

## OPENING LECTURE I

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### Stem Cells and Cancer Stem Cells

#### Alan Trounson

*California Institute for Regenerative Medicine, San Francisco CA, USA [atrounson@cirm.ca.gov](mailto:atrounson@cirm.ca.gov)*

The California Institute for Regenerative Medicine (CIRM) was established by the Californian voters to fund as a "priority stem cell research that has the greatest potential for therapies and cures, specifically focused on pluripotent stem cells and other vital opportunities". The funding is derived from the sale of general obligation Californian state bonds of \$US3 billion. Grants are made for basic and translational research leading to clinical trials. CIRM has been focused on stimulating embryonic stem cell (ESCs) research and induced pluripotent stem cells (iPSCs). However, CIRM also funds research into adult stem cells and cancer stem cells (CSCs).



Pluripotent stem cells are capable of forming all the cell types of the body and are under tight regulatory control that enables continuous proliferation in the undifferentiated state, yet are responsive to developmental cues that enable differentiation into a very wide variety of cell types. Cancer stem cells have many of the same properties of pluripotent stem cells and rely on common expression pathways utilized in development. CSCs arise when genetic or epigenetic insults accumulate in the adult stem cell or a downstream progenitor cell type that allows a transformation that uncouples proliferation from normal choices (quiescence, differentiation, senescence and apoptosis). Stem cells are normally maintained quiescent within a stromal niche. It is proposed that CSCs are likewise a rare cell type maintained under regulatory control within a niche, where they are resistant to chemo- and radiotherapy. Hence debulking tumor mass may not effectively eradicate the source of metastasis.

CIRM is supporting research aimed at determining the CSC phenotype – surface markers and self-renewal pathways, developing strategies to target CSCs by antibodies and other cytotoxins, and determining the biology of CSC formation and transition to aggressive proliferation. Recently, CIRM funded a number of major studies on CSCs together with the Canadian Cancer Stem Cell Consortium and the UK Medical Research Council. Targets included leukemia, solid tumors and glioblastoma<sup>1</sup>. These projects are funded to up to \$US40 million over 4 years in order to complete regulatory approval (IND) for initial clinical trials.

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# OPENING LECTURE II

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## Cancer Research for Cancer Prevention

### Christopher Paul Wild

*International Agency for Research on Cancer, 150 cours Albert-Thomas, 69372 Lyon, Cedex 08, France E-mail: director@iarc.fr*

#### Abstract

The global burden of cancer is estimated to double in the next 20 years with the current 12.5 million new cases per year rising to around 25 million by 2030. A majority of this increase will occur in the low and middle-income countries (LMC), where the health services are at present least able to cope with the challenge. This inequality is highlighted by the markedly lower cancer survival rates in LMC compared to economically richer countries. Much can be acted on now, for example to limit tobacco and alcohol use, to introduce vaccines against hepatitis B and human papilloma viruses, to combat excessive sunlight exposure, to promote an active lifestyle and to implement screening and early detection. However, research into implementation of such prevention strategies remains important. At the same time progress is needed to understand more about the causes of cancer. This implies research into aetiology must parallel that into cancer prevention; this combination should be the priority for cancer research in LMC in the coming decades.



Most cancers have an environmental cause, with exposures encompassing lifestyle, infections, radiation, natural and man-made chemicals and occupation. However, the precise contribution of specific environmental risk factors and their interaction, with each other and the genetic background of the individual, is difficult to elucidate. This is at least partially due to limitations in accurately measuring exposure. Recent advances in laboratory sciences have been paralleled by an increased understanding of mechanisms of carcinogenesis (e.g. epigenetics) to provide one promising avenue for the improvement of exposure assessment. Already progress has been made with exposure biomarkers such as carcinogens and their metabolites in various tissues and body fluids. However, there is also the exciting potential for new "omics" technologies to provide a step-change in environmental exposure assessment. In addition, the next-generation of biomarkers can also help establish the biological plausibility of exposure-disease associations and provide a bridge from epidemiology to data generated in animal and cell model studies of carcinogenesis.

Establishing aetiology is a first step in cancer prevention. However, novel biomarkers may also serve as intermediate endpoints in intervention studies, permitting a proof-of-principle to be established for a given intervention. In addition, biomarkers which help elucidate mechanisms of carcinogenesis in exposed people may provide a rationale for interventions per se by indicating ways in which the carcinogenic process can be modulated by lifestyle or clinical treatments.

Much remains to be accomplished in order to establish aetiology and provide the evidence-base for public health decisions on cancer prevention. Nevertheless, rapid advances in technology, the fresh understanding of carcinogenic mechanisms and the availability of large prospective cohort studies with bio-specimen repositories provide exciting new opportunities in aetiological research. Prevention strategies based on these foundations demand an interdisciplinary approach whereby the term translational cancer research includes translation from the laboratory to the clinic and from the laboratory to the population. Such a "two-way translation" holds rich promise in combating the projected increases in global cancer burden.

CPW acknowledges support from NIEHS, USA Grant no. ES06052.

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## OPENING LECTURE III

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# Long-term Impact of the World Cancer Declaration

## David Hill

*Director, Cancer Council Victoria and President, International Union Against Cancer*

### Abstract

The World Cancer Declaration (WCD) is an initiative of the International Union Against Cancer (UICC), which was adopted by delegates to the World Cancer Congress in Geneva, 2008. The WCD was written in consultation with a large number of stakeholders and outlines the broad global agenda for cancer control. It sets 11 targets to guide progress in reducing the global burden of cancer by 2020. The targets cover improved prevention, treatment, and care, 'enablers' of these desired outcomes, and tools for measuring and monitoring progress. These targets are ambitious, but have been judged to be attainable by the global cancer control community.

The WCD has been translated into a number of languages, as well as having been adapted for country- and region-specific applications. Through promotion on websites of the UICC and its member organizations, in particular the Lance Armstrong Foundation, over 100,000 individuals and around 700 organizations have signed on to the WCD, suggesting it can be a powerful focus for global cancer advocacy.

The WCD informs all the policies and programs of UICC itself and UICC endeavours through its leadership and partnerships to keep the WCD targets salient at national and international policy making forums. In the coming years, using the WCD as a 'roadmap' for activity, UICC will give special attention to targets that are most relevant to the capacities of a global, member-based organization with membership in over 100 countries. Examples of UICC's planned activities include; advocating for cancer to be included among Millennium Development Goals, concerted partnership action to address the challenge of non-communicable diseases generally, evidence-based public communication to promote prevention and dispel harmful myths about cancer, and policy change to enable access to essential medicines (in particular opioid analgesics).

A critical analysis will be presented covering current global cancer challenges; future trends in cancer and its determinants; and how the targets of the WCD will guide the required international responses to avert an impending disaster for developing as well as developed countries.



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### Notes

## SPECIAL SESSION I

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### **Pediatric Cancer: Current Status and Future Prospects**

**David Poplack**

*Texas Children's Cancer Center, Houston, Texas, U.S.A. DPoplack@txccc.org*

#### **Abstract**

Great progress has been made over the past 60 years in the treatment of childhood cancer. Improvements in the application of the main modalities of treatment—surgery, radiation and chemotherapy—have increased survival dramatically. In North America more than 75% of children are survivors of their cancer. This presentation will review the major factors responsible for this improved outcome and will highlight the major challenges pediatric oncologists will face in making cure a reality for all patients. Emphasis will be placed upon the unique challenges associated with the treatment of brain tumors and certain solid tumors that tend to present with metastases at the time of diagnosis. New biological concepts that have led to an increased understanding of childhood cancer will be discussed. In particular, the implications of recent technologic advances in the fields of genomics and proteomics will be highlighted. In addition, several newer therapeutic approaches emanating from the fields of nanotechnology, cell therapy and immunotherapy will be reviewed. An overall vision of treatment in the future will be discussed. Finally, the impact of the challenges faced by childhood cancer survivors will also be presented.



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## SYMPOSIUM I: TOBACCO and CANCER

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### Tobacco Cessation- a Key Part of Cancer Prevention and Control Strategy

**Dongbo Fu**

*World Health Organization, Geneva, Switzerland [fud@who.int](mailto:fud@who.int)*

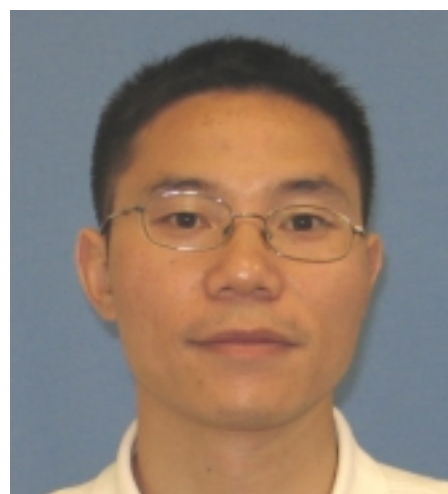
#### Abstract

Tobacco use is a major modifiable risk factor for non-communicable diseases (NCDs) including some types of cancer. Tobacco kills more than five million people annually. Tobacco-related deaths are projected to double by 2030 and reach more than eight million per year. Tobacco remains available as a consumer product because of its addictive properties and as a result of global market strategy that aggressively targets low- and middle-income countries. Nicotine is the major addictive component of tobacco, which makes tobacco users quickly dependent on it and then have to overcome both the physical and psychological effects of nicotine addiction in order to quit and to remain tobacco free. Tobacco use is also a repetitive habit and is very hard to break.

The association between tobacco smoking and cancer was demonstrated by Sir Richard Doll in 1950. After a half of a century the Report of the Surgeon General stated that cancer "was among the first diseases causally linked to smoking". Tobacco use is responsible for 1.8 million cancer deaths per year (60% of these deaths occur in low- and middle-income countries). Lung cancer is the leading cause of cancer death. 87% of lung cancer deaths can be attributed to tobacco use. Besides lung cancer, tobacco use causes increased risk for cancer of the mouth, nasal cavities, larynx, pharynx, oesophagus, stomach, liver, pancreas, kidney, bladder, uterine cervix, and myeloid leukaemia.

Taking urgent action to reverse the global tobacco epidemic, in particular, implementation of the WHO Framework Convention on Tobacco Control (WHO FCTC), the foundation and guide for global tobacco control, can and will save millions of lives. If adult consumption in the world were halved by 2020, it is estimated that approximately 180 million smoking-related deaths would be averted by 2050. WHO, in collaboration with global partners, is working with countries on the implementation of a package of six cost-effective policy interventions (the MPOWER package) to reduce tobacco use outlined in WHO's 2008-2013 Action Plan for the Global Strategy for the Prevention and Control of NCDs including cancer. Treatment of tobacco dependence is a key component of any comprehensive tobacco control strategy, but often overlooked. Countries' health systems hold the primary responsibility for treating tobacco dependence. Oncologists can play a key role in tobacco control as health role models in order to take action to help patients, influence other health professionals and advocate public policy. Oncologists are probably more powerful than other health workers in helping smokers to quit because cancer is a concern for many people.

In conclusion, a shifting tobacco epidemic, together with other factors, is likely to lead to a new epidemic of tobacco-induced cancers in developing countries. Together with other health professionals, oncologists can truly add value to the global tobacco control effort by promoting tobacco cessation in the practice, warning the public about the dangers of tobacco, and helping spearhead establishment of smoke-free environments in health-care settings. All these can be done through raising awareness among politicians, health professionals and society, eventually implementing the WHO FCTC at large.



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## SYMPOSIUM I: TOBACCO and CANCER

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### Tobacco Control Programmes Around the World

#### TH Lam

*Sir Robert Kotewall Professor in Public Health  
Director, School of Public Health, The University of Hong Kong, Hong Kong.*

#### Abstract

According to the World Health Organization (WHO), the tobacco epidemic killed 100 million people worldwide. Currently, smoking and tobacco use kills 5.4 million people globally each year. Unless urgent actions are taken, the death toll will increase to more than 8 million annually by 2030. The Framework Convention on Tobacco Control (FCTC) is the first international treaty of WHO. By November 2009, 168 countries (parties) have ratified the FCTC, but the USA has not.

WHO MPOWER 2008 is a package of six effective tobacco control policies: (1) Monitor tobacco use and prevention policies, (2) Protect people from tobacco smoke, (3) Offer help to quit tobacco use, (4) Warn about the dangers of tobacco, (5) Enforce bans on tobacco advertising, promotion and sponsorship, and (6) Raises taxes on tobacco. Progress in MPOWER in countries will be monitored regularly. However, the WHO 2009 report states that most governments are falling short in implementing the policies required



by FCTC. Less than 10% of the world's population are covered by any one of MPOWER measures. Despite some progress on smoke-free policies, most people are not protected from second-hand smoke.

It is important to note that there is a gap of two to three decades between the rise of tobacco consumption and the increase of tobacco deaths. Countries which started effective tobacco control policies several decades ago, mostly in the West, have seen decreasing smoking prevalence first, followed by decreasing deaths attributed to tobacco use 10-20 years later. Countries in which smoking prevalence have been increasing more recently see only small increase in tobacco deaths but the worst will come a few decades later, unless a large proportion of current smokers stop smoking now..

The multinational tobacco industry has been aggressively expanding its global market to middle and low income countries, especially those with weak tobacco control measures. Government political commitment and resources for tobacco control are often limited and insufficient to counteract the strategies of the tobacco industry and the oppositions from those with related interests. Health care professionals should take leading roles in tobacco control advocacy, especially in urging and supporting governments to adopt MPOWER nationally, and to help their patients to stop smoking.

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## SYMPOSIUM I: TOBACCO and CANCER

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### Smoke-free Generation

**Prakash C Gupta**

*Director, Healix - Sekhsaria Institute for Public Health, Navi Mumbai, India  
pcgupta@healis.org*

#### Abstract

On the face of it, smoke-free generation should happen without any attempt. Everyone: parents, teachers, politicians, society leaders, even the tobacco industry agrees that children should not use tobacco. Industry publically states that they do not market to children. Epidemiologists tell us that adults rarely, if ever, initiate tobacco use. Therefore smoke-free generation should happen in no time. The facts are quite different – the prevalence to tobacco use among children is increasing at many places and the age at initiation is getting younger. The vulnerable groups like women are using tobacco in greater numbers. In many places, tobacco use prevalence among girls is already higher than prevalence among adult women. The marketing techniques of the tobacco industry are getting more and more sophisticated and they are targeting successfully to the groups they want – younger children and girls. This is despite the fact that a ban on direct advertisement is in place and so are laws on smoke-free public places, even graphic warning labels have appeared.

