Eur J Cancer, Vol. 29A, No. 9, p. 1348, 1993.
Printed in Great Britain
0964-1947/93 $6.00 + 0.00

Book Review

Molecular Genetics of Pediatric Solid Tumors: Basic Concepts and Recent Advances

G.P. Tonini, R. Sansone and C.J. Thiele. Harwood Academic Publishers, 1992. ISBN 3 7186 5080 0. £25.00, US$45.00.

ONLY ONE in 800 children are affected by cancer which makes it a relatively rare disease. These children, however, have not received constant exposure to environmental carcinogens so what is responsible for their tumours? In many cases, either through family pedigree studies or mathematical considerations of incidence versus frequency of these cancers, it has been shown that they may be due, at least in part, to a hereditary predisposition. Histopathological analysis of many children's tumours show that they consist of relatively undifferentiated cells. Thus, it appears as if cells do not respond to the signals that normally tell them to differentiate during embryogenesis. The isolation of genes responsible for these phenotypes is therefore an exciting venture since we are not only looking at genes which cause cancer, but also genes which likely control normal developmental processes. This is an important consideration since, if cells become far too committed down to terminal differentiation, they lose their ability to divide in a controlled fashion which is a hallmark of cancer cells. The relationship between development and cancer has not gone unnoticed by laboratories specialising in the analysis of the genetic predisposition to cancer. The opportunity for fame and funding has made the study of childhood cancer very competitive and in many cases their analysis has been at the forefront of the highest technology in molecular biology. This fact makes 2 weeks a long time in the study of some of these tumours and it must always be accepted that books reviewing these topics will, inevitably, be somewhat out of date by the time the book is published. Given the now quite commonplace application of molecular diagnostics to genetic screening and genetic counselling and the future opportunities for gene and antisense oligonucleotide therapy it is important that clinicians and non-molecular scientists understand and incorporate the basic technology and jargon of molecular biology into their everyday thinking of clinical and biological problems. The declared aim of the book edited by Tonini *et al.* is to 'fill the gap between advanced research and clinical practice'. The book addresses three general areas; (1) the molecular biology of specific paediatric tumours incorporating cytogenetics of brain tumours, (2) review chapters about the genetics of cancer and (3) selected methodologies used in the analysis of cancer such as flow cytometry and transgenic mouse systems. The authorship is largely Italian based with a few chapters from the U.K., U.S.A. and Germany. The strengths of the book are undoubtedly the chapters written by several experts who have been actively involved in the analysis of tumours in which they have published extensively over the past few years, such as retinoblastoma, Wilms' tumour, neuroblastoma and rhabdomyosarcoma. Whilst it is hard to present data that is up to date in such a rapidly moving field, I felt that these chapters discussed the molecular mechanisms of oncogenesis in paediatric solid tumours in some detail and were well referenced. The more general chapters, however, I found less instructive and mainly presenting reportage. Thus, chapters about particular aspects of cancer such as 'fragile sites' and 'cellular oncogenes' are more philatelic without too much interpretation of the data. Although the aim of the book is to bridge the gap between front line science and clinical research, I thought that chapters on flow cytometry techniques and mouse neuroblastoma models somewhat out of place. Included in this volume are several chapters discussing chromosome abnormalities in childrens tumours which, although not strictly molecular, provide the background into the usefulness of these observations in gene cloning. However, there is considerable duplication of information within these review chapters, and between these and the specialist chapters. In addition, several chapters seem out of place in the molecular genetics background, such as the role of neuropeptides in neuroblastoma and it is not altogether clear why some have been included. Despite its strengths, I doubt that I would suggest reading this book from cover to cover but rather to consult it occasionally for specific information, especially since there have been a number of other books published over the past few years addressing the subject of tumour suppressor genes, many of which have covered the subject in far more detail.

Dr J.K. Cowell
Molecular Genetics Laboratory
ICRF Oncology Group
Institute of Child Health
30 Guilford Street
London WC1N 1EH
U.K.

