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5th International Conference on Cancer Prevention

Presented by ESMO

Report

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Publishing Working Group

St. Gallen, Switzerland 6–8 March 2008

Cancer Prevention 2008: time for networking among epidemiologists, medical oncologists and basic researchers

Introduction

From the 5th to the 8th of March 2008, the 5th International Conference on Cancer Prevention took place in St. Gallen, Switzerland and welcomed more than 180 participants. Although the view through the window of a snowy St. Gallen appeared very tempting, the interesting mixture of different subjects presented by a distinguished panel of speakers made it easy to stay indoors and listen.

The presentations covered all aspects of cancer prevention research, i.e. (cohort) studies carried out to identify cancer risk factors; experts' views on lifestyle interventions; chemoprevention; preventive vaccination; experts' views on cancer screening; and pitfalls in cancer prevention research.

Studies carried out to identify cancer risk factors

Paolo Vineis presented the results of the most recent update of the EPIC (European Prospective Investigation into Cancer) trial, which encompassed over 500,000 people. The EPIC trial was initially designed to study the relationship between diet and cancer, and recruitment took place between 1993 and 1998.
Dietary fiber appeared to protect people against colorectal cancer. A daily intake of more than 40 grams was associated with a 60% risk reduction. A high intake of red meat, however, was related to a 75% higher risk, which could be explained by an increased enteric production of the carcinogenic substance nitrosamine. Fish was related a 50% risk reduction. People with a high red meat/low fiber diet appeared to have the highest colorectal cancer risk.
In accordance with more than 100 previously performed studies, the EPIC study confirmed the positive correlation between body weight and breast cancer risk in postmenopausal women. This correlation can partially be explained by increased estrogen production in fat tissue, but there is also an association between body weight and cancer risk.

Experts' views on lifestyle interventions

Exercise and overweight

Michael Pollack gave a very interesting presentation about hyper-insulinism and cancer. Apart from its traditional glucose-regulating properties, insulin also acts on normal and transformed epithelial cells through Insulin Growth Factor (IGF)-binding sites. The hypothesis that a higher insulin level, caused by either a high carbohydrate intake or insulin resistance, can speed up cancer growth is underlined by a body of evidence.
Jee et al. have previously reported an inverse correlation between fasting glucose concentration and cancer mortality, which prevailed after correction for body mass index (BMI) (Jee et al. JAMA 2005;293:194-202.). In the Physicians Health Study the probability of dying from prostate cancer increased considerably with increasing BMI. Breast cancer risk doubles with increasing BMI. In the previously mentioned EPIC study, people with a high C-peptide concentration had a 70% increased risk for colorectal cancer in comparison with people who had a low C-peptide concentration.
Obesity leads to hyperinsulinism, but an increased carbohydrate intake could also lead to higher insulin concentrations in people who are not overweight. Exercise leads to a decrease in insulin production and could as such improve cancer prognosis. If hyperinsulinism were anticipated, the hormone could be measured, but its concentration can fluctuate considerably. The measurement of C-peptide is an attractive alternative. Its concentration tends to be more stable over time and it clearly correlates with insulin production.
In conclusion, diet and physical exercise are not only indicated to prevent cardiovascular disease, but have also proven effective against cancer.

Nicotine abuse

On behalf of the World Health Organization Luminita Sanda gave a presentation on the M-POWER program, which should lead to a sharp worldwide decrease in tobacco use. M-POWER stands for:

- **M**onitoring tobacco use and prevention policies
- **P**rotect people from tobacco smoke
- **O**ffer help to quit tobacco use
- **W**arn about the dangers of tobacco
- **E**nforce bans on tobacco advertising
- **R**aise taxes on tobacco

The tobacco industry has consistently misinformed the public and government with fancy phrases, such as "low tar" and "light" cigarettes. To date, a 70% increase in tobacco prices has led to a 25% decrease in mortality.
Jean King provided the audience with tools to transmit cancer prevention goals to society. Risk factors, such as tobacco use and excess weight, tend to occur more often in hard-to-reach populations. It is questionable whether medical professionals should be the ones to breach the barrier. There is a great need for social marketeers who can find out how the message should be brought to the consumers. On the other hand, cancer prevention deserves more attention in current daily practice and in medical school. Medical professionals should set the right example. It is disappointing to realize that in 7 out of 10 Western countries more than 20% of 3rd-year medical students are actually smokers.

Chemoprevention

Metformin

Metformin is usually well tolerated and known to decrease circulating insulin levels. The odds ratio for cancer is 0.62 for diabetics who use metformin in comparison with other diabetics. In cancer tissue cultures metformin has shown inhibiting properties. The development of metformin as a cancer preventing agent is still in the preclinical stage. Researchers are cautious because some cancer cells have been shown to produce vascular endothelial growth factor (VEGF) when metformin has led to glucose deprivation.