It is clear that the industry has figured out the ways to get around these hurdles. The public health community needs to devise and advocate ore effective tobacco control measures. The potential effectiveness of such measures can be gauged through so called ‘scream test.’ The policy that clearly passes scream test is plain packaging. In India, a ban on sale of tobacco products within 100 yards of the schools also passes this test. Another measure that passed the scream test in India was mandatory warning label of skull and bones on every tobacco package. Skull and bones is understood as danger sign even by illiterates in rural India and the tobacco industry lobbying was powerful enough to get the requirement of putting skull and bones declared as "optional." Industry supporting politicians advanced ridiculous arguments like the sign ‘skull and bones’ causing communal discard even though such assertion was completely rejected by all communities in population based surveys. We still have a lot of work to do and long way to go before we actualize our dream of a smoke-free generation.



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## SYMPOSIUM II: ENVIRONMENT/ OCCUPATION

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### A Global View of the Environmental and Occupational Cancers

**Mihi Yang**

*Sookmyung Women's University, Seoul, Republic of Korea myang@sm.ac.kr*

#### Abstract

This review is focused on environmental pollution and occupational exposure as causes of cancer. Approximately 2-8 % of all cancers are thought to be due to occupation. In addition, occupational and environmental cancers have their own characteristics, e.g. specific chemicals and cancers, multiple factors, multiple causation and interaction, or latency period. Concerning carcinogens, asbestos/silica/wood dust, soot/polycyclic aromatic hydrocarbons [benzo(a) pyrene], heavy metals(arsenic, chromium, nickel), aromatic amines (4-aminobiphenyl, benzidine), organic solvents (benzene or vinyl chloride), radiation/radon or indoor pollutants (formaldehyde, tobacco smoking) are mentioned with their specific cancers, e.g. lung, skin, and bladder cancers, mesothelioma or leukaemia, and exposure routes, rubber or pigment manufacturing, textile, painting, insulation, mining, etc. Moreover, the aspects of environmental and occupational cancers are quite different between global south and north. Thus, individual countries should prepare their own strategy due to their characteristics. The recent follow-up



of 15 million people in 5 Nordic countries shows a good example for developed countries. However, newly industrializing countries face increased burden of occupational and environmental cancers, because of several reasons, e.g. poor regulation and screening program for cancer. In a case of developed countries, they should consider low dose exposure to environmental and occupational carcinogens, thus, threshold levels are re-considerated. On the other hand, developing countries are still concerned about high dose exposure to the carcinogens with balance of their economical purpose. Particularly, newly industrializing Asian countries are suffering from preventable cancers in mining, agriculture, or industries without proper education for safe. Therefore, developed countries are expected to provide their experiences and knowledge for newly industrializing Asian countries. Finally, not only ambient conditions but also host conditions are continuously monitored with proper methods. For this purpose, specific quantitative biomarkers with molecular or genetic approaches should be further developed for early diagnosis or etiology of environmental and occupational cancers.

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## SYMPOSIUM II: ENVIRONMENT/ OCCUPATION

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### Gene-Environment Cancer Interaction

#### Michele Carbone

*Cancer Research Center of Hawaii & Department of Pathology, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, USA, mcarbone@crch.hawaii.edu*

#### Abstract

Many types of cancer are caused by interactions between genes and environment. Among them, malignant mesothelioma is a typical example. Malignant mesothelioma is a rare but very aggressive tumor that is often linked to asbestos exposure. The incidence of malignant mesothelioma ranges from 1 to 20/million in the western world. However, there have been several reports of clustering of malignant mesothelioma in certain areas, as in the case of the three villages of Tuzkoy, Karain and "Old" Sarihidir in Turkey, where about 50% of all deaths are caused by malignant mesothelioma. This unprecedented mesothelioma epidemic has initially been attributed to erionite exposure, a type of fibrous zeolite mineral commonly found in those areas in Turkey. Erionite has been demonstrated as one of the most potent inducer of malignant mesothelioma. However, it was later discovered that mesothelioma was prevalent in certain families but not in others, although on the basis of mineralogical studies, all the houses appear to contain similar amounts of erionite. These studies prompted a careful and detailed pedigree analysis of the three villages with high incidence of mesothelioma. The results showed familiar susceptibility to erionite carcinogenesis and mesothelioma. None of the family members who were born and raised outside these villages had developed mesothelioma. The results of mineralogical studies and pedigree analysis indicate that the mesothelioma epidemic in these villages is caused by gene-environment interaction. This discovery of gene-environment interaction in causing mesothelioma is supported by the studies of several US families that have incidences of mesothelioma similar to those found in the Turkish-villages families. It is possible that in the US "mesothelioma families", genetic predisposition and asbestos exposure interact in causing this disease. In collaboration with a team of scientists from the EPA, we found widespread erionite contamination in certain areas of the US. Therefore the research conducted in Turkey and in the US is complementary. The goals of our research are to identify novel preventive strategies for mesothelioma and to decrease mesothelioma-mortality among high-risk populations. In collaboration with Turkish scientists, we plan to conduct a clinical trial to test the validity of serological markers –osteopontin and SMRP (soluble mesothelin-related peptides)- for early detection of mesothelioma. Early detection is associated with more effective therapeutic options and an overall better prognosis. To develop novel effective therapeutic approaches, we need to identify the genes that make some people more susceptible to erionite and asbestos carcinogenesis. These studies are being conducted among members of high-risk mesothelioma families.

phone, by the financial support and promotion of Division of Health Policy, MOHW.



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## SYMPOSIUM II: ENVIRONMENT/ OCCUPATION

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### Cellular Telephones and Cancer

**Joachim Schüz**

*Institute of Cancer Epidemiology, Copenhagen, Denmark, joachim@cancer.dk*

#### Abstract

The widespread use of cellular telephones has raised concerns about possible adverse health effects, especially on the human brain due to the localized nature of exposure when holding the phone to the head. There are now a large number of epidemiologic studies investigating a possible association between cell phone use and brain tumour risk, but results are not entirely consistent. Incidence rates of brain tumours in the Nordic countries, utilizing population-based cancer registries with virtually complete registration, show a small but steady overall increase over the last decades, but this increase is strongest for benign tumours (meningioma) among elderly women. Faster growing malignant tumours (glioma) among young and middle-aged men, the group where a cell phone-related increase would be expected to occur first, did not show an increase in the time trends; for young men there was even an indication of a decline in recent years. In a large Danish nationwide cohort study including all 4 million adults with follow up for brain tumours until 2002, no association was seen between brain tumour risk and subscription of



a cell phone. A Swedish series of case-control studies showed an increased risk mainly for malignant tumours and acoustic neuroma already after few years of cell phone use and also among moderate cell phone users, but this finding is incompatible with the observed incidence rates. An international case-control study involving 7000 patients with brain tumours in 13 countries (Interphone study), of which most of the data has been published already, no overall association was seen, but a small risk increase for glioma among the most heaviest cell phone users cannot be excluded. Past cell phone use is difficult to assess, as study participants have difficulties to accurately recall how often they used their cell phone 10-15 years ago. In the Interphone study, methodological investigations were done to estimate the impact of error and bias, but there are both errors present that might lead to an underestimation or overestimation of a putative risk. With regard to other cancers than brain tumours, fewer studies have been done. In conclusion, there is some evidence against a substantial risk increase, but data on long-term heavy users of cell phones is still sparse as all studies conducted to date have included cancer cases only up to 2003 (therefore a long-term user of 10 or more years has started in 1993, the latest). Hence, the possibility of a small risk increase among this small group of long-term users of today's studies justifies further research with improved study methodology, as due to the widespread use of cell phones in the mid and late 1990s the group of long-term users is still growing immensely. Both follow up of gender- and age-specific brain tumour incidence rates and establishing prospective cohort studies for surveillance of adverse effects in cell phone users are suggested.

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## GLOBAL HEALTH INITIATIVES

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### New Hope In Health Foundation (SUVAK)

**A. Murat Tuncer** *Honorary President, New Hope in Health Foundation (SUVAK) murattuncer57@hotmail.com*

#### Abstract

SUVAK (New Hope in Health Foundation) has been carrying out two programs within the "Hand-in-Hand against Cancer" project; namely, the Cancer Registry Program and the Patient Advocacy Program. Both programs are carried out in collaboration with the Cancer Control Department, Ministry of Health of Turkey. While the Cancer Registry Program focuses on improving the quality of available cancer registries in four different cities of Turkey; within the scope of the Patient Advocacy Program, we are working to gather 18 different non-governmental organizations (NGOs), members of which include patients, their relatives, volunteers, and doctors and nurses from the field.

Cancer Registry Program: Our goals in this Program can be listed as creating and enhancing the cancer epidemiology and mortality database of Turkey; improving operations in the cancer registry centers in the four representative regions, which account for 12 % of Turkey's population; supporting cancer registries in 3 areas, namely training, equipment and motivational activities; and catch up with the world standards of cancer registry. Patient Advocacy Program: Within this Program, a platform named "Hand-in-Hand against Cancer" was established in order to gather 18 different NGOs under a single organizational structure. A formal application for transforming this platform into a federation was submitted to the authorizing bodies at the end of 2009, with a positive response strongly expected in 2010.




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### Strategies for Strengthening Cancer Civil Society – the Latin America Example

#### Cristina Parsons Perez

*American Cancer Society, New York City, US cristina.parsonsperez@cancer.org*

#### Abstract

A strong civil society, with professional and effective patient organizations is a critical factor in cancer control. In 2007, with the generous support from an educational grant from the Pfizer Foundation the American Cancer Society (ACS) launched the Latin America Regional Health Grants Program aimed at increasing the capacity of patient organizations and foster the growth of the cancer movement in the region. Traditionally, capacity building efforts for cancer nonprofits have focused either on strengthening organizational capacity or on supporting mission delivery programs. An approach combining these efforts would be of interest, as a patient organization's ability to implement programs effectively depends on the extent to which it has developed its core organizational capacities (capacities to lead, adapt, manage and execute). The Program recruited the 14 leading cancer NGOs of the region and combined 4 key strategies: programmatic strengthening; organizational strengthening; networking and cancer agenda building. Programmatic strengthening: In order to strengthen patient organization skills to drive cancer downstaging in the region, each NGO conducted a cancer early detection project with financial and technical on-the-ground support. Projects were in different areas reflecting organizational strengths, resources and opportunities. They included general public education, provision of screenings, healthcare professional training and advocacy. Organizational strengthening: Based on an individual organizational assessment, each NGO received a detailed capacity building plan with financial support for implementation (for example: strategic planning; staffing support; M&E, etc). This was the first time that organizations were involved in formal organizational assessments and formal organizational strengthening. All organizations showed capacity improvement, including in areas outside the area targeted with tailored support. Organizational capacity building showed positive gains in terms of the programmatic aspects of organizations, with organizations increasing their strategy alignment to mission and reporting improvement in the perceived quality of programs. As part of the Program, the organizations also received 4 trainings. Networking: A regional online network [www.redcancer.org](http://www.redcancer.org) was created to stimulate the creation of working relationships and exchange of best practices among Program NGOs. Increased collaboration was observed among organizations. Cancer Agenda Building: NGOs were supported in working with media, both individually and through regional initiatives. The strengthening of regional patient organizations with this Program will provide a strong network of effective and professional stakeholders capable of delivering high quality programs to impact the local cancer burden, as well as a group of patient organization leading the field of cancer advocacy. Combining programmatic support with organizational capacity building and networking is highly effective and has potential for replication in other regions of the world.



## GLOBAL HEALTH INITIATIVES

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### **Building Capacity of Cancer Civil Society in Southeast Asia**

**Suteera Nagavajara, Loyce Pace** *American Cancer Society, Washington D.C., USA*  
*suteera.nagavajara@cancer.org loyce.pace@cancer.org*

#### **Abstract**

**Background:** Effective cancer control requires a strong civil society and patient-centered government policies. Many cancer NGOs in Southeast Asia have not been able to effectively advocate for patients' rights and improved services as they often lack institutional capacity such as program planning and management, resource mobilization and strategic planning. The American Cancer Society (ACS) Asia Regional Cancer Control Program aims to improve access to and utilization of cancer control services in Southeast Asia and Taiwan by promoting a civil-society based information and advocacy movement. The Program engages 11 cancer control organizations in five countries.



**Objectives:** Add to evidence current analyses of national cancer contexts and civil society best practices; Build capacity of civil society to develop and manage effective cancer control programs; Foster civil society networks that promote expansion of cancer control initiatives and legislation

**Methods:** ACS delivers training and technical assistance to cancer organizations based on assessments, and awards annual grants to implement community-based cancer control interventions and campaigns.

**Results:** ACS conducted cancer control assessments in four countries, trained over 75 representatives from 16 cancer NGOs from five countries and funded 11 projects. NGOs reported having increased skills, knowledge and confidence level. They have expanded outreach activities and advocacy materials. Policy makers therefore increasingly hear NGOs' voices.

**Conclusion:** This program has led to greater effectiveness of civil society stakeholders; increased presence of NGOs and cancer issues on local, national, or regional public health agenda; and burgeoning network of cancer advocates.

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### **Cancer Foundation of India**

**Maqsood Siddiqi** *Cancer Foundation of India, Kolkata, India cfindia@hotmail.com*

#### **Abstract**

The Cancer Foundation of India (CFI) is a not-for-profit voluntary organization dedicated to campaign for cancer prevention and control in the country. It has its main office in Kolkata but endeavours to have its branches in all major towns of the country. The Foundation was started in 2002 as a consequence of the professional vision and personal commitment of a group of highly motivated clinicians, researchers, public health specialists and social activists. Through the activities of the organization, we are trying to fill in the gap that exists in cancer public health, education, man-power development, research and cancer survivor issues in India.

The CFI is the only knowledge based cancer NGO in the India that focuses on developing scientific information on Preventive Cancer Research and apply it towards promotion of Cancer Public Health Programmes. In addition, CFI's mission includes dissemination of information for improving cancer awareness and education among people, using interactive meetings, conference / symposia and through electronic media and press.

The Foundation has four operating themes which include, (1) Dissemination of authentic information for improving cancer awareness and education in general public through regular meetings on cancer awareness and community programs. (2) Research in cancer prevention through field and lab oriented work on topics of critical interests to the country such as epidemiology, chemoprevention, cancer vaccines, new detection methods and tests and tobacco control etc. (3) Development of human resource in cancer prevention and early treatment by holding workshops, interactive meetings, conference / symposia on topical themes and publishing protocols, manuals and innovative communication material in cancer prevention for medical and para-medical professionals, and (4) Service and Support to cancer survivors through a cancer helpline that provides counselling and clinical advice during and post-treatment status of patients and plans to develop a cancer survivor support centre.

