

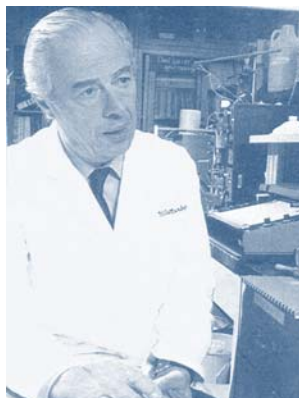
Prevention of Carcinogenesis of the Respiratory Tract by Chemopreventive Agents Delivered by Aerosol

Lee Wattenberg, MD

HIGHLIGHTS

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Dr. Lee Wattenberg

Biographical Sketch

Effective chemoprevention is extraordinarily difficult. I have often wondered about the optimal background for achieving this goal. My undergraduate education began when I entered the College of the City of New York in 1938. It was the postdepression period. Students were very serious as was I. The intellectual interplays were sharp and ferocious. Nothing was taken for granted. This was good experience for a potential scientist but somewhat irritating to others in social situations. The war years interrupted my education but then I entered the University of Minnesota Medical School in 1946, graduated in 1950 and then started training in Anatomic Pathology. Cancer became a central theme with a great deal of stimulation originating from the American Association for Cancer Research (AACR). I became an Instructor in the Department of Pathology at the University of Minnesota in 1956 and re-

mained in that department until the present except for two periods. The first was a year at the Chester Beatty Research Institute in London and the second, two years spent at the U.S. Army Walter Reed Medical Center (during the Korean War). The former provided insight as to the thought processes of the British scientists and their ways of doing research. The latter was a tour de force for observing the epidemiology of infectious diseases. It demonstrated how disease entities could be followed worldwide with great precision, strategies obviously important to cancer research.

I became interested in chemoprevention of cancer in about 1960 and several years thereafter published an overview paper entitled "Chemoprophylaxis of Chemical Carcinogenesis" (Cancer Research 26, 1520, 1966). The early years of chemoprevention had few participants. Two constant colleagues of great strength and intellectual abilities were Michael Sporn and Takashi Sugimura. The former provided an important American presence centered at the National Cancer Institute (USA) and the latter stimulated a vigorous effort amongst Japanese investigators at the National Cancer Center Research Institute (Japan) as well as elsewhere. Other scientists, many gifted and dedicated, followed in subsequent years but cancer chemoprevention never has had an adequate number of investigators. In 1992 I was elected President of the American Association of Cancer Research

which indicated recognition of the importance of the field. This past year Waun Ki Hong became the second "chemopreventer" to become President of the AACR, additional evidence of the field coming of age. The AACR constantly has been a very important force for chemoprevention. Although there has been a marked increase in the number of scientists contributing to the field it remains very much underexplored, particularly considering its importance.

Preventing Cancer of the Respiratory Tract – Use of Aerosol Technology

Cancer of the respiratory tract is the most common form of lethal cancer in men and women in the United States and most of the industrialized countries of the world. Chemoprevention thus far has been unsatisfactory. Few agents show efficacy and those that do have had only limited applicability. A strategy that appeared worth exploring was to administer chemopreventive agents by aerosol. This means of administration has several advantages. One is that the agent is delivered directly to the target tissue in an unmodified form. A second is the favorable ratio of concentrations of the agent reaching the respiratory tract as compared to that distributed throughout the systemic tissues. At the same dose, the initial concentration of the agent in the lung will be approximately thirty times greater when the

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Prevention of Carcinogenesis of the Respiratory Tract, continued

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compound is given by aerosol than if it were administered orally. This difference is made even more significant for agents that undergo metabolism in the systemic tissues. For many scientists there is a strangeness and unease about aerosol delivery. However it is being employed increasingly, not only for the treatment of respiratory diseases but also to meet special therapeutic demands of systemic diseases such as diabetes. In this instance reproducible delivery of insulin by aerosol is used in individuals for whom subcutaneous administration is undesirable.