News

Report of an International Workshop on Perspectives on Secondary Prevention of Laryngeal Cancer

G. Cortesina, P. Gabriele, C. Giordano, F. Merletti, A. Morrison, H.K. Mueller Hermelink, G. Palestro, G.L. Sannazzari, A. Sartoris, A. Sasco, N. Segnan, W. Steiner, G. Succo, B. Terracini, G. Valente and J. Vershulst

ON 21–23 NOVEMBER 1991, an international workshop aiming at evaluating the perspectives for secondary prevention of laryngeal

Correspondence to B. Terracini.
G. Cortesina, C. Giordano, A. Sartoris and G. Succo are at the ENT Clinic, University of Torino, Torino; P. Gabriele and G.L. Sannazzari are at the Department of Radiotherapy, University of Torino, Torino; F. Merletti and B. Terracini are at the Unit of Cancer Epidemiology, Department of Biomedical Sciences and Oncology, University of Torino, va Santena 7, 10126 Torino, Italy; * A. Morrison (deceased on 17 May 1992) was at the Department of Community Health, Brown University, Providence, Rhode Island, U.S.A.; M. Hermelink is at the Department of Pathology, University of Wurzburg, Wurzburg, Germany; G. Palestro and G. Valente are at the II Service of Histopathology, Department of Biomedical Sciences and Oncology, University of Torino, Torino, Italy; A. Sasco is at the International Agency for Research on Cancer, Lyon, France; N. Segnan is at the Service of Cancer Epidemiology, Department of Oncology, USL 1, Torino, Italy; W. Steiner is at the ENT Department, University of Goettingen, Goettingen, Germany; and J. Vershulst is at the Fondation Potmann, Bordeaux, France.
The above were participants to the workshop. Chairman: A. Sartoris. Rapporteur, Vice-Chairman N. Segrian and Chairman of the Oncological Committee of the Region Piemonte: B. Terracini.
Received and accepted 8 Feb. 1993.

cancer was held in Torino, Italy. The workshop was convened by the Institute of Otorhinolaryngology of the University of Torino and by the Oncological Committee of the Region Piemonte. The workshop (i) examined current knowledge on the natural history of laryngeal cancer; (ii) considered further knowledge needed in order to evaluate whether and how natural history can be modified by screening of asymptomatic persons; and (iii) drafted some recommendations for further work.

PRIMARY PREVENTION VS. EARLY DETECTION

There was a consensus of opinion that in order to prevent laryngeal cancer (and other tobacco- and alcohol-related diseases), smoking cessation and reduction of alcohol drinking are far more effective and probably less expensive than any well planned screening programme for early diagnosis. Although a probable rebound effect of properly advertised mass screening would be a reduction in tobacco consumption, research or intervention related to early diagnosis should by no means divert attention and resources from primary prevention.

NATURAL HISTORY OF LARYNGEAL PRE-INVASIVE LESIONS

Occurrence of cancer and preinvasive lesions

At least for populations living in Western countries, incidence and mortality rates of invasive cancer in the various segments of the head and neck are fairly well known from current statistics, including cancer registries. For men in northern Italy and other Mediterranean populations, the lifetime cumulative risk for laryngeal cancer (ICD-IX 161) is in the order of 2% and over 90% of laryngeal cancers are attributable to tobacco smoke, abuse of alcoholic beverages and the interaction between the two [1]. Some risk factors in the workplace have also been identified [2].

Hyperkeratosis without dysplasia, mild dysplasia (LIN I), moderate dysplasia (LIN II), severe dysplasia and carcinoma *in situ* are terms commonly used to describe histological changes thought to have a higher probability of progressing to carcinoma than normal laryngeal epithelium (i.e. precursor lesions). Some authors label both severe dysplasia and carcinoma *in situ* as LIN III.