All these activities are supported through planned, time-bound programmes supported and coordinated by national and international cancer institutions and agencies. In addition, the CFI has also encourages collaborative agreements with several Academic, Medical Research and Treatment institutions in India and abroad to facilitate its projects and programmes.



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## GLOBAL HEALTH INITIATIVES

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### **Cancer Control Planning by Civil Society ~Japan's challenge: all stakeholders gathered for better cancer control planning**

**Ryoji Noritake, Ken Hanioka**

*Health Policy Institute, Japan, Tokyo, Japan ryoji\_noritake@healthpolicy-institute.org*



#### **Abstract**

**Background:** Japan's cancer planning is now at the highest momentum with the CCPC, Cancer Control Promotion Council, proposing the Cancer Policy and Budgetary Recommendation. CCPC is a multi-stakeholder consultative body for the Minister of Health to pursue better cancer control in Japan. Japan's Cancer Control Act was enacted in 2007, and obligates the nation to establish CCPC including patient representatives. This abstract explains the methodology of the recommendation and the patient advocacy platform established by Health Policy Institute, Japan to facilitate this grass-rooted policy recommendation.

**Objectives:** On March 19, 2009, a Cancer Policy and Budgetary Recommendation was submitted to the Minister of Health by CCPC's own members. The scene was widely broadcasted across the nation. The recommendation is unique since CCPC's working group decided not to discuss exclusively amongst themselves; instead they asked the entire nation for better cancer control planning ideas including nation-wide survey and town meetings.

**Methods:** The working group implemented a nation-wide survey via regional cancer control planning councils. Patients, doctors, co-medicals, and academics gathered to respond to the survey. They also hosted two town meetings in Tokyo the capital, and Sendai the biggest city in northern mainland Japan.

Beforehand, Health Policy Institute, Japan, an independent think-tank, has established its Commission on Citizens and Health, a patient advocacy platform for patient centered health policy in 2007, and has been active to foster patient advocacy in Japan. CCPC's patient representatives are all the participants of HPI's Cancer Policy Summit, biannual assembly for regional patient representatives for sharing the best practices. These empowered patient advocates played a vital role to implement this grass-rooted policy proposal. HPI also provides overseas training and e-learning program for patient advocates.

**Results:** Reflecting the working group's outcome including vivid voices of patient advocates, CCPC proposed a drastic change of policy and budgetary planning process, from top-down to bottom-up. Also, they proposed 70 comprehensive recommendations based on the demands. Not only patient or community-centered, but also multi-stakeholder-centered cancer control planning was celebrated in Japan.

**Conclusion:** The Ministry of Health and CCPC have agreed to maintain this planning method and the CCPC's working group is currently formulating a revised recommendation for 2011. CCPC's cancer policy planning method can be duplicated by any governments and in any regions to accelerate the World Cancer Declaration. Political initiatives are still expected to fulfill the recommendations.

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#### Notes

## MOLECULAR MECHANISMS OF NUTRITION

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### Molecular Mechanisms of Genistein in Prostate Cancer

**Omer Kucuk**

*Winship Cancer Institute of Emory University, Atlanta, GA, USA*



#### Abstract

Dietary intake of soy products has been associated with a decreased risk of prostate cancer. Genistein is the principal isoflavone in soy, which has shown anti-cancer effects in cell culture, animal and human studies. Genistein is a selective estrogen receptor modulator (SERM) with greater preference for ER-beta compared to ER-alpha. Other potential mechanisms of action of genistein include its anti-oxidant and anti-inflammatory effects as well as inhibition and reversal of DNA methylation. Genistein has also been reported to lower serum VEGF levels and have anti-angiogenic activity. We have recently observed anti-RANKL activity as well. Genistein increases osteoprotegerin expression and decreases RANKL activation and MMP-9 activation, thereby preventing osteoporosis and bone metastases in a mouse model of prostate cancer bone metastases (Li et al. Cancer Research, 2006). We have also observed genistein induced inhibition of NF-kB and sensitization of prostate cancer cells to radiation and chemotherapy both in vitro and in vivo. Some of the genistein effects on prostate cancer may also be due to down-regulation of AR and up-regulation of Cx43. Tumor suppressor genes that are downregulated in prostate cancer may also be upregulated by genistein through demethylation of promoter regions of these genes. Potential benefits of genistein include prevention of prostate cancer, stabilization of advanced disease in patients with prostate cancer, and increasing the efficacy and decreasing the toxicities of androgen deprivation therapy, chemotherapy and radiation therapy.

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#### Notes

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## MOLECULAR MECHANISMS OF NUTRITION

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### **Cancer Prevention: Recommendations and Policies for Personal and Public Health Nutrition**

**Gulden Pekcan**

*Hacettepe University Faculty of Health Sciences Department of Nutrition and Dietetics, 06100 Sıhhiye, Ankara/Turkey  
gpekan@hacettepe.edu.tr*

#### **Abstract**

Cancer is a major cause of mortality throughout the world and is a largely preventable disease caused by a variety of factors. It was reported that up to 40% of all cancer deaths can be prevented by feasible and appropriate lifestyle changes such as; diet and by physical activity and maintenance of appropriate body weight and cessation of smoking. The dietary factors are estimated to account for approximately 30% of cancers in industrialized countries. So, diet and nutrition are important factors in the prevention, promotion and maintenance of good health throughout the entire life course. Public health goals are for populations, primarily for health professionals and are quantified where appropriate. "Population" includes the world population, national populations, population groups such as schoolchildren, hospital patients, and staff who



eat in canteens, generally or in specific settings. Personal recommendations are for people as communities, families, and as individuals. Public health strategies that promote healthy lifestyles (healthy diet, physical activity and cessation of smoking and alcohol intake) are likely to have significant benefits at the population level for reducing the incidence of cancers. Food-based dietary guidelines are prepared for increasing awareness on healthy nutrition and increasing physical activity. Public health is a public good. Its protection needs to be seen as a prime responsibility not just of people themselves and of government, but also of other relevant actors — policy-makers and decision-takers — in civil society, industry, the health and other professions, and elsewhere. Such actors need to recognise that their decisions influence public health and to act with that as one key consideration.

Maintaining body weight between the recommended limits, increasing physical activity, limiting the consumption of energy-dense foods and avoiding sugary (sugar added) drinks, eating mostly foods of plant origin mostly whole cereals, fresh fruits and vegetables in a great variety, limiting intake of red meat and avoiding processed meat such as; smoking, curing or salting, or addition of chemical preservatives, limiting alcoholic drinks and salt and avoiding salt-preserved, salted, or salty foods, aiming to meet nutritional needs through diet alone and preventing, promoting breastfeeding are the main public health strategies and personnel recommendations. All these strategies require a multisectoral approach involving the various relevant sectors and good planned, implemented and monitored Food and Nutrition Policies, including public health goals and personnel recommendations. Policy goals are specified generally for populations, and the recommendations derived from the public goals are for individuals. Recommendations vary for different countries and population groups. Reports prepared by The World Cancer Research Fund (WCRF), The American Institute for Cancer Research (AICR) and WHO Global Strategy on Diet, Physical Activity and Health (DPAS) could help countries to prepare the National Public Health Strategies for the Prevention of Cancer, considering the countries nutrition and dietary intake situations.

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#### Notes

## BREAST CANCER

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### **Mammography Screening: are the Real Benefits Outweighing the Burden on Women?**

**Doris Schopper** *Health Policy and Program Development, Wetzikon, Switzerland* [doris.schopper@bluewin.ch](mailto:doris.schopper@bluewin.ch)

#### **Abstract**

Randomised controlled trials showed that breast cancer screening by mammography reduces breast cancer mortality in women over age 50 by 25% to 30%. It was assumed that this effect would persist outside the controlled trial environment or even could be enhanced. Breast cancer screening programmes by mammography have now been operating for more than 10 years in fifteen countries. The impact of a mammography screening programme on breast cancer mortality has been studied in nine countries (Australia, Canada, Denmark, Finland, Iceland, Italy, the Netherlands, Spain, Sweden and the United Kingdom). Evidence from these programmes was analysed and confirms their role in reducing breast cancer mortality. Although evaluation design, time period studied, participation rates achieved differ, the trend in mortality reduction is consistent. The decrease observed in women invited to screening ranges from 16% to 36%. Breast cancer mortality reductions range from 24 to 48% in women having attended at least one screen after correcting for selection bias. Adjuvant therapy is estimated to contribute about one third to this decrease. Mammography screening programmes implemented for at least 10 years thus achieve a similar, but not greater mortality reduction as the randomised controlled trials. However, it may take some more years before the full impact of these mammography screening programmes can be assessed. As confirmed by numerous studies, the detection of breast cancer at an earlier stage and of smaller size (stage shifting) also leads to less invasive treatment, better prognosis and thus longer survival.



However, the benefits of screening clearly need to outweigh potential harms to recommend systematic screening. The two most important and debated harms are false positive results following mammography screening and overdiagnosis of breast cancer. False-positives are an inevitable part of breast cancer screening, are more frequent at first screening rounds than in subsequent rounds and can be reduced to less than 5% in good quality programmes. They mainly result in additional testing and anxiety. Findings from the randomized controlled trials and further studies have shown that the risk of overdiagnosis is modest. A further, although minimal risk inherent to mammography screening is breast cancer induced by ionizing radiation. Interval cancers may also be perceived as a hazard of screening. However, they are an inevitable part of the screening process. False-negative interval cancers should be reduced as much as possible by high-quality screening programmes.

The positive impact of screening programmes thus largely outweighs potential harms. This has been demonstrated in well-organised screening programmes set within relatively well-endowed health care systems and within female populations at relatively high risk of breast cancer. But what does this imply for settings in which the health system is more resource-constrained, where women over age 50 may have other priority diseases and where an organised high-quality mammography screening programme may be difficult to implement?

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### **Preventing Ovarian and/or Breast Cancer in Women at High Risk**

**Uziel Beller** *Shaare Zedek Medical Center, The Hebrew University of Jerusalem, Israel* [beller@szmc.org.il](mailto:beller@szmc.org.il)

#### **Abstract**

During the past two decades we have been exposed to a growing number of healthy women identified as carriers of a mutation in either BRCA1 or BRCA2 genes through inheritance from one of their parents. These women, some at a very young age, face the difficulties associated with the knowledge of their risk to develop breast/or ovarian cancer during their lifetime.

In certain ethnic groups such as the Ashkenazi Jews (AJ), that we encounter regularly, the percentage of the population carrying one of three common founder mutations is as high as 2.5%. Moreover, in a population study conducted in our institution on a random sample of 8,000 AJ men, 200 carriers were identified and the quoted frequency of the three mutations was confirmed. In addition, we evaluated the risk of developing a malignant tumor in these families and found it to be very high. This finding suggests that the questionable phenomenon of "Carriers with Low Risk" probably does not exist.



Given the fact that in our AJ ovarian cancer patients close to 40% will be found to be carriers of a mutation, a properly implemented and effective prevention strategy will eventually decrease the morbidity and mortality from this malignant tumor.

In order to achieve this goal we have established a free walk-in clinic for carriers in which we provide the full range of counseling, screening tests and interventions aimed at reducing the incidence of breast and ovarian cancer. These include chemo prevention, oral contraception, risk reducing surgeries, the use of PGD as well as routine screening by imaging and tumor markers.

This presentation will include analysis of our patients risk estimations, the counseling of younger and older carriers as well as the prevention measures advocated by our group.

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## BREAST CANCER

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### Gene-diet Interaction of Breast Cancer Risk

Sang-Ah Lee<sup>1</sup>, Minkyong Song<sup>2</sup>, Daehee Kang<sup>2,3</sup>

<sup>1</sup>Department of Preventive Medicine, Kangwon National University School of Medicine, Chuncheon, <sup>2</sup>Department of Preventive Medicine, Seoul National University College of Medicine, <sup>3</sup>Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence, Science and Technology and College of Medicine, Seoul National University, Seoul, Korea  
dhkang@snu.ac.kr

#### Abstract

Breast cancer is the most common cancer in women, which results from combined effects of genetic and environmental factors. In spite of the importance of dietary factors as major determinant of cancer development, dietary factors in breast cancer etiology render inconsistent results. Excess intake of alcohol is only one of a few proven risk factors for breast cancer development. Growing number of literature denote the importance of genetic susceptibility and the interaction between gene and diet in breast cancer development and/or prognosis. This gene-environment interaction may clarify the inconsistencies found in epidemiologic studies. Investigation of the gene-diet interaction provides not only the etiologic evidence in carcinogenesis but also a basis to cancer prevention in susceptible population.



Several prospective studies including Cancer Prevention Study-II Nutrition Cohort or Nurses' Health Study investigated the interactive effects between fruit and vegetable intake and the polymorphism of CAT, MPO, NOS3, HO-1 and MnSOD. Folate was examined in relation to variant MTHFR genotype 677TT and biomarkers levels of homocysteine concentrations or global DNA methylation. We also reported the gene-diet interaction of breast cancer risk in Korean women; antioxidant vitamins intake may modify the effect of ATM diplotype (ATTGT/ATTGT) or NOS3 genotype (-789 T>C and E298D G>T) on the breast cancer risk. The recent development of epidemiologic findings of gene-diet interaction in breast cancer risk will be summarized.

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#### Notes

## GYNECOLOGIC CANCER I

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### Prevention of Cervical Cancer: Methods and Organization

**Christine Bergeron** *Laboratoire Cerba, Cergy Pontoise, France E-mail : [bergeron@lab-cerba.com](mailto:bergeron@lab-cerba.com)*

#### Abstract

Cervical cancer is one of the rare cancers where there is easy access to the organ and the screening test is simple and relatively cheap. In addition, the slow progress of the disease means that there is a long period of time to detect precancerous lesions before they become invasive. The Pap screening has been very successful and has contributed to the substantial decline in the incidence and mortality of cervical cancer in the developed countries over recent decades. The successes have been particularly important in countries which have implemented population-based screening programmes like European Nordic Countries or United Kingdom. The burden remains particularly high in emerging countries where the coverage is very low because of a lack of resources, education and professionals. Invasive cervical cancer audit shows an absence of cervical screening in 2/3 of cases. Most of those are symptomatic cancers of a higher stage than the screen-detected ones. In the latter, the commonest factor is negative previous cytology of which abnormal cells are found in half of slides on review. In some cases there are delays for colposcopy and/or treatment. It shows the importance of compliance with recommendations for regular screening and investigation that can be best obtained in organized screening programmes. Efforts must particularly focus on improving coverage especially among underprivileged populations. The HPV 16/18 vaccine has been developed thanks to virus-like particles (VLPs) which are non-infectious but which provoke the production of neutralising antibodies. However, the current vaccines only provide protection against 70% of cervical cancers. Also, they do not protect women who are already infected by HPV 16 or 18. This implies vaccinating much earlier than the average age of the first sexual experience. If women are vaccinated between 10 and 15 years old, the time necessary to begin to see the impact on this vaccinated population on the incidence of cervical cancer will be at least 20 years. The time necessary to see the total impact of vaccination, with the entire generation of women having been vaccinated, will be closer to 30-50 years. It is therefore evident that there can be no question of ending screening when vaccination is introduced. The impact of vaccination will also greatly depend on vaccination coverage. The impact of vaccination on cervical screening programme by cytology will be much earlier and depends of the catch up population concerned by the vaccination programme (16-25 years). For the young vaccinated women, primary HPV testing with triage by cytology and prolonged screening interval would be probably the best scenario. HPV screening on self sampled material in women who have not routine Pap screening could also become more important. These issues emphasize the importance of the synergy between prophylactic vaccination for the young and adapted cervical cancer screening test for the non vaccinated women in the future. Only organized programmes will permit to control the coverage of the population and follow appropriately the positive cases.