Aerosol Delivery of Glucocorticoids – Budesonide, a Widely Used Antiasthmatic shows Potent Chemopreventive Activity

Several attributes are favorable for candidate chemopreventive compounds: it is essential for a compound to have efficacy; the compound must have an acceptable risk; information as to mechanism of action should be known; and the prior use of the compound either as a medicinal or for some other purpose is very helpful in indicating potential applicability for human use. Glucocorticoids can have all four of these attributes. As will be discussed below, they have chemopreventive efficacy and acceptable risk when administered by aerosol. Much is known about their mechanisms of action. They have the capacity to act as differentiating agents for lung, the ability to decrease formation of prostaglandins (suppression of phospholipase A₂ activity) and COX 2 synthesis, they can inhibit cell proliferation by effects on nuclear transcription and they also have the capacity to enhance cell-cell contacts. Each of these by itself has the potential of providing an inhibitory effect on carcinogenesis. Which combination of these mechanisms is responsible for the overall chemopreventive effects of glucocorticoid on carcinogenesis of the respiratory tract remains to be established. Finally, they manifest the fourth attribute. Glucocorticoids have been administered by aerosol to millions of asthmatics. A great deal is known about their adverse effects and acceptable dose levels (4-6).

The initial experiments that were carried out with glucocorticoids

entailed oral administration of dexamethasone. The compound was administered in the postinitiation period to A/J strain mice given benzo[a]pyrene as the carcinogen. The dexamethasone produced about 60% reduction in pulmonary tumor formation (7,8). However the oral dose was much too high to be applicable to the human so it was decided to try aerosol administration. Based on the properties of the various antiasthmatic glucocorticoids that had been used in humans, the second-generation compound, budesonide, was selected for investigation (4,6,7). This compound proved to be a potent inhibitor of pulmonary tumor formation in the A/J mouse model (9). At a dose of 25 µg/kg body weight administered for 20 seconds three times a week, a 60% reduction of pulmonary adenomas was produced (10). This dose corresponds to that used in humans for control of moderately severe asthma and is well tolerated (4). Comparable data were obtained with a second antiasthmatic glucocorticoid, beclomethasone dipropionate (4). A finding of potential interest with regard to the inhibitory effects of the glucocorticoids is that their potency is enhanced by the coadministration of myo-inositol in the diet (7,8,10). Myo-Inositol is a naturally occurring compound which has virtually no toxicity (11,12). Accordingly, its enhancing effect on the glucocorticoids could be of importance. Further studies of budesonide administered as a single compound in the mouse model have shown that it can inhibit late stages in the carcinogenic sequence, i.e. the progression of pulmonary adenomas to adenocarcinomas (unpublished).

Investigations of the effects of budesonide in smokers with bronchial dysplasia have been initiated by Stephen Lam and his colleagues. A Phase IIa study has been conducted to determine the potential effect of inhaled budesonide 800 µg twice daily in smokers with bronchial lesions. The results should be reported shortly.

Chemoprevention with 5-Fluorouracil

5-Fluorouracil (5-FU) is widely used for the chemotherapy of cancer. However, it also has been employed as a chemopreventive agent. It was the first

agent extensively used for chemoprevention of cancer in the human. This particular usage was in preventing the progression of the premalignant keratoses of the skin to cancer (13,14). Experimental studies in animals also demonstrated chemoprevention of epidermal carcinogenesis by 5-FU (15). 5-FU is generally administered intravenously, since absorption from the gastrointestinal tract is unpredictable and incomplete. However Tatsumura *et al* carried out experiments to determine if 5-FU could be administered by aerosol for the treatment of cancer of the lung (16). The results of this study have a direct bearing on the possible use of 5-FU for chemoprevention of carcinogenesis of the respiratory tract. In initial work, they performed tissue distribution studies and showed that administration of 5-FU by aerosol to dogs resulted in accumulation of the compound in the trachea, bronchi and regional lymph nodes. In contrast, the levels in other organs were very low. Only a very low concentration of 5-FU was found in the serum. When the compound was administered by aerosol to human subjects with lung cancers, similar data on tissue distribution were obtained.