Reliable figures on incidence or prevalence of precursor lesions are scarce, because of methodological limitations typical of population-based surveys of asymptomatic and/or non-lethal conditions. Estimates from autopsy series might reflect selection bias, which might operate to a varying extent in different series. Nevertheless, lifetime cumulative rates of carcinoma *in situ* as high as 16% (two-thirds in the true and one-third in the false vocal cords) have been reported in the classic study of Auerbach *et al.* [3]. In this study, no carcinoma *in situ* was identified among 204 persons who were either lifelong non-smokers or ex-smokers, whereas percentage prevalences were 10.4, 15.8 and 18.4 among current smokers of, respectively, less than one pack, one to two packs and more than two packs/day. In addition, the proportion of persons in which the highest number of cell rows in the basal layer of the vocal cord exceeded four increased from 33% among never smokers to 90% among current heavy smokers. In another post mortem series including 148 cases, prevalence of dysplasia/ carcinoma *in situ* of the vocal cords was correlated with smoking habits, and ranged between 4% in non-smokers and ex-smokers and 47% among current heavy smokers [4].

Some prevalence studies on clinical variables have been reported: one of the largest was carried out in Germany during 1978–1980 [5] on 6899 workers engaged in a variety of activities. The data base included 85% men, 80% were aged 30–60, 58% were smokers or ex-smokers, 10% were heavy drinkers and 33% were office workers. Ear, nose and throat (ENT) symptoms were present in 58%; 36% had previously consulted an ENT specialist, whereas 18% were currently undergoing treatment by an ENT specialist. 103 were diagnosed with chronic laryngitis and 93 were found or suspected to have a laryngeal precancerous lesion. The latter figure corresponds with a prevalence of 1.3%, which in fact ranged between 0.2% in non-smokers and 3.2% in heavy smokers, and between 0.8% in non-drinkers and 5% in those drinking more than 120 g ethanol/day. On histology, 28 laryngeal dysplasias and five squamous cell carcinomas were detected. A previous study in Hungary had yielded comparable prevalence estimates [6].

Survival of patients with invasive cancer

A population-based 5-year survival rate of 63% was estimated in northern Italy for patients diagnosed with laryngeal cancer around 1980 [7]. Other reports give similar figures [8–11].

Progression and regression of premalignant lesions

The practice of totally removing a lesion impairs the distinction between progression and appearance of a new lesion as well as the recognition of an actually regressing lesion.

Follow-up of precursor lesions has been the object of several clinical reports, a number of which are summarised in Table 1. These studies and their results are not strictly comparable. Heterogeneity regards: (i) diagnostic criteria and terminology; (ii) proportion of lesions exclusively treated through biopsy; (iii) criteria for taking into account information on smoking; (iv) proportion of persons dying during follow-up because of other smoking-related diseases, and (v) precision of reporting number of persons lost to follow-up. Finally, none of these studies were analysed in terms of person-years of observation, so that risk cannot be estimated adequately. However, in spite of all these shortcomings, findings consistently suggest that probability of progression to invasive cancer increases with severity of original diagnosis.

According to clinicians, in the larynx, age (as well as sex and topographical) distribution is similar for carcinoma *in situ* and for invasive carcinoma. Thus, it can be argued that progression from the former to the latter might occur more rapidly than, say, in the uterine cervix (where the age distribution of carcinoma *in situ* anticipates for decades that of invasive carcinoma). This might have implications both for understanding the natural history of the disease and for treatment. Nevertheless, the higher prevalence of carcinoma *in situ* in autopsy series than the cumulative incidence rate of invasive carcinoma indicates that far less than 100% of the former progress to the latter. In addition, decisions on mass screening would require an estimate of the proportion (as yet uncertain) of invasive carcinomas developing from precursors (as opposed to *de novo* lesions).

Clinicians' experience also suggests that the probability and timing of progression/regression of precursors are strongly influenced by the continuation/discontinuation of exposure to smoking and other irritants. This is confirmed by the lower prevalence at autopsy of carcinoma *in situ* and other precursors in ex-smokers than in current light smokers [3, 4]. In a clinical study [12], among patients originally diagnosed with mild, moderate and severe dysplasia, those found to regress to normal during follow-up were, respectively, 87/128, 4/9 and 4/10.