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### Visual Inspection with Acetic Acid (VIA) and Visual Inspection with Lugol's Iodine (VILI)

**R. Sankaranarayanan** *Early Detection & Prevention Group (EDP) and Screening Group (SCR) International Agency for Research on Cancer (WHO-IARC) France [Sankar@iarc.fr](mailto:Sankar@iarc.fr)*

#### Abstract

Cervical cancer continues to be a major cancer in low and medium resourced countries of sub-Saharan Africa, South and South East Asia and Latin America, despite its high preventability by screening and human papillomavirus (HPV) vaccination. Four fifths of the estimated annual global burden of 500,000 new cases and 280,000 deaths occur in these countries due to lack of effective screening programs. While the currently available evidence supports the introduction of HPV vaccines, there are several challenges such as current high costs that need to be resolved before vaccination can be widely implemented through public health services. Although Pap smear screening has substantially reduced cervical cancer burden in developed countries, the complex inputs in sample collection, processing, reading and reporting of smears required for effective cytology screening and the limited success of cytology screening South and Central America have encouraged evaluation of alternative screening methods such as HPV testing, visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI) as well as new paradigms such as single or twice in a life time screening and single visit approach to maximise treatment of women with precancerous lesions. The visual screening methods are provider dependent tests and thus their test positivity rates have varied between 5-40% in different studies; their sensitivity to detect high grade cervical intraepithelial neoplasia (CIN 2-3 lesions) varied between 30-90% and specificity between 40-90%. The quality assurance for visual screening can be particularly challenging, although nurse and health worker providers can be rapidly trained in performing visual screening. There are several manuals and teaching aids available for training test providers. In a randomized trial in South Africa, cryotherapy for HPV test-positive women resulted in 77% decline in the prevalence of CIN 2-3 lesions, while VIA followed by cryotherapy resulted in a 37% lower prevalence. A single round of VIA screening resulted in 35% reduction in cervical cancer mortality in a randomized trial in South India. The current evidence would suggest that in clinical settings, it may be prudent to use both VIA and VILI as visual screening methods. Visual screening may be implemented in resource poor settings in a phased manner until an affordable and feasible HPV test becomes available as it will help in the development of the infrastructure and



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## GYNECOLOGIC CANCER I

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### How to Treat Preinvasive Cervical Lesions

**Mahmood Shafi** *Department of Gynaecological Oncology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, England CB2 0QQ*  
[mahmood.shafi@addenbrookes.nhs.uk](mailto:mahmood.shafi@addenbrookes.nhs.uk)

#### Abstract

Cervical cancer is both preventable and curable. It has a long natural history with a prolonged pre-cancerous phase that is easily detectable and treatable. Assessment of women presenting with abnormal cervical cytology and the selection of those requiring treatment relies mainly on colposcopic impressions of the cervical transformation zone and histological appraisal of directed punch biopsies. There is variation in the assessment of cytology, colposcopy and histology findings, and therefore the 'final' diagnosis involves all three disciplines. The need to maximise clinical resources, achieve quicker and more effective management of patients, limit postoperative complications and preserve reproductive function has led to the popularity of local excisional methods for cervical premalignancy. Although the cure rates for all local ablative and excisional methods are more than 90% after one treatment, the excisional methods provide a more reliable histopathological diagnosis and the patient may be treated at the initial visit. Cure rates correlate principally with the extent of the cervical intraepithelial neoplasia (CIN).

The conservative methods of treatment are divided into ablative and excisional techniques. The cure rates for both techniques are over 90%. Meta-analyses have shown no obviously superior surgical technique for eradicating CIN and for reducing the risk of future invasive disease.

The aim of treatment is to remove the entire transformation zone (TZ) and the choice of the appropriate techniques relies on the individual case, the colposcopic appearance, depth, severity and size of the lesion, the type of the TZ, the age and the fertility wishes of the woman as well as the clinician's experience and preference and equipment availability.

Recent meta-analyses and large linkage studies revealed that the excisional methods of treatment, namely cold knife cone biopsy (CKC), laser conisation and LLETZ, are related to an increased risk of preterm delivery and low birth weight. LLETZ was also significantly associated with increased risk of premature rupture of membranes. Laser conisation and CKC were also related to an increased risk of perinatal mortality and severe prematurity. Laser ablation and other destructive techniques have no adverse effect. Adverse outcomes are most likely related to the proportion of the cervical volume and endocervical canal that is removed rather than the actual depth of the excision or the individual treatment method. Caution is recommended in the treatment of young women with mild cervical abnormalities and women should be counseled about risks accordingly. Every effort should be made to eradicate the lesion without removing excess healthy cervical tissue.




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human resources required for screening, diagnosis and treatment and as and when the the affordable HPV test becomes available, it may be incorporated as the primary screening test and VIA/VILI may be used for triaging HPV positive women. A simple, user-friendly affordable, faster (results within 3 hours) and accurate HPV test (careHPV test) suitable for use in low-resource settings will be commercially available in the near future.

## CYTOPATHOLOGY

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### Conventional and Liquid Based Techniques in Gynecologic Cytology

**Gamze Mocan Kuzey** *Near East University, Faculty of Medicine, Lefkolia – Turkish Republic of Northern Cyprus*  
*gm\_kuzey@yahoo.com*

#### Abstract

The conventional Pap test has been mainstay of cervical cancer prevention for more than 60 years. The incidence of cervical carcinoma has shown decline due to Pap test screening. By this success, it has been accepted as the most known successful screening test. The success of Pap test depends on the quality of obtaining and fixation of the sample, preparation, and cytologic examination. The success also depends on the performance of the cytopathologist, control of the positive and negative reports and ancillary techniques. Image analysers (rescreening), archiving, consultation and use of common terminology in reporting (Bethesda System 2001) also play an important role. The spectrum of cervical cytologic abnormalities ranges from equivocal changes to the pathognomic nuclear and cytoplasmic effects of HPV infection to severe cytologic neoplastic changes. New alternative technologies, as liquid-based cytology, have lead to increased accuracy in diagnosis. The new technology LCB has certain advantages like better quality of fixation, cleaner background, increased cellularity, less screening period and glass slides and better cellular detail. LBC decreases inadequacy by 50% and increases



LSIL by 50-60% and HSIL by 30-50%. LBC uses immunohistochemistry for p16 for diagnosis. p16 is a cyclin dependent kinase which is not expressed in normal squamous cells and whose expression increases due to genomic expression of HPV. Cytoactiv (HPV L1), a capsid protein antigen, is used for prognosis in HPV. L1 positive cells indicate a remission of lesion and L1 negative cells indicate progression to cancer. LBC-HPV typing is done through DNA extraction, PCR and hybridization. Between 2005 and 2008, using LBC-HPV typing HPV-16 was the most common type of HPV detected at Hacettepe University, Faculty of Medicine, Department of Pathology, Cytology Unit, seen in approximately 45% of cases, followed by HPV-53, -18, -81, -68 and -6. The preliminary results included all cytology groups. The low risk HPV types were 17% and high risk HPV types were 80%. Single HPV infections were observed in 80% and multiple infections were observed in 20% of cases. HPV was detected in 70 out of 128 cases (54.7%). HPV was detected in 7.3% of negative cases. If we scan the worldwide distribution of HPV types in cytologically normal women, Spain has the lowest HPV distribution in the world with 1.4% and Nigeria has the highest distribution with 25.6%. In the very near future, it is probable that HPV will be more integrated in the next Bethesda terminology and cytology.

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### Lessons Learned from Successful Papanicolaou Cytologic Cervical Cancer Prevention in the Socialist Republic of Vietnam

**Eric J Suba, Stephen S Raab** *The Viet/American Cervical Cancer Prevention Project, San Francisco, California, USA*  
*eric.suba@kp.org*

#### Abstract

Background: Cervical cancer is the leading cause of cancer-related death among women in many developing countries. After documenting in 1996 that the Vietnam War had contributed to the problem of cervical cancer in Vietnam, we participated in a volunteer grassroots effort to establish Papanicolaou cytology-based cervical cancer prevention services in southern Vietnam and performed root cause analyses of real-world obstacles to success. After Papanicolaou screening was introduced to southern Vietnam in 1998, cervical cancer incidence rates declined from 29.2/100,000 in 1998 to 16.5/100,000 in 2004. Cervical cancer rates in northern Vietnam, which were judged insufficiently high to warrant mass screening, increased from 4.4/100,000 in 1990 to 9.5/100,000 in 2004. This is one of the first reports of a real-world cervical cancer prevention effort being associated with a decisive impact on health outcomes in a contemporary developing country.



Methods: Root cause analyses were employed to inform the best routes for improving health outcomes among populations for the same reasons that compulsive diagnostic workups are employed to inform the best routes for improving health outcomes among individuals. Because root cause analysis documents that critical real-world obstacles to successful cervical cancer prevention involve people far more than technology, successful disease prevention requires social change far more than technological innovation. We performed an exercise in Positive Deviance, which is an approach to social change that identifies behaviors and strategies used by successful outliers and encourages the adoption of successful behaviors and strategies by others.

Findings: Successful cervical cancer prevention in Vietnam required empowered progressive Vietnamese leadership coupled with an ideological commitment to improving health outcomes as rapidly as possible among as many people as possible. Papanicolaou screening is feasible anywhere cervical screening is appropriate. Cytology will remain an indispensable technological component of all possible preventive solutions to the problem

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## CYTOPATHOLOGY

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### Role of Fine Needle Aspiration in Breast Cancer Diagnosis

#### Roque G Wiseman Pinto

*Past President India Academy of Cytologists, Professor & Head of Pathology- Goa Medical College, Goa- India, Professor Incharge - Medical Education Cell, Goa Medical College. rgwpinto@gmail.com*

#### Abstract

Breast cancer is the commonest cancer in women in Urban parts of India whereas in rural areas of India the Cancer of the Cervix is the commonest cancer in women.

In Goa breast cancer is the commonest cancer in women with the change in life style, diet, habits and environment. Breast Cancer Diagnosis and Prevention has now become an important part of Public Health Care in different parts of the world.

Fine Needle Aspiration Cytology ( FNAC) an important modality in the diagnosis of breast Cancer is highly cost- effective, efficient , rapid,& painless. Around 70 % to 80% of breast cancers in the developing countries present with palpable masses and FNAC is the most & efficient method of diagnosis combining with clinical examination and sonomammography. FNAC material can also be used to perform ancillary studies, such as immunostains, molecular and genetic studies.

FNAC is definitely useful both in diagnosis as well as typing the breast cancer, histologicxally such as Infiltrating duct Carcinoma , Lobular Carcinoma, Colloid Carcinoma, Metaplastic Carcinoma, Neuro endocrine Carcinoma , Lymphoma, Sarcoma, as well as in grading the breast cancer.

FNAC also helps in Prognosticating the tumor. A Positive diagnosis of Cancer is definitive, when used along with Clinical examination and sonomammography. A Negative diagnosis on cytology would require a further histopathological evaluation. Smears of nipple discharge are also used in diagnosis. FNAC is also beneficial to diagnose metastases of breast cancer in axillary as well as other lymph nodes, subcutaneous metastases, metastases in other sites and organs as well as recurrent breast cancer and cancer in the contralateral breast. FNAC is definitely still a revolutionary modality in the diagnosis of primary breast cancer, as well as metastases & recurrence.

However, the FNAC must be done by an experienced cytologist with the proper technique & expertise. An experienced Cytopathologist would bring down the false positive and false negative rates and make the diagnosis very accurate, specific & sensitive. This will go a long way in the health Care Management of Breast Cancer in different Countries of the world. FNAC technique could be aspiration or non aspirating (Capillary), as well as image guided or non image guided. established 10-year cancer control plan (2006-2015). This 10-year Plan for Cancer Control aims at decreasing cancer mortality in year 2015 through comprehensive control program and full government support regarding health equity, and alignment with worldwide effort for cancer control.




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#### Notes

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of cervical cancer. It is uncertain whether liquid-based collection systems, visual screening methods, or HPV screening will improve on the performance of Papanicolaou screening for cervical cancer prevention. It will not be known for many more years whether HPV vaccination will prevent cancer or, in the worst case, do harm. Nobel laureate Harald zur Hausen predicts that even the best-case scenario of HPV vaccination will require booster doses.

Conclusions: If our goal is to improve health outcomes as rapidly as possible among as many people as possible, then Papanicolaou screening services (with or without non-cytologic screening services) should be implemented without further delay in any setting where cervical screening is appropriate but unavailable, with consideration given to HPV vaccination after, rather than before, the possibility has been excluded that HPV vaccination may be ineffective for cervical cancer prevention, or full coverage of target demographic groups by screening services has been achieved, whichever happens first. Competing ideological commitments embraced by the Bill & Melinda Gates Foundation engender dangerous alternative strategies that may decelerate global reductions in cervical cancer-related mortality. Problems that find solution when given several thousand dollars of philanthropic donor support earmarked for development may resist solution when given many millions earmarked for research. Money, like other health interventions, has a therapeutic index.