Based on this background information, a treatment study was carried out on ten human subjects with lung cancer. Several went into complete remission, others had partial remissions and others did not respond. An important aspect of their work, which relates to the use of aerosol 5-FU for chemoprevention, is that they found very little toxicity (16). In view of the low toxicity and some responses with lung cancer, it appeared possible that aerosol 5-FU might be applicable to chemoprevention of carcinogenesis of the respiratory tract, particularly in high risk individuals. Accordingly, we conducted a study of its chemopreventive capacities in an animal model.

The model chosen for determining the chemopreventive efficacy of 5-FU was squamous cell carcinoma of the upper respiratory tract (oropharynx, larynx and trachea) of the hamster induced by administering 6 doses of MNU intratracheally using a modification of previously used procedures. 5-FU was administered by aerosol starting one week after the last dose of carcinogen. The 5-FU administrations resulted in a decreased

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Congress Report: Tumor Prevention and Genetics 2002

Second International Conference and 7th Annual Meeting of The International Society of Cancer Chemoprevention (ISCaC). St.Gallen 14th to 16th of February, 2002.

Rudolf Morant



Saint Gallen, Switzerland

The three-day conference at the University of St.Gallen attracted 230 participants from 30 countries. The conference was cosponsored by the International Society of Cancer Chemoprevention (President: F.Meysken, Irvine, USA), the European School of Oncology (Director: A.Costa,Pavia, Italy) and by the local host, St.Gallen Oncology Conferences represented by HJ.Senn and R.Morant (St.Gallen, Switzerland).

The participants represented various backgrounds ranging from basic scientists and geneticists to clinical urologists, gynecologists, medical oncologists, surgeons and epidemiologists, offering an opportunity for interesting interactions and discussions how to advance this field.

The topics covered the search for and the assessment of new cancer susceptibility genes and preclinical models of cancer chemoprevention. A more detailed discussion involved clinical chemoprevention and screening efforts of skin tumors, breast cancer, prostate cancer and colorectal carcinomas. D.L. Wickerham (NSABP, Pittsburgh, USA) discussed the current large STAR trial. This randomized study compares tamoxifen to raloxifene

in the prevention of breast cancer in high-risk women and has already randomized more than 12000 women (target: 22000). He also discussed, why the findings of the NSABP-P1, a significant reduction of breast cancer incidence by nearly 50% with tamoxifen prevention, were not yet more widely incorporated into clinical practice. T. Powles (Royal Marsden Hospital, London, UK) warned, that there were no data yet to prove the efficacy of tamoxifen in the subgroup of women with high penetrance breast cancer predisposing gene mutations. J. Cuzick (Imperial Cancer Research Fund, London,UK) discussed the planned IBIS-2 trial, which will compare tamoxifen with the very promising drug anastrozole. This aromatase inhibitor has been recently proven superior to tamoxifen in the adjuvant setting (ATAC trial).

A very lively discussion, moderated by M. Osborne (Strang Cancer Prevention Center, New York, USA) and J.Cuzick involved the controversial views of the value of mammography screening by A. Miller (Deutsches Krebsforschungszentrum Heidelberg, Germany) and S. Feig (Mount Sinai Medical Center, New York, USA). The

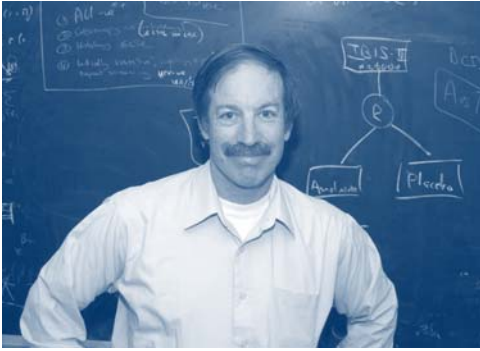
current discussions were initiated by two Lancet papers (2001, 2002) by Gotzsche and Olsen. G. Rennert (National Breast Cancer Screening Program, Haifa, Israel) discussed the political dimensions and influences of screening programs. In spite of these discussions the vast majority of researchers in the field continue to support mammography screening.

