate research in Europe and remain competitive, the last thing we need is more regulations.

How will the introduction of novel agents be affected?
Tumour genetic profiles will be used to correlate the activity or failure of treatment. Oncologists, surgeons and pathologists will have to co-operate closely if biopsies are to be taken in time, in an adequate way, and frozen or stored in particular conditions. We need to have teams of doctors working together and it is already difficult.

Further, if we make it even harder to circulate samples between centres, hospitals will be discouraged from taking part in interdisciplinary research in which tumour samples are sent to the laboratory with the most experience in evaluating tumour markers. Regulators, instead of understanding how crucial this work is, are conservative and finally, negative.

Surely there is some benefit from all the information collected?
Quite the reverse. If you overload researchers with irrelevant information such as the exact date an appendix was removed, the most important aspect of a patient's chart could be missed. The danger of this happening is greater now than before.

How can young researchers be encouraged?
Programmes and grants enable researchers to travel and work in other countries, which is positive. But there may not be 100 candidates applying, because only the motivated take these opportunities. It is not true in southern Europe and in other regions of the world, such as China, India and Brazil.

Are there any solutions?
Patient groups such as Europa Donna could approach patients about clinical trials, and may be more effective than doctors. But there are few such groups for other tumours and ultimately patient care will be affected if we can't get trials up and running.

We will only have good clinical research if there are people eager to carry it out.