## MIDDLE EAST CHILDRENS CANCER ASSOCIATION

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### **Pediatric Acute Myeloid Leukemia: Current and Future Approaches to Treatment**

**Franklin O Smith** *Cincinnati Children's Hospital Medical Center and University of Cincinnati College of Medicine, Ohio, USA frank.smith@cchmc.org*

#### **Abstract**

Pediatric acute myeloid leukemia (AML) is a highly heterogeneous disease with variable presentation and clinical outcomes. AML is characterized by significant biologic complexity with a large number of genomic and epigenomic alterations. Over the past several decades, cooperative pediatric cancer groups worldwide have optimized the use of cytarabine, anthracyclines, allogeneic hematopoietic stem cell transplantation and supportive care, with cure rates now approaching 60%. It is unlikely that further significant improvements in outcome will result from refinements of these modalities. Current efforts are now focused on risk group identification with risk-based therapy, new approaches to treatment based on biologic targets and more selective use of allogeneic transplantation. Towards these ends, there has been outstanding recent progress defining high-, intermediate- and low-risk groups based on: response to therapy and measurements of minimal residual disease; cytogenetics; and an ever evolving number of molecular and genetic abnormalities, well exemplified by mutations in FLT3, nucleophosmin, c-kit and CEBPA. New approaches to treatment are targeting a multitude of targets, including cell surface antigens, FLT3 and proteasome inhibition, as examples. Allogeneic transplantation is no longer utilized for cytogenetically determined good-risk patients in CR1 whose AML is characterized by core-binding factor abnormalities. While the use of matched related donors are still used for intermediate-risk patients in CR1, the role of allogeneic transplantation for high-risk patients is currently the subject of prospective clinical trials.



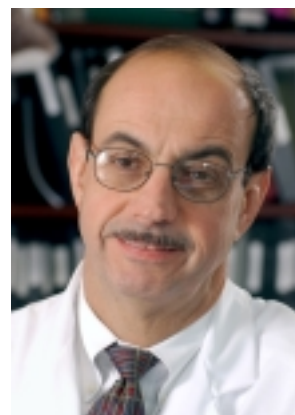
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### **Pathogenesis and Epidemiology of Acute Myeloblastic Leukemia (AML)**

**Joseph Mirro** *Vice President Cancer Services, Aurora Health Care, Milwaukee WI, USA Clinical Professor of Pediatrics, Children's Hospital of Wisconsin, University of Wisconsin, Milwaukee School of Medicine joseph.mirro@aurora.org*

#### **Abstract**

The epidemiology of AML will be reviewed, but the frequency, morphology, and pathogenesis appears identical in developed and developing countries. Our therapeutic success and cure of AML has been much slower than other types of leukemia. This undoubtedly results from the complex molecular pathogenesis of AML with its inherent resistance to standard chemotherapy. The recent identification of molecular abnormalities in AML is increasing our understanding of molecular pathogenesis and providing new therapeutic options. AML has a stable genome and unlike childhood ALL, cases of AML contain less recurring copy number abnormalities, less gene deletions, and less gene duplications. Also unlike childhood ALL that often contain recurring molecular abnormalities in differentiation pathways [for example: abnormalities of PAX 5 or IKZF1 (Ikars) which occur in 60% of B-cell ALL cases] AML cases do not have recurring focal pathway abnormalities. However, the widespread adoption of the WHO classification of AML has improved our ability to identify good, standard, or poor prognosis AML as a result of a limited number of recurring genetic translocation.



Recent investigations have advanced this classification by demonstrating that specific molecular abnormalities such as mutated NPM1, FLT3-internal tandem duplications (FLT3-ITD) mutated KIT effect prognosis within known cytogenetic prognostic groups. Molecular abnormalities are now becoming extremely important in the 45% of AML cases that have normal karyotype. Specific molecular abnormalities are permitting the stratification of AML cases with normal karyotype into prognostic groups and more importantly are suggesting targeted therapeutic approaches.

The potential biological effects of selected molecular abnormalities will be presented and discussed (e.g., the FLT-3 signal transduction pathway will be reviewed). Since the molecular abnormalities in childhood AML cases appear similar to those found in adult AML cases (as has been shown for phenotype, cytogenetic translocations, prognosis and response to therapy), there is a great deal we can learn from adult studies. Adult clinical data demonstrating the adverse prognosis of mutated KIT or the relatively good prognosis of mutated NPM1 and CEBPA in patients on standard chemotherapy will be reviewed. However, the effects of these molecular abnormalities are complex and, since many cases have multiple abnormalities, the effects of multiple abnormalities in single cases will also be discussed. Finally, adult studies suggest potential therapeutic approaches such as the selected use of the HD Ara-C (in patients with CBF abnormalities), mylotarg in slow responders having t8:21 and inv. 16, Sirafenib (NexavorR), and FLT-3 inhibitors (CEP-701) in patients with FLT3-ITD or FLT3 mutations and Dasatinib (in patients with CBF AML). It is becoming clear that AML often contains multiple molecular abnormalities and our treatment may have to be specifically targeted to the abnormalities identified in each case.

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## MIDDLE EAST CHILDRENS CANCER ASSOCIATION

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### Myelodysplastic Syndromes in Children

**Yaddanapudi Ravindranath** *Children's Hospital of Michigan and Wayne State University School of Medicine. Detroit, Michigan, USA. ravi@med.wayne.edu*

#### Abstract

The myelodysplastic syndromes (MDS) are a group of clonal disorders characterized by ineffective haematopoiesis, cytopenias, morphologic dysplasia and leukemic transformation. FAB and WHO classifications are generally used for classifying and prognosticating MDS. These systems are largely based on adult MDS. In contrast to adults, de novo MDS is less common in children and more often arise on the background of congenital/constitutional disorder. Hypoplasia of marrow is seen more often than hyperplasia. In childhood, MDS, accounts for less than 5% of all hematopoietic neoplasms in patients less than 14 years of age (Niemeyer, Katz; BJH 2008). To accommodate for the characteristics of pediatric MDS, a simple classification scheme based on morphological features and conforming with the WHO suggestions was proposed. Refractory Anemia (RA) with ringed sideroblasts and MDS associated with del(5q) chromosome are exceedingly rare in children. Presentation with neutropenia and thrombocytopenia (Refractory Cytopenia-RC) is more common than with RA. To accommodate these characteristics of pediatric MDS, a simple classification scheme based on morphological features and conforming with the WHO suggestions was proposed (Hasle et al, 2003). It recognizes three diagnostic groups: RC (BM blasts <5%), RAEB (BM blasts 5–20%) and RAEB-T (BM blasts 20–30%). Myeloid leukaemia developing in a patient previously diagnosed with MDS is referred to as myelodysplasia-related AML (MDR-AML, BM blasts  $\geq$ 30%). The dysplastic prodrome of AML in Down syndrome is classified within myeloid leukaemia in Down syndrome and excluded from population-based studies of MDS. Per definition, 'secondary' MDS describes MDS following chemo- or radiation-therapy, congenital BM failure disorders, or acquired aplastic anaemia and that in familial disease. All remaining cases are referred to as 'primary' MDS although predisposing genetic lesions may have to be presumed in these cases as well. The molecular pathology of the bone marrow failure syndromes suggest that defects in DNA repair, disordered ribosome biogenesis and telomere maintenance play a central role in the development of MDS. Therapy of MDS is based on underlying cause. For example the MDS of Down syndrome is highly curable with chemotherapy. For RC associated with BM failure syndromes, stem cell transplantation remains the only curative option.



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#### Notes

## LUNG GENETIC FACTORS

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### Genetic Susceptibility in Lung Cancer

**Ismail Savas** *Ankara University, The Faculty of Medicine, The Department of Chest Diseases , Ankara savas@medicine.ankara.edu.tr*

#### Abstract

Lung cancer is the most common cause of cancer death in the world. Lung cancer has been shown as an example of a malignancy which is determined by the environment, cigarette smoking, certain occupation, asbestos exposure, shipbuilding and petroleum refining. Cigarette smoking is the main reason of lung cancer. Recently dietary factors , enviromental tobacco smoke (passive smoking) have been shown to be associated with increased risk factors of lung cancer. Shopland et al. Showed that 90 % of lung cancer in men and 78% in women were directly attributable to tobacco smoking. Tokuhata and Lilienfeld showed epidemiologic data for familial aggregation of lung cancer over 40 years ago. They found a relative risk of 2-2.5 for mortality due to lung cancer in cigarette smoking relatives of cases as compared to smoking relatives of controls. We investigated the family predisposition for lung and other cancers, additionally the relationship of this predisposition to age, gender, smoking habits and cell types. Positive family history for cancer estimated in 38% of 213 individuals with lung cancer. In these individuals, 41.9% had lung cancer, 19% had gastrointestinal system cancer, 7.6% had breast cancer, 5.7% had prostate cancer, 25.7% had other system cancers (larinx, skin, bone, hematologic system, central nervous system). In control group, positive family history for the cancer was 21.5% and this was statistically significant ( $p < 0.001$ ). In the family members of patients with lung cancer, the risks of lung, gastrointestinal system and breast cancer development were increased. The presence of head-neck, bladder, prostate, lung and kidney cancers in the history of the patients increase the risk of lung cancer, supporting the genetic transition. Genetic susceptibilty could be modulated by genetic variants in genes involved in many cellular process such as carcinogen metabolism, DNA repair, cell cycle checkpoint control, apoptosis, telemore integration and microenvironment control. There are a few phase I and II xenobiotic enzymes metabolized the tobacco carcinogens. These are CYP1A1, CYP1B1, CYP2A6, CYP2A13, CYP2C9, CYP2D6, CYP2E1, Myeloperoxidase, GST ( glutathion s transferase family) , NAT ( N-acetyl transferases family), UDP- glucuronyl transferase family , Sulfotransferase family. DNA damage and repair capacity is crucial to maintain genomic integrity. Common genetic variants in genes involved in repair pathways have been reported in many lung cancer susceptibility studies. Cell cycle regulatory network is essential for cells to undergo replication, division, proliferation and differentiation. Abnormalities of cell cycle regulation genes are observed in a variety of human malignancies including lung cancer. Apoptosis plays an important role in cellular defense mechanism. Telomere and telomerase, tumor microenvironment, inflammation, growth factors, methylation related genes are also contribute to lung cancer susceptibility models.



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### Is Familial Risk a Question?

**Tuncay Göksel** *Ege University, Medical School, Dept. of Pulmonary Medicine Izmir, Turkey tuncay.goksel@ege.edu.tr*

#### Abstract

Lung cancer is an increasing problem in the whole world. The rise in the incidence of lung cancer has been closely linked to increased cigarette smoking. Approximately, fewer than 15% of all smokers develop lung cancer, 10% of the patients are non-smokers. Except environmental etiological factors, it is obvious that individual predisposition creates risk. This individual predisposition can be related to genetic or familial susceptibility. The familial component to lung cancer risk has been investigated in many case-control studies for a long time. In these studies, the odds ratio of family history ranges from 1.3 to 7.2. Sharing environmental exposures can contribute to this rise in familial lung cancer risk. Even after adjusting for environmental risk factors, it has been shown that the risk of lung cancer increases among first degree relatives. Also, the increasing risk leads to onset of lung cancer in earlier years. Furthermore, combination of cigarette smoking and family history cause to increase the risk of lung cancer.



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## LUNG GENETIC FACTORS

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### Risk Assessment of Carcinogenetic Hazards

**Ismail Celik**

*Hacettepe Univ. Inst. of Oncology, Dept. of Preventive Oncology, Ankara-TURKIYE cismail@hacettepe.edu.tr*

#### Abstract

Risk assessment comprises four components: hazard identification, dose response assessment, exposure assessment and risk characterisation. The term toxicity assessment is sometimes used as an alternative to refer to both hazard identification and dose-response assessment. Information about classification of chemicals according to their carcinogenicity are conducted by different international organizations:

I) IARC classification involves 5 main categories according to carcinogenetic potentials of substances: Group 1: Carcinogenic to humans, Group 2A: Probably carcinogenic to humans, Group 2B: Possibly carcinogenic to humans, Group 3: Unclassifiable as to carcinogenicity in humans, Group 4: Probably not carcinogenic to humans.

II) NTP report groups carcinogens under two main categories, and substances that are not found to be a carcinogen are not listed: 1) Known to be human carcinogens: There is sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer. 2) Reasonably anticipated to be human carcinogens: There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded, or there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors.

III) EPA guidelines recognise three broad categories of data for hazard identification for carcinogens: (1) human data (primarily epidemiological); (2) results of long-term experimental animal bioassays; and (3) supporting data, including a variety of short-term tests for genotoxicity and other relevant properties, pharmacokinetic and metabolic studies, and structure-activity relationships. In hazard identification of carcinogens human data, animal data, and supporting evidence are combined to characterize the weight-of-evidence regarding the agent's potential as a human carcinogen into one of several hierarchic categories: Group A: Carcinogenic to Humans: Agents with adequate human data to demonstrate the causal association of the agent with human cancer (typically epidemiologic data). Group B: Probably Carcinogenic to Humans: Agents with sufficient evidence (i.e., indicative of a causal relationship) from animal bioassay data, but either limited human evidence (i.e., indicative of a possible causal relationship, but not exclusive of alternative explanations; Group B1), or with little or no human data (Group B2). Group C: Possibly Carcinogenic to Humans: Agents with limited animal evidence and little or no human data. Group D: Not Classifiable as to Human Carcinogenicity: Agents without adequate data either to support or refute human carcinogenicity. Group E: Evidence of Non-carcinogenicity for Humans: Agents that show no evidence for carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.



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#### Notes

## PREVENTION APPROACHES

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### Chemoprevention by Foods

**Omer Kucuk**

*Winship Cancer Institute of Emory University, Atlanta, GA, USA*

#### Abstract

It is estimated that thirty-five percent of all cancers are attributable to dietary factors. Dietary intake of vegetables and fruits has been associated with a decreased risk of certain cancers. In addition, Mediterranean diet rich in vegetables, fruit, fish, olive oil, olives and tomato products has been associated with a lower cancer risk. Asian diet rich in soy products is another example of a cancer preventive diet. However, the precise anti-cancer role and mechanisms of various dietary compounds have not been completely elucidated. Specific dietary compounds such as carotenoids, isoflavones, and polyphenols have been investigated in cell culture and animal model studies as well as clinical trials. Among carotenoids, lycopene has been found to have potential chemopreventive effects in several cancers. Among soy isoflavones, genistein has been associated with potent anti-tumor and cancer preventive effects. Other promising chemopreventive compounds in foods include green tea polyphenols, curcumin, and indole-3-carbinole. Synergistic effects of different chemopreventive compounds in the diet have been reported. It is very important to investigate potential chemopreventive and therapeutic effects of a wide range of dietary compounds alone and in combination in well designed pre-clinical and clinical studies. Mechanistic studies should be included to understand mechanisms of action of these compounds as well as discovery of new biomarkers which may be modulated by dietary compounds. Recent recognition of epigenetics as a central issue in cancer biology and potential modulation of epigenetic factors by dietary compounds will be discussed.