SCREENING

General

The definition of screening as "the application of a relatively simple, inexpensive test to a large number of persons in order to classify them as likely or unlikely to have the cancer that is the object of the screen" [13] was unanimously accepted. No experiences of screening for laryngeal cancer in the general population or unselected subgroups have been reported, nor was the larynx included among the cancer sites so far considered in overall surveys of screening for cancer [14–17]. No participant to the workshop was aware of any on-going study designed to evaluate the efficacy of any suggested tool for the identification of asymptomatic laryngeal cancer. (The workshop adopted the operational definition of "symptom" as a condition leading somebody to seek medical care.)

Thus, no data are available in order to quantify problems commonly encountered in cancer screening, such as lead time and length bias and number or proportion of interval cases. In addition, there is no information on whether potentialities for progression are the same for histologically similar symptomatic and asymptomatic precursor lesions.

Diagnostic tests

Both rigid and optic fibre laryngoscopy may be promising for large preventive campaigns addressed to asymptomatic persons. The former (i.e. a magnifying laryngopharyngoscope with a 90-degree optic) has been used in the domain of preventive programmes in Germany [5]. Dr W. Steiner reported that this technique proved to be valid, and that in his experience, compared to flexible laryngoscopy, the instrument is easier to handle and allows for a better field visualisation, is cheaper and easier to disinfect.

ENT clinicians in Torino have tested optic fibre laryngoscopy in 2200 subjects attending the out-patient clinic for symptoms unrelated to the larynx [18]. Among these subjects, on the basis of tobacco, alcohol and occupational anamneses, 1598, 387 and 215 were considered at low, medium and high risk, respectively, of exposure to carcinogenic agents. Six dysplasias, two carcinomas *in situ* and a few dyskeratoses were identified in the high-risk group. Post-trial monitoring for false negatives lasted 1 year. Sensitivity and specificity (the end point including dysplasia as well as cancer) were 100 and 96%, respectively. The test—if performed by a skilled physician—requires 5 min, is acceptable and side-effects were reported to be negligible. The possibility that images are collected by a technician and reviewed by a qualified endoscopist may be explored.

Pros and cons of the two procedures require quantification: in particular, there is a need for quality control studies, including assessment of both intra- and interobserver diagnostic variability and validity vs. a gold standard.

As for other tests, stroboscopy and voice analysis were unanimously considered to be irrelevant to mass screening. Characteristics of sputum cytology and brush cytological smears have been estimated to a very limited extent, and mainly within a clinical perspective [19]. In one study on heavy smokers [20], 1.4% of 4416 smears showed squamous cell dysplasia and 2 subjects were diagnosed as having a carcinoma on this basis. In another study [21], the proportion of patients with a "positive" sputum cytology correlated to clinical T factors (according to TNM classification), ranging from 29% in T1 to 79% in T4 lesions. In another study, results of brush cytological smears and those of punch biopsies agreed in 50/60 subjects [22]. Discomfort of those being examined and financial cost should discourage the application of these screening tests within interventions addressed to asymptomatic persons.

PATHOLOGICAL DIAGNOSIS OF PRE-INVASIVE LESIONS

Reliability of histological classification

Reproducibility of histological diagnosis of precursor lesions has largely been neglected. In one study, 30 of 92 patients classified as hyperplasia with atypia at the time of revision of the original histological slides, had in fact been previously classified as carcinomas *in situ* and had received radiotherapy [23].

Also, the correspondence between clinical and histological terms (such as catarrhal, hyperplastic laryngitis, chronic laryngitis with either red or white pachydermia etc.) remains to be quantified.

Histological and laboratory techniques

A number of predictors of progression of non-invasive lesions have been suggested by histopathologists, including immunohistochemical demonstration of either antibodies against type IV collagen and laminin in the basement membrane or intermediate filaments such as cytokeratins and involucrin, demonstration of growth fraction (K167, PCNA) and mitotic and DNA index. Conceptually, both DNA ploidy and oncogene expression are promising but require further exploratory studies.