Estrogen receptor(ER)-positive breast cancer and selective estrogen response modulators

In the BCPT-P1-study premenopausal and postmenopausal women were treated with either a placebo or 5 years of tamoxifen. Treatment with tamoxifen led to a 49% risk reduction for invasive breast cancer. Regarding the major adverse effects (endometrial cancer, pulmonary embolism, deep venous thrombosis and stroke) there were no significant differences between the two treatment arms. In the MORE study, 5 years of treatment with raloxifene led to an overall 72% reduction in invasive breast cancer and an 84% reduction in ER-positive breast cancer.

In the NSABP-STAR trial women were treated with either 5 years of tamoxifen or 5 years of raloxifene. Both treatment arms were comparable in terms of breast cancer risk. Raloxifene appeared to have a more favorable safety profile (lower endometrial cancer risk, 30% fewer thromboembolic events).

The numbers needed to treat to prevent one breast cancer death (303 for tamoxifen and 323 for raloxifene) compare favorably with the numbers needed to treat with statins to prevent one cardiovascular death (atorvastatin 294).

Prof. Dr. med. Hans-Jörg Senn, Co-Chairman of CAP 2008, stated several times that it is about time for ASCO and ESMO to provide guidelines on the preventive use of selective estrogen receptor modulators in high risk women. For example, a 60-year old postmenopausal woman with one 1st degree breast cancer relative has a 22% chance of developing breast cancer before her 90th birthday (GAIL model, **www.cancer.gov/bcrisktool/**). For such women, preventive treatment could be justified.

ER-positive breast cancer and aromatase inhibitors

Jack Cuzick discussed the topic of breast cancer prevention with aromatase inhibitors. Phase III trials in which SERMS and aromatase inhibitors are being compared are ongoing. The ATAC trial compared the benefit of anastrozole and tamoxifen in the adjuvant setting. In the anastrozole group the number of contra-lateral breast cancers was 50% lower. At a median duration of 9 years follow-up this risk reduction is still present. A comparable result has emerged from the MA-17, B-33, IES and BIG-1-98 trials. From these data one could conclude that treatment with aromatase inhibitors may prevent 75% of all invasive breast cancers. Aromatase inhibitors have been shown to increase fracture risk, and upfront bone mineral density measurement should be incorporated in the treatment schedule.

ER-negative breast cancer and fenretinide

Retinoids have been studied as chemo-preventive agents in clinical trials due to their established role in regulating cell growth, differentiation and apoptosis in preclinical models. Experimental evidence suggests that retinoids affect gene expression both directly, by activating and/or repressing specific genes, and indirectly, by interfering with different signal transduction pathways. Induction of apoptosis is a unique feature of fenretinide, the most widely studied retinoid in clinical trials on breast cancer chemoprevention due to its selective accumulation in breast tissue and to its favorable toxicological profile. In a phase III breast cancer prevention trial, fenretinide showed a durable trend to a reduction of second (ER-+ and ER-) breast malignancies in premenopausal women [hazard ratio (HR) = 0.62, 95% confidence interval (CI), 0.46-0.83]. At present, research focuses on the interaction between retinoids and breast cancer stem cells, the identification of agents which could collaborate with retinoids and the identification of subgroups which benefit the most from retinoid treatment.

Non-steroidal anti-inflammatory drugs (NSAIDs) and colorectal cancer prevention

After an inflammatory stimulus arachidonic acid can be transformed to prostaglandins through the lipoxygenase and cyclo-oxygenase pathway. Prostaglandins can stimulate cell proliferation and inhibit cell apoptosis. The cyclo-oxygenase pathway has been shown to be active in all stages of colorectal cancer and it can be inhibited by aspirin and NSAIDs. Agents that specifically inhibit cyclo-oxygenase-2 are supposed to be safer regarding the risk of gastrointestinal bleeding, but cardiovascular risk appears to be higher, probably due to inhibition of prostaglandin I_2.

In observational studies, sporadic colorectal cancer risk appears to be lowered (about 20% risk reduction) by the use of aspirin, but there is a latency period of 10 years (with adverse effects), before this occurs. Chemoprevention trials have been performed in high-risk populations as well as in the general population. Daniel Pelot discussed the unpublished results of a phase III study, which compared the preventive effect of a-difluoromethylornithine (DFMO) and sulindac with placebo after previous polypectomy in 375 patients randomized over a period of 8 years. The former treatment led to a 70% reduction in adenoma recurrence; the risk of developing an advanced adenoma was even more reduced (92%). Gastrointestinal toxicity and cardiovascular toxicity risk appeared to be comparable in the treatment and the placebo group. Trials with other NSAIDs (rofecoxib, celecoxib) have also shown a reduction in the number of adenomas and sporadic colorectal cancers, but the safety profile appeared less favorable.

Several studies have evaluated the chemopreventive effect of NSAIDs in high-risk populations (Familial Adenomatous Polyposis, Hereditary Non-Polyposis Colorectal Cancer). At present, it is questionable whether the cost-benefit ratio justifies chemoprevention with either NSAIDs or aspirin in high-risk subgroups of the general population. Currently, the International Society of Cancer Prevention is developing guidelines which are about to be published in a leading scientific cancer journal.