E. Klein (Cleveland Clinic, USA), chairman of the current SELECT trial, discussed the chemoprevention of prostate cancer with selenium and/or vitamin E. Results of this large randomized US trial of the SWOG (South West Oncology Group) are not to be expected before the year 2013. G. Bartsch (Innsbruck, Austria) reported the significant drop in mortality from prostate cancer following PSA mass screening in the state of Tyrol and gave a current update of the screening process. As it is not a randomized trial, HP Schmid (Kantonsspital St.Gallen, Switzerland), advised against introducing mass screening of PSA before the availability of the data from the large randomized trials in Europe (European Randomized Study of Screening for Prostate Cancer, ERSPC) and America (Prostate, Lung, Colon and Ovary Cancer Screening Project, PLCO).

After interesting discussions of epidemiology (P. Boyle, Istituto Europeo di Oncologia, Milano, Italy), genetics (HJ Müller, Basle University, Switzerland) and possible approaches to chemoprevention (M. Lipkin, Strang Cancer Prevention Center, New York, USA), G.Rennert (National Cancer Control Center, Haifa, Israel) reported the encouraging results of screening for fecal occult blood (FOB) in Israel. This low-technology, cost-effective measure has been shown to lower mortality from colorectal cancer in several randomized trials by 15-30%. An alterna-

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Profile — Jack Cuzick, PhD



Biographical sketch

Jack Cuzick, Ph.D., began life as a pure mathematician, with an undergraduate degree in the subject from Harvey Mudd College in Claremont, California, a Masters degree from the University of London, and a PhD degree from the Claremont Graduate School in 1974. His thesis was on the sample path oscillatory behaviour of Gaussian stochastic processes and led to studies of such arcane subjects as fractional dimension. His first academic job was as an Assistant Professor in the Department of Mathematical Statistics at Columbia University in New York, where he worked on problems in theoretical statistics in Herbert Robbins' group. That activity evolved into an interest in the methods for analysis of clinical trials, and in 1978 he obtained a one-year IARC fellowship to learn more about the practical aspects of clinical trials with Richard Peto and Richard Doll in Oxford. He soon became more interested in the analytic problems of real clinical trials and stayed on in Oxford for 4 years, initially working on the MRC treatment trials for multiple myeloma.

At that time it became clear that clinical trials offered an opportunity to learn much more about disease, than simply which treatment is most efficacious, and he began a series of epidemiological case-control studies to study disease aetiology linked to clinical trials in multiple myeloma, non-Hodgkin's lymphoma and later pancreas and breast cancer. When Richard Doll retired for the first time (as the then Regius Professor of Medicine) in 1982 (he still continues an amazing pace of activity at age of almost 90), Prof. Cuzick moved to London to set up his own group at the Imperial Cancer Research Fund. By that stage his focus was directed towards prevention and screening, and his inaugural lecture was entitled 'The Prevention of Breast

Cancer'. The experience in clinical trials and epidemiology gained in Oxford provided an excellent background for tackling problems in this 'interface' area. The Department has since grown substantially, with a number of independent groups working on screening and prevention studies for a range of cancers. It has recently moved to the Wolfson Institute of Preventive Medicine at St Bartholomew's Medical School, where Jack Cuzick is now Professor of Epidemiology, Mathematics and Statistics at Queen Mary and the London College in the University of London. The group continues to be supported by Cancer Research UK, which is the new charity arising from the merger of the Imperial Cancer Research Fund and the Cancer Research Campaign.

Group structure

The group now comprises 31 members of which there are 3 group leaders and 2 team leaders (Figure 1). The group comprises 8 Statisticians, 2 Clinicians, 10 Data Managers, 5 Research Nurses, 4 Laboratory Scientists and 2 Administrative staff.