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### Surgical Prevention

**Iskender Sayek** *Department of Surgery, Hacettepe University School of Medicine*

#### Abstract

Surgery is the most important treatment modality in the treatment of various organ cancers. Surgery may as well be used for prevention of cancer for certain organs and pathologies. It can be used as a method both for primary and secondary prevention. Primary prevention includes interventions before cancer develops, whereas secondary prevention includes interventions at the early stage and steps taken to prevent cancer recurrence. The risk factors or presence of premalignant pathologies have to be determined in order to use surgery for prevention of cancer. The best examples for primary prevention of breast, colorectal and cervical cancer.

Breast cancer which is the most common cancer in women. A strong family history is an important risk factor for breast cancer especially with the presence of BRCA1/2 mutations. Besides chemoprevention prophylactic mastectomy is an option for prevention, which involves the removal of most of the breast epithelium. Potential indications are presence of atypical lobular or ductal hyperplasia or lobular carcinoma in-situ and those with an increased genetic risk based on BRCA1/2 mutation or strong family history.

Bilateral prophylactic mastectomy has been shown to be effective to reduce the development of breast cancer in high-risk women. Various methods of mastectomy could be used for prevention which could be based on the patient's decision. Contralateral mastectomy in women with breast cancer have also been performed for prevention. A Cochrane systematic review on prophylactic mastectomy for the prevention of breast cancer concludes that prophylactic mastectomy is effective in reducing the incidence of, and death from breast cancer but more rigorous prospective studies are needed. Prophylactic oophorectomy as well could be used in breast cancer prevention.

Colorectal cancer prevention as well could be achieved with surgery. This could either be primary or secondary prevention. Patients with familial polyposis syndromes or with chronic ulcerative colitis Colectomy or proctocolectomy is indicated virtually in all patients with classical form of familial adenomatous polyposis. Patients with chronic ulcerative colitis also deserves a colectomy or proctocolectomy for cancer prevention.

Some other pathologies as well could be treated surgically for prevention of cancer development which will be discussed during the presentation.



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## PREVENTION APPROACHES

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### Chemoprevention of Inflammation-Associated Cancer

**Young-Joon Surh**

*WCU Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Sciences and College of Pharmacy, Seoul National University, Seoul 151-742, South Korea surh@plaza.snu.ac.kr (surhyoungjoon@yahoo.co.kr)*

#### Abstract

There are multiple lines of compelling evidence supporting the association between inflammatory tissue damage and cancer. A new horizon in chemoprevention research is the recent discovery of molecular links between inflammation and cancer. Components of the cell signaling network, especially those converge on the ubiquitous eukaryotic redox-sensitive transcription factor, nuclear factor-kappaB (NF- $\kappa$ B), have been implicated in pathogenesis of many inflammation-associated disorders. Chemoprevention is an attempt to use either naturally occurring or synthetic substances to intervene in or halt the progress of carcinogenesis, before the malignancy manifests. Numerous phytochemicals derived from dietary and medicinal plants have been reported to inhibit, retard, or reverse a specific stage of the carcinogenic process. A wide array of molecules and events are involved in relaying intracellular signals to maintain cellular homeostasis. Cancer arises when fine-tuning of the sophisticated cellular growth signaling network is deregulated or disrupted. Since the intracellular signaling network often goes awry in carcinogenesis, it is fairly rational to target the cell signaling cascades for achieving chemoprevention. Targeted modulation or restoration of the specific intracellular signaling pathways by use of phytochemicals thus offers a unique strategy for preventing abnormal cell proliferation and other malfunctions associated with multistage carcinogenesis. A wide variety of chemopreventive and chemoprotective agents can alter or correct undesired cellular functions caused by abnormal pro-inflammatory signal transmission mediated by NF- $\kappa$ B. Modulation of cellular signaling involved in chronic inflammatory response by anti-inflammatory agents hence provides a rational and pragmatic strategy in molecular target-based chemoprevention and cytoprotection. Nuclear transcription factor erythroid 2p45 (NF-E2)-related factor 2 (Nrf2) plays a crucial role in up-regulating cytoprotective gene induction. Many chemopreventive substances derived from edible plants have been found to activate this particular redox-sensitive transcription factor, thereby attenuating inflammatory damage and tumorigenesis.



**References:** 1. Surh Y-J (2003) Cancer chemoprevention with dietary phytochemicals. *Nature Reviews Cancer* 3: 768-780. 2. Kundu, J.K., Na, H.-K., and Surh, Y.-J. (2008) Intracellular signaling molecules as targets of selected dietary chemopreventive agents. In: *Dietary Modulation of Cell Signaling Pathways* (Y.-J. Surh, Z. Dong, E. Cadenas, and L. Packer, Eds.), CRC Press-Taylor & Francis, pp. 1-44. 3. Kundu, J.K. and Surh, Y.-J. (2009) Chemoprevention with dietary phytochemicals: redox-sensitive transcription factors as prime targets. *Phytochem. Rev.*, 8: 333-347

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#### Notes

## GYNECOLOGIC CANCERS II

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### Genetic Basis of Gynecologic Cancers

**Walter H. Gotlieb**

*Segal Cancer Center, McGill University, Montreal Canada. walter.gotlieb@mcgill.ca*



#### Abstract

**Background:** A better appreciation of the molecular changes involved in gynecologic cancers, provides opportunities to understand clinical behavior and response to treatment, and is becoming the basis for the development of new approaches to prevention, screening, diagnosis, and targeted therapies.

**Endometrial cancer:** The most frequent genetic alteration reported in type I or endometrioid cancers (80%) is in the tumor suppressor gene PTEN. In addition PI3K activating mutations are seen in about one third of cancers, and are most common in tumors that also bear a PTEN mutation. Other genetic changes, occasionally can coexist with PTEN mutations, including mutations in K-ras (10-30%), and microsatellite instability (up to 40%). In families with hereditary type I endometrial cancer (i.e. HNPCC), the cause is due to germline mutations of these genes, whereas in the somatic cases, the cause is mainly inactivation due to hypermethylation of the MLH1 gene. Finally, a gain in function mutation in the  $\beta$ -catenin gene, is another genetic alteration that is present in 20-40% of cancers. On the other hand, serous endometrial cancers, also called type II cancers, have a completely different molecular background and are associated in 80-90% with p53 mutations, 45% with inactivations of p16, 70% with Her2/neu gene amplifications, and 60% have reduced E-cadherin expression.

**Ovarian cancer:** two major paradigm shifts in our understanding of the pathogenesis of epithelial ovarian cancer (EOC) were lately introduced, based on clinical, pathological, and molecular genetic studies. EOC were considered to be derived from malignant transformation of the epithelium of the ovarian surface, which is contiguous with the peritoneal mesothelium. An as yet undefined proportion of high grade serous tumors are now known to arise from the fallopian tube. EOC tumors are further divided into 2 groups. Group I type EOCs are slow growing tumors, generally confined to the ovary at diagnosis, that develop from low grade tumors. Drastically different, are the group II type tumors, which are rapidly growing, highly aggressive neoplasms, believed to arise de novo, with no detectable precursor lesions. This difference has crucial implications for screening, as it is believed today that group II tumors transit extremely rapidly to diffuse disease, not allowing enough time for presently available screening techniques or early detection. Type I, or proliferative serous tumors, are characterized by sequential mutations in K-ras, B-raf, and HER2/neu oncogenes. In contrast, these genes are not mutated in the type II, or high grade serous carcinomas (HGSC). These tumors are characterized by mutant p53, in greater than 80% of cases. It has also been recently reported that HGSC may develop from p53 mutated intraepithelial carcinomas in the fallopian tube. Mutations of BRCA genes constitute the basis for the most common hereditary HGSCs. In addition, somatic dysfunctions of the BRCA genes (mostly by LOH and/or promoter hypermethylation) have been described in sporadic HGSCs .

**Cervical cancer:** This cancer is very particular: it is caused by the HPV virus, the molecular pathway involved is well established, screening can detect pre-cancerous lesions, and a vaccine is available for prevention.

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### Screening for Ovarian Cancer, the UK Experience

**Ranjit Machanda** *UK*

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## GYNECOLOGIC CANCERS II

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### Krukenberg Tumors and Pseudomyxoma Peritonei

**Soon-Beom Kang**

*Seoul National University College of Medicine, Seoul, Korea ksboo308@plaza.snu.ac.kr*

#### Abstract

I. Krukenberg tumor: A tumor of the ovary caused by the spread of malignancy whose primary site arose in the gastrointestinal tract. When cancer spreads to an ovary, the tumor in the ovary is called a Krukenberg tumor. The Patients often come to the attention of their doctor when they present complaining of abdominal or pelvic pain, bloatedness, vaginal bleeding, a change in their menstrual habit or pain during intercourse. These symptoms are non-specific and a diagnosis can only be made following CT scans, laparotomy and/or a biopsy of the ovary.

There is some debate over the exact mechanism of metastasis of the tumor cells from the stomach, appendix or colon to the ovaries; recently some researchers have suggested that lymphatic, or hematogenous spread is more likely, as most of these tumors are found on the inside of the ovaries.

An important clue that differentiates primary tumors from metastatic tumors is bilaterality. Other predominant features of metastatic tumors often involve the presence of signet ring cells, surface involvement by tumor cells, and extensive extra-ovarian tumor, whereas features of primary ovarian neoplasms include smooth external surfaces as well as a complex papillary pattern. Management of the tumor must involve finding and treating the primary cancer. In general, most cases of Krukenberg tumor have a poor prognosis and radical operation such as removal of the ovaries can improve survival only in cases of solitary ovarian metastasis or local extended disease. Cancer chemotherapy and radiotherapy before surgery may be used to shrink the tumor and facilitate its removal.

II. Pseudomyxoma peritonei: Pseudomyxoma peritonei (PMP) is an uncommon tumor known for its production of mucus in the abdominal cavity. Unlike most cancers, PMP rarely spreads through the lymphatic system or through the bloodstream. PMP is most commonly associated with cancer of the appendix; mucinous tumors of the ovary have also been implicated. Symptoms may include abdominal or pelvic pain and/or bloating, distension, digestive disorders, weight changes, increased girth and infertility. Diagnosis is confirmed through pathology. Diagnostic tests may include CT scans, and the evaluation of tumor markers. A distinctive feature is its distribution in the abdomen. The tendency is to spare the peritoneal surfaces of the bowel, whereas large-volume disease affects the greater omentum, right hemidiaphragm, right retro-hepatic space, ligament of Treitz, left abdominal gutter, and pelvis.

Treatment for PMP ranges from watchful waiting to debulking and cytoreductive surgery. Most commonly, treatment for PMP involves surgery performed by specific specialists trained in treating this disease. When appropriate, surgery may include intraperitoneal hyperthermic chemotherapy, or post operative systemic chemotherapy. In debulking procedure, the surgeon attempts to remove as much tumor as possible, while cytoreductive surgery involves surgical removal of the peritoneum and any adjacent organs which appear to have tumor seeding. Chemotherapy may be recommended following debulking procedure. PMP may recur following surgery and chemotherapy. Oral and intravenous chemotherapy has become more commonly used during the past five years. Some patients have experienced stability in tumor growth through treatment with various systemic chemotherapies.




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## PATHOLOGY

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### The Pattern of HPV in Malaysian Cervical Cancer

**Lai-Meng Looi** *Department of Pathology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; email: looilmm@ummc.edu.my*

#### Abstract

Cervical carcinoma is the second leading cancer among Malaysian women, constituting 11% of female malignancies. Histologically, the majority are squamous carcinoma and adenocarcinoma (and variant forms). Adenocarcinoma has been increasing in prevalence and now forms >30% of cervical carcinomas compared to 25% in early 1990s. Ethnic variations also occur. Human papillomavirus (HPV) is recognised globally as an important causative agent. HPV 16 and 18 are the most frequently encountered types although population variations are recognized. With licensing of HPV vaccines, it is vital to establish local HPV profiles for better prevention planning. There is scanty published work on HPV in Malaysian cervical carcinoma except for 2 studies which reported HPV 16 in about 75% and HPV 18 in 40-65% of cervical cancers. For further clarification, a study was undertaken at the University Malaya Medical Centre (UMMC), Kuala Lumpur using a two-pronged approach comparing archived formalin-fixed, paraffin-embedded cervical carcinoma material with fresh cancer material.



Genomic study: The 2 cohorts were investigated by HPV PCR using type-specific primers to HPV 6, 11,

16 and 18. All positive cases were confirmed via dot blot hybridization using cloned digoxigenin-labeled whole genomic probes. Negative cases were subjected to PCR for HPV L1 ORF (as a screening test for any HPV type). HPV PCR was performed only on material with successful amplification of the ubiquitous beta-globin gene. Normal cervix tissue from non-malignant hysterectomies served as controls. The b-globin segment was detected in only 24% of archived paraffin-embedded cancers compared with 100% of fresh tissue, indicating reduced DNA viability in archived tissues. HPV was detected in 69% archived cases, 88% fresh cases and 5% of normal cervixes. HPV 16 was the most common type in both cohorts, comprising 79% and 55% of HPV in archived and fresh cases respectively. HPV 18 formed 5% of HPV types in archived and 13% in fresh cases. Together HPV 16 and 18 accounted for 84% and 68% of HPV in archived and fresh cases respectively. Other HPV types constituted 16% of HPV types in archived versus 32% in fresh cases. HPV was detected more frequently in squamous carcinoma (82%) than adenocarcinoma (71%). In both, HPV 16 was the most common type. Notably, HPV 18 was more prominent in adenocarcinomas (25% of HPV types) compared with squamous carcinoma (7% of HPV types). HPV visualization: Using the same genomic probes as dot blot hybridization HPV 16 was successfully detected in CaSki cells and HPV 18 in HeLa cells. A comparison of NISH with gold standard PCR showed 90% concordance, which augurs well for NISH as a detection method in routine histopathology.

In summary, studies at the UMMC show that HPV occurs in >80% of cervical carcinoma, with HPV 16 being the most common type and HPV 16+18 constituting about 70% of HPV types. These figures are similar to most populations worldwide. HPV 18 is encountered more commonly in adenocarcinoma compared with squamous carcinoma. An increasing prevalence of adenocarcinoma since mid 1990's is noted and deserve further investigation

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### Fine Needle Aspiration Biopsy of Hepatocellular Carcinoma: Diagnostic Issues and Challenges

**Aileen Wee** *Department of Pathology, Yong Loo Lin School of Medicine, National University of Singapore National University Hospital, Singapore aileen\_wee@nuhs.edu.sg*

#### Abstract

Major diagnostic issues in liver fine needle aspiration biopsy (FNA) are: (i) distinction of benign hepatocellular nodules, namely, large regenerative nodule, dysplastic nodule, focal nodular hyperplasia and hepatocellular adenoma, from reactive hepatocytes, (ii) distinction of well-differentiated HCC (WD-HCC) from benign hepatocellular nodules, (iii) distinction of poorly differentiated HCC (PD-HCC) from intrahepatic cholangiocarcinoma (CC) and metastatic carcinomas, (iv) determination of histogenesis of malignant tumour, and (v) determination of primary site of origin of malignant tumour.