Preventive vaccination

Hepatitis B

Mei-Whei Chang told the audience about the successful hepatitis B vaccination program in Taiwan. Hepatitis B vaccination can prevent infection and subsequent cirrhosis and malignancy.

The peak prevalence of hepatocellullar cancer (HCC) is seen at the beginning of the 7th decade and at least 40 years are needed to gain advantage from vaccination. In spite of this, childhood HCC is not an uncommon phenomenon. Peri-natal transmission accounts for 50% of all hepatitis B cases. All this underlines the need for vaccination in the 1st weeks after birth. In HbsAg-positive women the 1st vaccination should be given within 24 hours after delivery. In the other patients, vaccination could be postponed for a few weeks.

The introduction of this post-delivery vaccination program 20 years ago has resulted in a 90% reduction of sero-positivity amongst children (from 10-17% to 1-1.7%). The additive value of antiviral therapy for sero-positive women in the last trimester is still under evaluation.

Human papillomavirus vaccination

John Schiller advised the audience not to wait any longer for cheaper vaccines against the common human papillomaviruses (HPV 16 and 18). HPV infection results in an 80% lifetime risk of cervical cancer. Two vaccines (Merck/Gardasil and GSK/Cervarix) have been registered for vaccination against HPV16 and HPV18. These two genotypes account for 70 % of all cervical cancers worldwide. In registration studies, Gardasil and Cervarix have been shown to lead to seroconversion in 99% of cases. Vaccination can prevent cervical, vaginal and vulval cancer, genital warts and diagnostic therapeutic procedures as indicated by the results of the Papanicolau-smear. In order of priority, Schiller mentioned 3 groups:

1. Young females before they become sexually active (at 10-14 years of age)
2. Sexually active HPV-negative females
3. Males

Awareness amongst public authorities and general practitioners should be stimulated. The additive importance of circumcision needs to be remembered.

Experts' views on cancer screening

Prostate cancer

Prostate cancer is a disease with a high prevalence, a well-defined histological precursor lesion and a long latency. Prostate specific antigen (PSA) testing in the general population has certain disadvantages. Previous trials have shown that screening with the currently used cut off point (4.0 µg/L) results in an over-diagnosis of 50%. If a higher cut off point is chosen, the specificity improves, but the sensitivity lowers. A lower cut off point would do exactly the opposite. Fritz Schroeder gave the audience the following example: If a PSA concentration higher than 2.5 µg/L would warrant prostate biopsy in the United States, 2.74 million men would need a biopsy every year. This figure would lead to 25.6 times more prostate cancer cases than the 30350 men expected to die in that year. Therefore PSA testing only does not suffice as a screening tool. A more differentiating test, such as the combination of PSA indexed for prostate volume (as measured by means of transrectal ultrasonography) and abnormal digital rectal examination, may have a more adequate sensitivity/specificity profile.

At present, men who wish to undergo PSA testing should be informed about the possible consequences (**www.uroweb.org**).

Lung cancer

Fergus Gleeson addressed the question of whether computer tomography (CT) screening for lung cancer could reduce lung cancer mortality. He gave an overview of the studies published so far. Although low-dose CT detects early lung cancer, CT screening did not appear to lead to a stage shift and there was no reduction in mortality.

Pitfalls of cancer prevention research

David Ransohoff gave an interesting lecture about the pitfalls of biomarker research. A researcher should always ask: "What might be wrong with my results and conclusions?" Progress is based on considering alternative explanations and avoiding over-interpretation. But this applies to the editorial board of scientific journals as well; every editorial board should have a forensic epidemiologist, who reads all manuscripts.

Ransohoff illustrated his lecture with the concept of proteomics research. There is a continuous storm of publications on gene array assays. Reproducibility is poor due to fundamental problems in study design. Systemic differences between treatment groups, such as specimen handling and date of measurement, are sometimes overlooked (bias). Many researchers apply a multivariable predictive model with a large number of variables to a small number of subjects (chance). Statistical fitting leads to irreproducibility in independent groups. Overlap between the initial study group, the training set and the validation set can make things even worse. A trial should be designed to minimize bias and chance. Both should be looked at while interpreting the results and should be addressed in the discussion of the manuscript.

Conclusion

The 5th International Conference on Cancer Prevention gave a complete overview of cancer prevention standards, basic research and future goals.
However, it was strange to see that industry and medical oncologists were virtually absent during this conference. Only 2% of cancer research funds are invested in prevention research. Medical oncologists and industry do not seem to be interested in prevention research, but this lack of interest cannot be justified. Medical Oncology professors in university hospitals around the world should join the International Society of Cancer Prevention in an effort to set up an international cancer prevention research network. Such a network could eventually answer the question: "Is an ounce of prevention worth more than a pound of treatment?"

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Printing Salvioni Arti Grafiche S.A.

Content provided by the
ESMO Congress Department

Printed in Switzerland

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