Programme structure Introduction

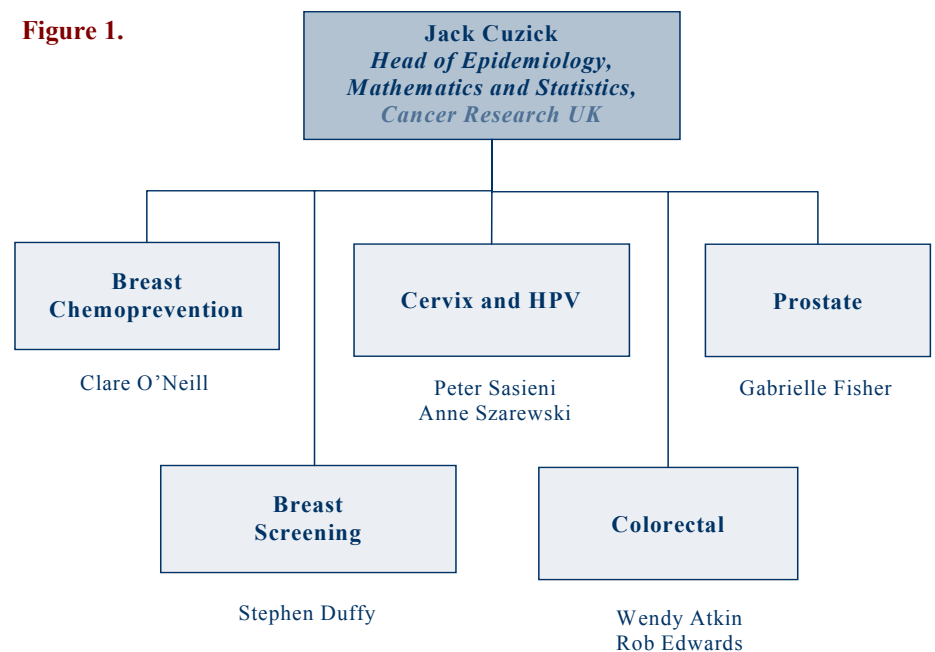
The broad remit of the group relates to any aspect of cancer epidemiology, but it has a very clear focus on screening and prevention. Although these two activities have a different scientific basis at the fundamental level, from

a public health point of view screening and prevention are closely linked. Screening is an activity in which interventions are offered to the whole population. It not only provides an excellent opportunity to deliver health education messages about prevention to the general public, but also a prime opportunity to identify high risk individuals who would benefit from targeted interventions such as chemoprevention. Currently this opportunity is not well exploited, and ways to make this a more routine activity are being developed. A particularly important example is breast cancer, where mammograms are only used for early detection of small cancers. However, they also provide information about the tissue structure of the breast via regions of radiographic density, and this is currently the single best predictor of breast cancer risk in terms of population attributable risk. Other well-defined areas also exist, including targeted use of COX-2 inhibitors and other agents in individuals found to have large or high risk adenomas on endoscopic screening for bowel cancer, and use of immunostimulants or other agents such as indole-3-carbinol in women with abnormal Pap smears.

Breast Cancer Chemoprevention

The IBIS research programme has been
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Figure 1.



investigating breast cancer chemoprevention since 1985. The IBIS-I trial which commenced in 1992 studied the use of tamoxifen among a group of 7139 women aged 35 to 70 with an increased risk of developing breast cancer. These women were largely recruited from UK and Australian centres, although there was much interest from other European groups. The first analysis of the IBIS-I data was published recently (IBIS, 2002) and indicates that tamoxifen can reduce breast cancer incidence by about one third. This is supported by our overview of all breast cancer prevention trials (Cuzick, *et al.* 2002), where it is clear that tamoxifen reduces ER positive breast cancer by about one-half, but has no effect on ER negative cancers. These data have also contributed to a heightened awareness of the increased risk of thromboembolic events associated with the use of tamoxifen. Women in the IBIS-I trial continue to be monitored and followed up for long-term assessment.

The IBIS-II trial is about to commence recruitment. This trial is split into two strata, both of which involve postmenopausal women only. The prevention stratum will compare the aromatase inhibitor anastrozole against placebo among women at increased risk of breast cancer. The ductal carcinoma *in situ* (DCIS) stratum will compare anastrozole against tamoxifen in women who have had a local excision with clear margins. Ethical and scientific approvals have been obtained and the trial will be launched late in 2002. There has been considerable interest from many centres around the world, and it is planned that the 10,000 women required will be recruited within the next 4 years. These studies are also being used to evaluate a range of biomarkers to predict breast cancer development, and who is most likely to benefit from endocrine chemoprevention. Other smaller pilot studies using the LHRH agonist goserelin plus raloxifene, as an add-back, are currently ongoing to evaluate the feasibility of this approach in very high risk premenopausal women. The coordination and data management for all aspects of IBIS research is organised and conducted within the department.