Collection of material and material processing in histology

Twenty years ago, criteria were proposed [24] for evaluating laryngeal biopsy material (such as choice of site, processing, handling of small lesions, stripping, orientation and number of sections). These criteria are still adequate, but very little information is available on the extent of their application across countries and in hospitals within the same country.

THERAPY OF PRE-INVASIVE LESIONS

No randomised clinical trial has evaluated results of different therapeutic options. However, there was a consensus of opinion that therapy of laryngeal non-invasive lesions must be conservative. Endoscopic microsurgery (exeresis/biopsy, laser) may be the best method. Radiotherapy should find no applications apart from highly diffuse non-invasive lesions, early recurrences and invasive cancers.

Given the limited knowledge on natural history of precursor lesions (ranging from hyperkeratosis to carcinoma *in situ*), there was agreement that follow-up should be very strict, i.e. every 3 months for 5 years or more.

It is not known whether stopping smoke *alone* (without any more aggressive treatment) is sufficient to predict regression of precursor lesions of varying severity. This should not refrain ENT physicians to encourage their patients to quit smoking.

EARLY DIAGNOSIS: ADVANTAGES AND POSSIBLE DISADVANTAGES

It was unanimously recognised that some of the prerequisites for mass screening of asymptomatic precursors of laryngeal cancers are currently met: (i) a sizable (albeit difficult to estimate) proportion of invasive cancers develop from poorly symptomatic or asymptomatic conditions which are easy to detect, diagnose and treat; (ii) adequate instruments are available for performing endoscopies—including tissue collection for histology, if required—on a mass scale, with limited individual discomfort; (iii) reliability and cost of the diagnostic techniques require quantification but are likely to be acceptable; (iv) treatment

Table 1. Clinical studies on the follow-up of precursors of laryngeal cancer

Reference	Length of follow-up (months)	Original lesion	*n*	Progressing to malignant (%)
Kleinsasser 1963 [25]	?	Squamous cell hyperplasia	61	8
		Hyperplasia + atypia	5	20
		Carcinoma *in situ*	20	90
Delemarre 1970 [26]*	?	Squamous cell hyperplasia	20	15
		Hyperplasia + atypia	26	23
		Carcinoma *in situ*	8	50
Hellquist *et al.* 1982 [27]	Up to 156	Hyperplasia/keratosis	98	2
		Moderate dysplasia	24	13
		Severe dysplasia	39	25
Barnes and Gnepp 1985 [28]	?	Hyperkeratosis, no dysplasia	225	3
Olde-Kalter *et al.* 1987 [23]	60–232, average 100	Squamous cell hyperplasia	35	6
		Hyperplasia + atypia	50	24
		Carcinoma *in situ*	8	50
Silaminiku *et al.* 1989 [29]	60–300	Keratosis without atypia	604	3
		Keratosis + mild dysplasia	204	7
		Keratosis + moderate dysplasia	23	17
		Keratosis + severe dysplasia	90	25
Hoislet *et al.* 1989 [12]	11–128, average 64	Mild dysplasia	128	5
		Moderate dysplasia	9	40
		Severe dysplasia/carcinoma *in situ*	10	40
Valente 1991 (personal communication)	33 months†	Hyperkeratosis, no dysplasia	39	10
	36 months†	Mild dysplasia		15
	48 months†	Moderate dysplasia		18
	27 months†	Severe dysplasia		44

*It is unclear whether these cases have been included in those reported in [23].
†Mean interval between diagnosis of precursor and diagnosis of invasive cancer.

(decortication) is harmless, inexpensive and effective. W. Steiner reported that in Germany it was estimated that there is sufficient ENT and pathological manpower to carry out a mass programme and preliminary cost–benefit analyses suggest that the programme might be economically justifiable, at least in that country.