The role of percutaneous guided FNA in the diagnosis of HCC has evolved. Advances in imaging modalities have obviated the need for tissue confirmation in clinically obvious cases of HCC (EASL, Barcelona, 2000). Tissue characterization of small well-differentiated hepatocellular nodules (< 2 cm size) detected on surveillance of high-risk cirrhotic patients is the new challenge. Risk of needle track implantation has led to increasing popularity of core needle biopsy. Endoscopic ultrasound-guided FNA (EUS-FNA) is the latest diagnostic and staging tool. It can access left lobe of liver, hilum, proximal right lobe, gallbladder, extrahepatic biliary system and perihilar lymph nodes. This technique is useful for small and deep-seated left lobe lesions below CT/MRI resolution or not accessible to percutaneous FNA. As such, EUS-FNA is good for early detection of multifocal HCC in cirrhosis and accurate number of lesions (intrahepatic staging of HCC) for transplantation eligibility purposes.



Optimal results are obtained with dedicated radiologist/endosonographer-cytopathologist team on-site; combined cytohistological approach;

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## PATHOLOGY

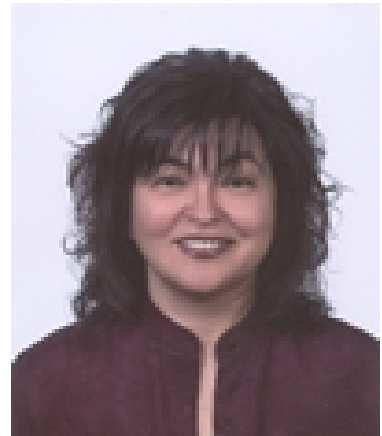
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### Preinvasive Epithelial Lesions of the Lung

**Serpil Dizbay Sak** *Ankara University Medical School, Department of Pathology sak@medicine.ankara.edu.tr*

#### Abstract

Lung cancer is the most common cancer in the world. The most effective treatment is surgery for non-small cell lung carcinoma, but more than 70% of the patients have unresectable advanced disease at the time of diagnosis. The mortality of lung cancer have not significantly improved in the last decades, despite new drugs and development of multidisciplinary therapeutic approaches. Improving the survival rate requires understanding of early steps of carcinogenesis and detecting high risk patients. Lung carcinogenesis is a multistep process leading to an accumulation of molecular abnormalities due to exposure to carcinogens, mainly related to tobacco. There are some morphological changes paralleling the accumulation of molecular abnormalities which are defined as preneoplastic lesions. There are three recognized preneoplastic lesions in the lung, the first two being bronchial squamous dysplasia / in situ carcinoma, preceding invasive squamous cell carcinoma (SCC) and basaloid carcinoma; and atypical adenomatous hyperplasia (AAH), representing the preneoplastic condition for a subset of adenocarcinoma, namely bronchioloalveolar carcinoma (BAC). Pathogenesis of SCC begins with allelic loss of multiple tumor suppressor gene loci in normal appearing epithelium of smokers; followed by telomere attrition in squamous metaplasia; telomerase reactivation, p53 /p16 inactivation and cyclin D1 / E overexpression in different stages of dysplasia, resulting in carcinoma in situ and invasive cancer at the end. On the other hand, the pathogenesis of adenocarcinoma involves at least two different pathways depending on the smoking status. The non-smoker pathway involves mutations and /or amplifications of EGFR; the other pathway which is most frequently observed in smokers, requires K-ras mutations and p53 and p16 inactivation. However, these pathways are related with the development of peripheral adenocarcinoma, whereas pathogenesis of central and mucinous adenocarcinoma is not determined. The third and last preneoplastic lesion in the lung is diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH), that has been associated with a higher rate of carcinoid tumors and represents a putative precursor for pulmonary carcinoids. There is no molecular marker to distinguish DIPNECH from reactive neuroendocrine proliferation. Currently, there is no morphological lesion that has been described as a precursor for small cell lung carcinoma, which comprise about 20% of pulmonary carcinomas.




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#### Notes

judicious use of immunohistochemical tests; and close clinicopathological correlation. On-site service provides rapid smears for assessment of adequacy and triage of specimens. Smears are air-dried and stained with May-Grünwald-Giemsa (MGG) as well as fixed in 95% alcohol and stained by the Papanicolaou method. Particulate material is retrieved and formalin-fixed for cell block preparation. FNA needles with guillotine mechanism may provide microbiopsy cores.

HCC is highly heterogeneous - variants include HCC with fatty change, small cell change, and clear cell, sarcomatoid and giant cell types. Combined HCC-CC is rare. Aspirating different parts of the tumour may yield more classic features; thus, obviating the need for costly ancillary tests. Various tumours may mimic HCC and its variants. Cytological features of malignancy are wanting at WD-HCC end whereas resemblance to hepatocytes is lacking at PD-HCC end. A pitfall is the "nodule-in-nodule" lesion in which a HCC subnodule arises within a "parent" nodule, be it dysplastic or regenerative; raising the issue of adequacy of FNA evaluation given the focality of proliferative clones within such nodules. Small HCC, like the other hepatocellular nodules, are prone to fatty change. Cytodifferentiation of highly WD-HCC from other well-differentiated hepatocellular nodules is extremely challenging; indeterminate reports are oftentimes rendered.

The objectives of immunohistochemistry are (i) to prove the neoplastic/malignant status of a well-differentiated hepatocellular nodule; and (ii) to ascertain the histogenesis of an obviously malignant lesion. Useful immunostains include HepPar1, glypican-3, CD34, pCEA and CD10. CK7/CK19 demonstrates ductular reaction which should be lacking within and at invasive front of HCC. A panel of glypican-3, HepPar1, MOC-31 and CK7 is helpful in diagnosing and differentiating HCC from metastatic adenocarcinoma.

## MIDDLE EAST CHILDRENS CANCER ASSOCIATION

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### Priorities in Paediatric Cancer Research

**Richard Sullivan** *Kings Health Partners Integrated Cancer Centre - European Institute of Oncology (KHP-IEO) Centre for OncoPolicy, Guy's Hospital, London* [Rsullivan@doctors.org.uk](mailto:Rsullivan@doctors.org.uk)

#### Abstract

Paediatric oncology has delivered major advances in control and cure, with in some cases, a 60% reduction in mortality over the last forty years. However, major issues remain for the paediatric research community – long term toxicity from current regimens, intractable tumours, major differences in Europe in outcomes (e.g. a 3 fold difference in age standardised mortality between the best and worst performing countries), and the role of developed countries in research into childhood cancers in low-middle countries where the majority of the paediatric burden will fall in the next fifty years, to name but a few. Prioritisation of paediatric R&D is increasingly necessary in light of the economic pressures on funding, global challenges of the disease burden and the trans-national nature of much of current R&D. In collaboration with the SIOP Europe under the umbrella of the EUROCANCERCOMMS project a major policy review of paediatric research has been undertaken to inform paediatric R&D prioritisation and communication. Paediatric oncology research accounted for around 5% of the total USA/European cancer R&D over the last 5 years. With the shifting demographic changes (low total fertility rate in Europe and huge population expansions in Asia, Near and Middle East) we have analysed the global relative commitment of countries to this research area. Countries such as Turkey, India and Brazil have high relative commitments to paediatric research (>1.5) compared to OECD countries with lower than expected activities. New data has found variable clinical trial activity with on average around 5% of research activity trial related but with some countries (Sweden, Netherlands, France) engaged in much higher levels (>10% of their total activity). Furthermore in comparison to the USA paediatric oncology clinical trial activity is higher (11% compared with 7%). This study has also analysed the distributed funding of paediatric R&D compared to country burdens and domains of research. One of the most important findings is that much of the research relies on short term, non-core funding indicative of a fragile economic model. This new data derived from economic, demographic and bibliometrics analysis will be linked to core issues around the political process of prioritisation in paediatric oncology R&D.



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### The Etiology of Childhood Cancer

**Logan G. Spector** *Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA, [spector@umn.edu](mailto:spector@umn.edu)*

#### Abstract

The etiology of childhood cancer has been investigated for roughly fifty years, during which time many clues but few concrete avenues for prevention have been generated. A few risk factors - inherited syndromes, high-dose irradiation, and high birth weight – are well established but collectively account for a small proportion of cases. Several proposed risk factors – neonatal vitamin K administration, ultrasounds - have been conclusively dismissed as well. However, in between is a wide array of potential risk factors for which a causal role remains uncertain. The major impediment to progress in the field is the rarity of childhood cancer, which limits sample sizes and often necessitates data collection based solely on recall. Nevertheless there is reason to be optimistic that we can unravel the persistent mystery of childhood cancer causation as epidemiology enters the genomic era. Genome-wide association studies of childhood cancers have begun to appear and have identified several loci with a high degree of confidence, although these, too, explain a small proportion of etiology. Gene-environment interactions may account for the missing heritability and, if so, their confirmation will tend to enhance the credibility of associations with the underlying environmental risk factors. While the bulk of etiologic research to date has been carried out in North America and Europe, it will be necessary to expand studies to other populations in order to increase sample sizes for this set of rare diseases and to fully understand the impact of exposures and genetic backgrounds that are common elsewhere. The second half-century of research into the causes of childhood cancer should produce answers at a continually increasing pace.



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MIDDLE EAST CHILDRENS CANCER ASSOCIATION

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## Epidemiology of Childhood Cancer in Turkey

**Tezer Kutluk** *Hacettepe University Faculty of Medicine, 06100 Ankara-Turkey tkutluk@tr.net*

### Abstract

Each year 3000 new cancer cases in children are expected in Turkey. The records kept properly since 1971 at Hacettepe University as a leading pediatric oncology center in Turkey. 6566 children with lymphoma and solid tumors diagnosed between 1971 and 2004 at Hacettepe University. In all 6566 cases, median age at diagnosis was 4.5 years (0-18) and male/female ratio was 1.57. Distribution of cases in disease groups were [median age in years, male/female]: Lymphomas and other RES tumors (n=2184) 33.3% [7, 1501/571]; CNS tumors (n=986) 15% [7, 470/385]; Sympathetic system tumors (n=629) 9.6% [3, 331/249]; Retinoblastoma (n=208) 3.2% [2.5, 101/69]; Renal tumors (n=605) 9.2% [3, 308/260]; Hepatic tumors (n=115) 1.8% [2.5, 56/44]; Malignant bone tumors (n=394) 6% [12, 200/163]; Soft tissue tumors (n=646) 9.8% [5, 357/239]; Germ cell, trophoblastic and other gonadal (n=451) 6.9% [2.5, 184/223]; Carcinomas and other malignant epithelial tumors (n=269) 4.1% [13, 135/108]; Others/unspecified malignant tumors (n=79) 1.2% [6, 51/27]. In all cases, five-year overall survival rates increased from 24% in 1970s to 36% in 1980s, to 49% in 1990s and to 58% in 2000s ( $p<0.01$ ). Lymphomas were more common than CNS tumors in this database. This started to change in favour of CNS tumors in recent years which is related with both the incidence and referral patterns to our center.



Turkish Pediatric Oncology (TPOG) and Pediatric Hematology Society (TPHD) established a web-based database in 2002 for the registry of all pediatric cancer cases. 10059 cases were registered between 2002-2008 from 63 centers. The tumor type by age groups in 10059 children with cancer are summarized in Table. The overall survival rate at 7th year was found as 65% by Kaplan-Meier Analysis. Lymphomas were exceeding the CNS tumors on this registry. This could be related with the referral patterns from neurosurgery clinics to pediatric oncology clinics. We had an impression that most of the children with CNS tumors who are not required chemotherapy are not referred to the pediatric oncology clinics. Five year survival rate is at acceptable level since it does not reflect the protocol based survival data. Since there is no nationwide data source regarding the survival rates for childhood cancer.

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### Notes

## SPECIAL SESSION II: APOCP HISTORY

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# History of the Asian Pacific Organization for Cancer Prevention

**Kazuo Tajima**

*Director, Aichi Cancer Center Research Institute, Nagoya, Japan, ktajima@aichi-cc.jp*

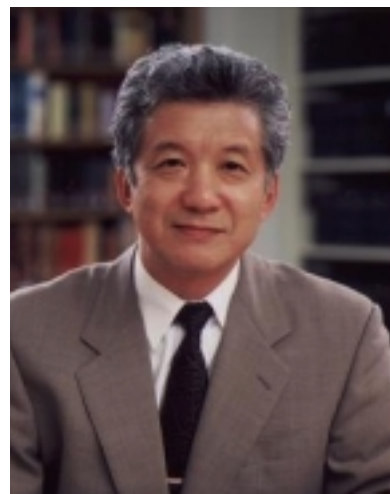
### Abstract

With the rapid increment in cancer incidence and deaths in Asian countries, the World Health Organization (WHO) has begun to stress the important health issue of cancer control in Asia. In 2000 we established a new academic organization, the Asian Pacific Organization for Cancer Prevention (APOCP), to marry the efforts of workers in all of the different disciplines having a bearing on the cancer control and prevention. The APOCP has its roots in 1999 with Dr. Malcolm Moore and various other colleagues as its prime movers. The founding conference was held in Pattaya, Thailand chaired by Dr. Somyos Deerasamee, National Cancer Institute, Thailand, in 2000 and was attended by around 50 scientists from 15 countries.

From the constitution of the APOCP, the APOCP has three main aims for cancer prevention and control in Asian Pacific areas. The first is to provide opportunities for expert researchers to exchange mutual information for cancer prevention in the Asian Pacific area. We therefore launched a specialist journal, the Asian Pacific Journal of Cancer Prevention, and built on the start made in Pattaya by organizing regular conferences, including biennial general assemblies (APOCP-GA) and regional meetings. The first APOCP-GA was held in Nagoya, Japan chaired by Dr. Kunio Aoki in 2001. The second aim is to promote collaborative studies on cancer epidemiology and prevention. Since April of 2000, I myself have promoted international collaborative studies, especially in Northeast and Southeast Asia as a chairperson of the study groups of the Special Priority Area for Cancer Epidemiology sponsored by the Japanese Ministry of Education, Science, Sports, Culture and Technology. The third is to promote implementation programs for cancer prevention and control in the Asian Pacific area. To further this cooperative effort with the APOCP, the UICC Asia Regional Office was established in 2008, mainly supported by the UICC Japan Committee chaired by Dr. Tomoyuki Kitagawa. The primary aims are to assist Dr. Moore as Chief Editor of the APJCP as well as to stage various events for enhancing awareness of cancer across the region. As UICC strategic leader for Cancer Prevention & Early Detection in Asia, I believe cancer prevention programs in the Asian Pacific area can be best promoted related to UICC activities.