Work on evaluating breast cancer screening is headed up by Professor Stephen

Duffy who is a recent addition to the department. In addition to studies evaluating the randomised trials, current efforts are focussed on evaluating service screening and the use of mammographic density as a risk factor for cancer. It has been known for decades that mammographic density is related to breast cancer risk (Warner, *et al.* 1992). Various measures of breast density are available, but overall a mammogram showing a majority of dense tissue is associated with an approximate doubling of risk of breast cancer, and that this can account for 25-30% of breast cancer cases, as compared to the 5% typically observed for other major breast cancer risk factors. Breast density is also related to other known risk factors for breast cancer. More interestingly, breast density is alterable, being reduced in response to antiestrogenic stimuli from tamoxifen or isoflavones (Atkinson, *et al.* 1999; Jakes, *et al.* 2002).

Breast density also has a potential role in early interpretation of chemoprevention studies. The fact that it is strongly related to risk of breast cancer, and that it is amenable to reduction from antiestrogenic treatment strongly suggest that changes in density might be a suitable early indicator of efficacy in chemoprevention trials. To qualify as such, it needs to be demonstrated that an induced reduction in breast density confers a reduction in subsequent risk of breast cancer at the individual level. Studies within IBIS are under way to address this question.

Cervix Cancer

HPV infection is necessary for the development of cervical cancer. For this reason we have been investigating whether testing women for HPV infection could be used in a screening programme to identify those who have early stages of disease that could, if left untreated, turn into cancer. A 12,000 women multi-centre screening study has recently been completed, using HPV testing which has demonstrated a much higher sensitivity (98%) than the Pap smear (79%) but lower specificity (93.4% vs 95.9%, respectively)

Another issue, understanding is the duration of protection associated with a negative HPV test. We are looking at 3000 women who were tested by cytology and

HPV testing 5 years ago, to assess persistence and the long-term prognostic value of both negative and positive HPV tests. All untreated women who took part in the original study are asked to come for repeat cytology and HPV testing. Other studies are evaluating the use of self-sampling for HPV as a simple method of improving compliance to screening.

We are also interested in other factors that influence why some women with HPV infections go on to get cervical cancer, whilst the vast majority do not. Clearly the host immune response is important and certain chemoprevention agents may boost this response.

Diindolymethane (DIM) is a metabolic product of indole-3-carbinol (I3C) which is a naturally occurring chemical in brassica (vegetables such as cabbage and broccoli). DIM and I3C have been shown to have various properties (such as causing apoptosis) in cell culture that make them promising chemo-preventative agents. Limited clinical experience suggests that DIM is extremely well tolerated and may be effective in treating human papillomavirus (HPV) related disease. Two randomised controlled clinical trials of DIM and cervical neoplasia are currently being organised. One large study (3000 women) will recruit women who have a mildly abnormal cervical smear. They will take either DIM or placebo for six months before being evaluated (and if necessary definitively treated) at colposcopy. The second trial will be smaller and will study women who have been referred for colposcopy. Where clinically acceptable, these women will be closely monitored by colposcopy for up to 6 months to see whether DIM can facilitate disease regression.

Methods for evaluating Pap smear screening programmes using case-control methods are also being developed and implemented. Unfortunately, the conventional Pap smear has had little or no impact on cervical cancer rates in developing countries. A variety of different cervical screening tests on 5000 women in a region of Peru in the Amazonian jungle are being evaluated. In this setting test needs to be cheap and simple with immediate treatment by cryotherapy. The direct

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Profile—Cuzick, Continued

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visual inspection of the cervix (after application of dilute acetic acid) is one possibility, but there are concerns about both sensitivity and over-treatment due to poor specificity. HPV testing may be useful in both instances as well as newer proliferation markers, such as p16. Initial screening is now complete for this group and we are currently in the process of completing the follow-up.

Vaccination against HPV is also an important long-term strategy which may eventually obviate the need for screening. This is particularly important for the developing world, and possibilities for a vaccination trial in Peru are being explored.