Nevertheless, at present, information is lacking on the following points, which are crucial in planning and implementing any screening programme:

(1) Feasibility of the creation of nominal rosters of members of potential target population(s), defined on the basis of either presence/absence of symptoms, or exposure/non-exposure to risk factors or other criteria.
(2) Response of the target population, including individuals' acceptance to undergo the tests offered within the programme.
(3) Presumable length of DPCP (detectable preclinical phase), an estimate of which would allow realistic suggestions on length of interval between tests.
(4) Prevalence of individuals with DPCP, in order to estimate resources which are needed for their treatment.
(5) Similarities/differences of progression/regression potentialities between premalignant lesions encountered in the course of mass screening and those identified in clinical work.
(6) Estimates (on the basis of several alternative assumptions) of increased effectiveness introduced by early treatment.
(7) Possible consequences of overtreatment.
(8) Other aspects of cost vs. benefit evaluation.

Given the extreme rarity of laryngeal cancer in non-smokers and non-drinkers, a programme for early diagnosis would be much more efficient if targeted towards at-risk groups, such as smokers (any quantity), heavy smokers (e.g. over 20 cigarettes/day for more than 20 years), heavy drinkers (e.g. over 100 g alcohol/day for more than 20 years), or groups of workers with high/long exposure to recognised occupational carcinogens in the workplace. In intervention programmes, each of these categories would require an operational definition and should be complemented by a code of practice for identifying and contacting individuals belonging to them. Numerically, workers

occupationally exposed to laryngeal carcinogens are far less than smokers and heavy drinkers.

PERSPECTIVES OF STUDY

There was a consensus of opinion on two basic issues: (i) demonstration of efficacy of a screening programme for early diagnosis of laryngeal cancer requires studies designed as randomised trials: the simple comparison—between compliers and non-compliers—of subsequent incidence of invasive cancer or mortality would not provide sufficient guarantee of control of confounding variables. (ii) Both potential screening tests and features of screening process have not been investigated to an extent sufficient for planning and/or undertaking an adequate controlled trial.

On the other hand, limited intervention programmes aimed at identifying and treating laryngeal lesions considered to be cancer precursors have started or are being planned in several countries.

The rationale underlying these on-going programmes is that it is biologically plausible that the early recognition and treatment of an alleged precursor will increase chance of cure. However, they have not been designed in order to, and do not have the potential for, quantifying the efficacy, if any, of screening programmes for the early diagnosis of laryngeal cancer. On the other hand, these programmes (particularly if complemented by additional methodological investigations) might help in obtaining a reply to precise and specific issues such as:

1. Quantification and comparison of characteristics (sensitivity, specificity, acceptability, side-effects, including side-effects of diagnostic decortication) of different tests suggested for early diagnosis of precursors.
2. Assessment of precision and validity of diagnostic procedures, including intra- and interobserver comparisons (both within the same team and among teams).
3. Reconstruction of the natural history of the disease and potentialities of different precursors to progress to cancer, with adequate statistical analyses (such as computation of person-years of observation broken down by age and calendar period), and taking into account exposure to risk factors and presence/absence of symptoms. Perhaps this goal could be achieved through reviews of available studies, including meta-analysis. Most likely, however, there is a need for further studies and these, in order to reach an adequate statistical power, would probably have to be multicentric.
4. Estimate of prevalence of precursors in autopsy series, controlling for selection bias leading to autopsy and estimate of association of prevalence to exposure to risk factors.
5. Assessment of the role, in the carcinogenic process, of oncogenic expression, evidence of viral infection (particularly HPV 16/18), and phenotype for debrisoquine metabolism.
6. Cost–benefit analyses of population-addressed interventions, under several assumptions of levels of effectiveness.

Systematic, population-based interventions for screening for early recognition of preneoplastic laryngeal lesions should wait for a better definition of the abovementioned issues. In any case, investigators embarking in these studies should ensure that their implementation by no means interferes with the goal of reducing tobacco smoking habits.