Dr. Yun-Ok Ahn (Korea) and Dr. Thiravud Khuhaprema (Thailand) organized the 2nd and 3rd APOCP-GAs in 2004 and 2006, respectively. Since 2006 Dr. Keun-Young Yoo, Professor of the Seoul National University, has acted as Secretary-General of the APOCP, taking over from myself as Founding-Chairman. Dr. You-Lin Qiao (China) organized the 4th APOCP-GA in 2008 and the present 5th APOCP-GA has Dr. Murat Tuncer (Turkey) as its President. In addition, regional conferences have been held in Izmir, Khon Kaen, Rasht, and Nagoya, along with a number of specialist meetings.

In the present panel, I would like to introduce the history of the APOCP on behalf of its members and refer to future directions.



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## APOCP GENERAL ASSEMBLY

### APOCP Report

**Keun-Young Yoo** *Secretary-General, APOCP, kyyoo@ncc.re.kr*

The Asian Pacific Organization for Cancer Prevention (APOCP) is a non-political and non-profit organization, aiming for cancer prevention in Asian Pacific area. The main objectives continue to be to provide many opportunities for expert researchers to exchange mutual information for cancer prevention, to promote collaborative studies on cancer epidemiology and prevention, and to facilitate the implementation of active programs for cancer prevention. To this end further regional meetings are planned, including one in Korea in 2011.

One of the important activities of the APOCP is publishing the APJCP, as an official publication of the APOCP, the UICC Asia Regional Office for Cancer Control (UICC-ARO), and the International Association of Cancer Registries (IACR). I hope that the APJCP will continue to function to disseminate and exchange information of mutual interest in all areas of cancer control in the Asian Pacific and the world. It is hoped that the APOCP will be established as a legal entity within the near future so that we can build on a firm base. The future success of the APOCP/ APJCP will depend on your collaboration and positive achievements.

### APJCP Report

**Malcolm Moore** *Head UICC-ARO, Chief Editor APJCP, apocpcontrol@yahoo.com*

#### Contributions to APJCP Papers 2007-2009

Fields	Turkey	Iran	Central*		Thailand	Indonesia	China	Japan	West**		Total (%)						
	Arabia	Pakistan	India	Malaysia	Vietnam	Korea	Australia	Editors									
<b>Education/Smoking</b>	13	2	2	4	0	12	3M1	5	0	1	1	2	6	0	9	5	<b>66</b> (13)
<b>Epidemiology</b>	3	3	42	20	3	34 N1	11	11	1	6	9	4	16	5	13	4	<b>186</b> (35)
<b>Secondary Prevention</b>	7	2	10	1	1	6 S1	40	4	0	0	2	0	1	1	4	0	<b>80</b> (15)
<b>Toxicological Pathology</b>	0	2	2	1	0	19	11	2	0 B1	0	2	0	19	2	1	0	<b>62</b> (12)
<b>Clinical</b>	18	4	14	14	0	11 N1	48	14	0 B1	0	5	0	2	0	1	0	<b>133</b> (25)
<b>Total</b>	<b>41(8)</b>	<b>13(2)</b>	<b>70(13)</b>	<b>40(8)</b>	<b>4(1)</b>	<b>85(16)</b>	<b>114(22)</b>	<b>36(7)</b>	<b>3(1)</b>	<b>7(1)</b>	<b>19(4)</b>	<b>6(1)</b>	<b>44(8)</b>	<b>8(2)</b>	<b>28(5)</b>	<b>9(2)</b>	<b>527</b> (100)

\*Central Asia, Kyrgystan and Mongolia; \*\*Western World, USA and Europe, South America; M, Myanmar; N, Nepa;; S, Sri Lanka

### APOCP 5th GA Report - 6th APOCP GA Introduction

**Murat Tuncer** *President, APOCP 5th GA*

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SYMPOSIA

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SYMPOSIUM III: INFECTION and CANCER

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## **Cancer in Hepatitis Infections**

**Baruch S Blumberg**

USA

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 SYMPOSIUM III: INFECTION and CANCER
 

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## Gastric Cancer Development by *Helicobacter Pylori* Infection -Important Roles of Activation-Induced Cytidine Deaminase (AID) in Induction of Gene Mutations and Genomic Instability during Inflammation-Associated Carcinogenesis

Tsutomu Chiba, Hiroyuki Marusawa

Department of Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto University, Kyoto 606-8507, Japan  
chiba@kuhp.kyoto-u.ac.jp

### Abstract

*Helicobacter pylori* (*H.pylori*) infection plays important roles in gastric carcinogenesis, and gastric cancer development is characterized by accumulation of various gene mutations and genome instability. However, the mechanisms of how *H.pylori* infection induces gene mutations and genome instability in the gastric mucosal cells leading to gastric cancer development is unknown. Activation-induced cytidine deaminase (AID) is exclusively expressed in B lymphocytes under physiological condition and is essential for class switch recombination and somatic hypermutation of immunoglobulin genes. Here, we found that AID-transgenic mice developed not only lymphoma but also gastric cancer. Moreover, we revealed ectopic expression of AID in *H.pylori*-positive human gastritis mucosa as well as in gastric cancer tissues, whereas no AID expression was present in non-infected normal mucosa. Furthermore, *H.pylori* eradication reduced the increased levels of AID expression. In vitro studies showed that (1) AID protein as well as mRNA was induced by *H.pylori* infection in association with induction of various p53



and  $\beta$ -catenin gene mutations in human gastric epithelial cells. (2) Only CagPAI-positive strains could induce AID expression, and moreover, AID expression induced by CagA (-) *H.pylori* was slightly less than that by wild type strain. (3) *H.pylori*-induced AID expression was abolished by blocking NF- $\kappa$ B activation. (4) AID was also induced by various proinflammatory cytokines such as TNF- $\alpha$  and IL-1 $\beta$ . (5) AID gene introduction into gastric mucosal cells accelerated p53 gene mutations, and inhibition of AID using AID siRNA significantly reduced *H.pylori*-induced p53 gene mutations. (6) AID induction in the gastric mucosal cells mainly induces C to T or G to A transition, although other mutations also occurred. (7) AID induction caused both amplification and deletion of various genes in gastric mucosal cells, and *H.pylori* infection to gastric mucosal cells also induced copy number alterations of various genes. (8) Finally, in *H.pylori*-infected human gastric mucosa high levels of AID expression was associated with frequent p53 gene mutations, whereas in *H.pylori*-negative gastric mucosa, no or low AID expression was accompanied by no or low frequency of p53 gene mutation. In conclusion, *H.pylori* infection induces ectopic AID expression in the gastric mucosal cells via NF- $\kappa$ B activation in association with induction of various gene mutations. Thus, AID appears to play crucial roles in *H.pylori*-induced gastric carcinogenesis by enhancing gene mutations and genome instability in the gastric mucosal cells.

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SYMPOSIUM III: INFECTION and CANCER

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**HPV Infection and Cancer: Randomised Controlled Trials Comparing Cytology- and HPV-based Cervical Cancer Screening**

**Marc Arbyn**

*Unit of Cancer Epidemiology, Scientific Institute of Public Health, Brussels, Belgium marc.arbyn@iph.fgov.be*

**Abstract**

Recently published randomized clinical trials, conducted in four European countries and Canada, consistently showed that HPV screening has a higher sensitivity for present or incipient high-grade cervical intra-epithelial neoplasia (CIN) or adenocarcinoma in situ than conventional cytology (pooled sensitivity ratio: 1.58 (95% CI: 1.36-1.83, p for inter-study heterogeneity not significant). However, in the ARTISTIC trial (UK), HPV screening was not more sensitive than screening with liquid-based cytology in detecting CIN2+ (pooled ratio 1.06; 95% CI: 0.87-1.69). The gain in sensitivity by adding cytology to HPV screening was small and statistically non-significant (pooled ratio: 1.04; 95% CI: 0.87 to 1.25).

The increased number of screen-positive women that results from HPV testing requires adequate triage strategies.

The most important aim of the trials was to demonstrate over time a reduced cumulative incidence of cervical intraepithelial neoplasia (CIN) of grade 3 or worse (CIN3+) among women who tested baseline HPV negative compared to those who had normal cytology (relative risk [RR] lower than 1). Lower cumulative incidence of CIN3+ can be considered as a proxy for decreased incidence of cancer. This outcome was observed in all the trials that have published longitudinal outcomes of the second screening round, 3-6 years after the first round: RR= 0.53 in the Swedish and English trial, 0.45 in the Dutch trial, 0.29 in the first phase of the Italian trial, with confidence intervals always excluding unity.

Moreover, recent data from the Italian trial showed reduced incidence of invasive cervical cancer in HPV-negative vs cytology negative women (zero cases, versus 9 cases, p=0.004).

These data indicate that HPV screening picks up more progressing cervical lesions than cytology and provides evidence for cervical cancer screening with an HPV assay followed by triage of HPV positive women. More in-depth meta-analyses and research should define best triage policies, target age groups and screening intervals, taking into account that certain future generations of women will have a lower background risk for developing cervical cancer (precursors) because of HPV vaccination.

References: Arbyn M, Sasieni P, Meijer CJ, Clavel C, Koliopoulos G, Dillner J. Chapter 9: Clinical applications of HPV testing: a summary of meta-analyses. *Vaccine* 2006; 24 (SUPPL. 3): S78-S89. Arbyn M, Ronco G, Meijer CJLM, Naucler P. Trials comparing cytology with HPV screening. *Lancet Oncol* 2009; 10: 935-6.

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## SYMPOSIUM III: NUTRITION and CANCER

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### Nutrition and Cancer: Difference between Two Sides of the Pacific

**Laurence Kolonel**

*Cancer Research Center, University of Hawaii, Honolulu HI, USA [lkolonel@crch.hawaii.edu](mailto:lkolonel@crch.hawaii.edu)*

#### Abstract

Experts estimate that about 40% of all cancers in western developed countries are attributable to unhealthy diets and the related factors of excessive body weight and lack of physical activity. In the past, cancer patterns differed dramatically between Southeast Asian countries bordering the Pacific Ocean on the west (such as Japan and China) and North American countries bordering the Pacific on the east (such as the US and Canada). Much of the variation could be related to differences in diets among these countries, although other factors (such as varying prevalence of hepatitis A and other infectious agents) no doubt also contributed. Characteristically, diets in Asia were lower in energy and in fat content (especially animal fat) compared to the diets in North America. Research on populations who moved to the US from Asia, such as the studies we conducted on migrants from Japan to Hawaii, showed that dietary changes, even in adulthood, could dramatically alter cancer risks within a single generation. For example, the incidence of gastric cancer decreased, while the incidence of cancers of the breast, prostate and large bowel increased in the migrants. As a general rule, cancer patterns in the migrants came to resemble those of the host country. With growing economic prosperity, globalization of trade, and international expansion in the food industry, diets in Southeast Asian countries have become more cosmopolitan and varied over the past several decades. The dietary transition to more calorie-dense foods in these countries, together with increasingly sedentary lifestyles, has been paralleled by changing trends in the incidence of diet-related cancers. The direction of these changes corresponds to what was seen earlier in the migrant populations to the West; thus, incidence rates of breast and colon cancer have been increasing in Japan and China, while cancer of the stomach has been showing some decline. If current trends continue, the incidence of diet-related cancers will become more similar on both sides of the Pacific over time. Already, the incidence of colon cancer is similar for populations in the US and Japan. However, for other sites, it will probably take many decades before the actual incidence rates show significant overlap.



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**SYMPOSIUM III: NUTRITION and CANCER**

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**Food, Nutrition, Physical Activity and the Prevention of Cancer****Eva Negri, Claudio Pelucchi***Istituto di Ricerche Farmacologiche "Mario Negri" eva.negri@marionegri.it***Abstract**

The association of nutrition, physical activity and selected dietary aspects with cancer risk was investigated in an Italian multicentric network of case-control studies including over 20,000 cases of 20 different cancer sites and 18,000 controls.

We found increased risks of colorectal, endometrial and postmenopausal breast cancer in obese men and women. However, while overweight and obesity account for about 14% of cancer deaths in US men and 20% in US women these figures are lower in Italy, i.e. about 3-5%, on account of the lower prevalence of overweight.

Physical activity was inversely associated with colorectal and breast cancer risk. For most cancer sites, the addition of a portion of fruit or vegetables per day led to a decline in the relative risk of the order of 10-20%, and about 20-60 % of digestive tract cancers were attributable to low vegetable consumption. Allium vegetables consumption was also a favourable correlate of cancer risk in Italy.

Whole grains were favorable indicators for the risk of several cancer sites, while, in contrast, refined grain intake and a diet with a high glycaemic load were associated to increased risk of stomach, colorectal and upper digestive tract cancers. Olive oil and other monounsaturated and unsaturated fats were inversely related to cancer of the breast, ovarian, colorectal, but mostly of upper digestive and respiratory tract cancers. For these neoplasms, the RR difference between extreme levels of olive oil versus butter consumption reached a factor 4 to 5, pointing to olive oil as a relevant favourable factor of Mediterranean diet on cancer risk.

Inverse relations between folate intake and cancers of the upper aero-digestive tract, large bowel, breast and prostate were found, while no significant relation emerged with ovarian and renal cell cancers. Flavonoids are a group of over 5,000 polyphenolic compounds present in fruit, vegetables, and beverages of plant origin. with antioxidant, antimutagenic, and antiproliferative properties in vitro. The findings of this large series of Italian case-control studies provide support for a protective role of flavanones on upper aerodigestive tract, proanthocyanidins on gastric cancer, flavonols and proanthocyanidins on colorectal, flavonols and flavones on breast, and isoflavones on ovarian cancers. We then calculated a score summarizing eight of the major characteristics of the Mediterranean diet, i.e. high consumption of cereals, legumes, fruit, vegetables, low consumption of meat, milk or dairy products, high monounsaturated/saturated fat ratio, and moderate alcohol intake. This a priori defined nutritional pattern was associated with a decreased risk of cancers of the upper aero-digestive tract: The odds ratios for subjects with  $\geq 6$  Mediterranean characteristics, compared with those with  $< 3$ , were 0.40 for oral and pharyngeal, 0.26 for oesophageal and 0.23 for laryngeal cancer.

In conclusion, findings from our network of case-control studies, support a protective role of several aspects of the Mediterranean diet and of physical activity on the risk of several common cancers, and a negative one of obesity.



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