1. Tuyns AJ, Esteve J, Raymond L, *et al.* Cancer of the larynx/hypopharynx, tobacco and alcohol. The IARC International case–control study in Torino and Varese (Italy), Zaragoza and Navarra (Spain), Geneva (Switzerland) and Calvados (France). *Int J Cancer* 1988, **41**, 483–491.
2. Siemiatycki J, ed. *Risk Factors for Cancer in the Workplace.* Boca Raton, CRC Press, 1991.
3. Auerbach O, Hammond EC, Garfinkel L. Histologic changes in the larynx in relation to smoking habits. *Cancer* 1970, **25**, 92–104.
4. Mueller KM, Krohn BR. Smoking habits and their relationship to precancerous lesions of the larynx. *J Cancer Res Clin Oncol* 1980, **96**, 211–217.
5. Steiner W. Krebsvorsorge- und Frueherkennungsuntersuchungen der oberen Luft- und Speisewege. Ergebnise und Folgerungen aus drei Feldstudien. *MD-GBK* 1988, **53**, 25–31.
6. Farago L. Bericht ueber oto-rhino-laryngologische Krebsreihenuntersuchungen. *Mschr Ohrenheilk Laryngo-Rhinol* 1968, **102**, 588–601.
7. Micheli A, Baldasseroni A, Bruzzi P, *et al.* La sopravvivenza per tumori dell' apparato respiratorio: dati italiani su base di popolazione e confronti internazionali. *Ann Ist Super Sanita'* 1992, **28**, 71–90.
8. Cancer Registry of Norway. *Survival of cancer patients. Cases diagnosed in Norway* 1968–1975. Oslo, 1980.
9. Centre de Lutte contre le Cancer. *Enquete Permanente sur le Cancer. Resultats et Analyse de la Survie.* Doin Editeurs, Paris 1986.
10. Hakulinen T, Pukkala E, Hakama M, Lehtonen M, Saxen E, Teppo L. Survival of cancer patients in Finland 1953–74. *Ann Clin Res* 1981, **13** (suppl. 31), 1–101.
11. Registre Genevois des Tumeurs. *Cancer a Geneve: Incidence, Mortalité, Survie* 1970–86. Geneve, 1988.
12. Hoislet PE, Nielsen VM, Palvio D. Premalignant lesions of the larynx. A follow-up study. *Acta Otolaryngol* 1989, **107**, 150–155.
13. Cole P, Morrison AS. Basic issues in population screening for cancer. *J Natl Cancer Inst* 1980, **64**, 1263–1272.
14. Hakama M, Beral V, Cullen J, Parkin M. UICC Workshop on evaluating interventions to reduce cancer risk. *Int J Cancer* 1989, **43**, 967–969.
15. Miller AB. *Screening for Cancer.* New York, Academic Press, 1985.
16. Miller AB, Chamberlain J, Day NE, Hakama M, Prorok PC. Report on a workshop of the UICC project on evaluation of screening for cancer. *Int J Cancer* 1990, **46**, 761–769.
17. Prorok PC, Chamberlain J, Day NE, Hakama M, Miller AB. UICC workshop on the evaluation of screening programmes for cancer. *Int J Cancer* 1984, **34**, 1–4.
18. Succo G, Giordano C, Sorrentino R, Riva F, Boggero R, Sartoris A. Pre-invasive laryngeal cancer detection: screening and identification of high risk groups. *Med Sci Res* 1992, **202**, 11–12.
19. Lundgren J. The role of smear cytology in cancer of the larynx. In Ferleto A, ed. *Cancer of the Larynx.* Boca Raton, CRC Press, 1988, 77–89.
20. Ambrosch P, Ernst M, Pesch HJ, Steiner W. Endoskopischzytologisches Screening im oberen Aero-Digestivtrakt von Risikopersonen. *Arch Otorhinolaryngol* 1984, (Suppl. II), 87–89.
21. Matsuda M, Nagumo S, Horai T, Yoshino K. Cytological diagnosis of laryngeal and hypopharyngeal squamous cell carcinoma in sputum. *Acta Cytol* 1988, **32**, 655–657.
22. Gaafar H, Hussein M, El-Assi H. Cytopathology in cancer of the larynx. *J Otorhinolaryngol Relat Spec* 1989, **51**, 216–220.
23. Olde Kalter P, Lubsen H, Delemarre JFM, Snow GB. Squamous cell hyperplasia of the larynx (A clinical follow up study). *J Laryngol Otol* 1987, **101**, 579–588.
24. Bauer WC, McGavran MH. Carcinoma *in situ* and evaluation of epithelial changes in laryngopharyngeal biopsies. *J Am Med Assoc* 1972, **221**, 72–75.
25. Kleinsasser O. Ueber den Krankeheitsverlauf bei Epithelhyperplasien der Kehlkopfschleimhaut und die Entstehung von Karzinomen. *Ztschr f Laryngol Rhinol* 1963, **42**, 541–588.
26. Delemarre JFM. Den betekenis van de plaveiselcellige hyperplasie van het larynxepitheel. Thesis, Amsterdam, 1970 (quoted by Olde-Kalter *et al.*).
27. Hellquist H, Lundgren J, Olofsson J. Hyperplasia, dysplasia and carcinoma in situ of the vocal cord. A follow-up study. *Clin Otorinolaryngol* 1982, 7, 11–27.
28. Barnes L, Gnepp DL. Diseases of the larynx, hypopharynx and esophagus. In Barnes L, ed. *Surgical Pathology of the Head and Neck*, New York, Marcel Dekker, 1985, 156–158.
29. Silaminiku B, Bauer W, Painter C, Sessions D. The transformation of laryngeal keratosis into invasive carcinoma. *Am J Otolaryngol* 1989, **10**, 42–54.

The European School of Oncology

1993 FORTHCOMING EDUCATIONAL EVENTS

19th - 21st July
Training Course: Site: Vienna, Austria
Genito-Urinary Tract Tumours
L. Denis (BE), M. Marberger (AT)

***

8th - 10th September
Seminar: Site: Venice, Italy
Tumour Imaging
D. Bragg (US)

***

14th - 17th September
Training Course: Site: Moscow, CIS
Lung Cancer
M. Davydov (CIS), N. van Zandwijk (NL)

***

16th - 19th September
Training Course: Site: Athens, Greece
New Drugs in Cancer Therapy
N. Pavlidis (GR)

***

30th September - 2nd October
Training Course: Site: Vienna, Austria
Head and Neck Tumours
G.B. Snow (NL), B. Maciejewski (PL)

***

2nd - 4th October
Training Course: Site: New York, USA
Psychosocial Factors in Cancer Risk and Survival
J. Holland (US)

***

4th - 7th October
Advanced Residential Course: Site: Orta San Giulio, Italy
Breast Cancer
U. Veronesi (IT), M. Osborne (US)

17th - 21st October
Training Course: Site: Copenhagen, Denmark
Palliative Care of Cancer Patients
O.S. Nielsen (DK), V. Ventafridda (IT)

***

18th - 22nd October
Training Course: Site: Athens, Greece
Lymphomas
G. Pangalis (GR), A. Polliack (IL)

***

18th - 22nd October
Training Course: Site: Brussels, Belgium
Cancer Clinical Trials
J.G. McVie (GB), M. Baum (GB), D. Riley (GB), C. Molin (SE)

***

19th - 21st October
Seminar: Site: Venice, Italy
Growth Factors
M. Sporn (US)

***

25th - 29th October
Training Course: Site: Vienna, Austria
Good Clinical Practice
Friedman (US)

***

19th - 21st November
Seminar: Site: Venice, Italy
Gynaecological & Breast Tumours: Diagnostic and Prognostic Factors
A. Weger (SE), P. van Diest (NL), J. Lindholm (SE)

***

12th - 13th November
Training Course: Site: Vienna, Austria
Lung Cancer
Neumann (AT), N. van Zandwijk (NL)

For Advanced Residential Courses held in Italy, the registration fee is 650 ECU.
For Seminars held in Italy, the registration fee is 400 ECU.

For further information contact:
The Secretariat, European School of Oncology,
Via Venezian 18, 20133 Milan, Italy
Tel: (+ 39 2)70635923-2364283 Fax: (+ 39 2)2664662