Colorectal Cancer

Current work on colorectal cancer is focused on screening by flexible sigmoidoscopy. It is likely that a single test provided around age 60 may offer substantial long-term protection against cancer in the distal bowel. A trial of 200,000 men and women aged 55-64 is ongoing to evaluate this. Baseline screens have all been completed and a high yield of the precursor adenomas was obtained (UK Flexible Sigmoidoscopy Screening Trial Investigators, 2002). In particular we identified about 5% of the population with high risk adenomas who are most likely to need additional surveillance and who would benefit from chemoprevention strategies. Future work will focus on the risk in these individuals, and the ability of chemopreventive agents to reduce it.

Prostate

A great deal of screening activity and some chemoprevention trials are ongoing for prostate cancer. A key to the success and proper focus of these activities is a better understanding of the natural history of

early lesions. Our research aims to improve the management of patients diagnosed with early prostate cancer. The work will also provide much needed information about the natural history of the disease.

We are investigating the outcome of disease in a population-based cohort of men with clinically localized disease who were treated by "watchful waiting" or hormones only. Neither the causes, nor the factors affecting tumour progression are well understood. However it is known that in a large proportion of histological proven cases, the cancer will not progress within the man's lifetime. We aim to develop prognostic models to address these issues and to identify new additional markers of disease progression by analysing data on several thousand men, aged <76 years, with clinically localized disease diagnosed after the widespread use of the PSA test. The work will result in a fully documented tissue micro array resource of a well-defined cohort. This will be used to assess the prognostic value of new markers suggested from gene and protein expression studies.

Statistical methodology

The department also has an active interest in developing and studying new statistical techniques for use in epidemiological studies and clinical trials. The work goes hand-in-hand with specific projects and adds an important and satisfying dimension to our work.

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Congress Report: Tumor Prevention and Genetics 2002, continued

tive method of screening was presented by J.Cuzick with the presentation of the current mass screening trial using flexible sigmoidoscopy.

The abstracts of the conference have been published in Supplement 1, vol 38 of the *European Journal of Cancer*, February 2002 and the full manuscripts will be published in *Recent Results in Cancer Research* by Springer in fall of 2002.

The third international Conference on Tumor Prevention and Genetics is already scheduled to be held on February 12 to 14, 2004 in St.Gallen, Switzerland.

Prevention of Carcinogenesis of the Respiratory Tract, continued

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incidence of infiltrating squamous carcinomas. Control animals showed about a 30% incidence of infiltrating squamous cell carcinomas. This incidence was reduced to 15% in a group receiving dose of 5-FU of 1.45 mg/kg and 10% in hamsters receiving a dose of 2.08 mg/kg of 5-FU. Cheilitis did not occur nor was there an effect on the leukocyte count or differential (17).

Efficacy against squamous cell carcinogenesis of the respiratory tract is important because of its high incidence in this anatomic region and the poor response to available chemopreventive agents. The chemoprevention work with 5-FU described is in an early phase of its development. The magnitude of the inhibition that can be obtained with aerosol 5-FU and the conditions under which it occurs remain to be established. An issue of importance with 5-FU is its safety. In the limited administration by aerosol to humans and in the animal studies, significant toxicity was not encountered. Further work is required to confirm these data. Aerosol administration provides an optimal delivery system to the respiratory tract. The studies with 5-FU draws attention to the possibility of employing chemopreventive agents that could not be given by other routes of administration.

In summary, we are engaged in a chemoprevention program focusing on prevention of cancer of the respiratory tract. Considerable emphasis is being placed on aerosol delivery. This procedure produces a favorable ratio of the dose delivered to the target organ to that of systemic tissues. Good techniques are available for delivery of chemopreventive agents by aerosol. With these techniques initial success has been obtained with two compounds, budesonide and 5-FU. The former has an excellent record of efficacy in preclinical animal models and has reached the stage of a Phase IIa clinical trial in the human aimed at evaluating its efficacy in reversing or preventing progression of bronchial dysplasias. The second compound, 5-FU, is in an early stage of investigation. It provides evidence that aerosol administration may broaden the range of potent chemopreventive agents that can be used for preventing cancers of the respiratory tract.

Much of the support for the research described above has come from the Contracts Program of the Chemopreventive

Agent Research Development Research Group at the National Cancer Institute.

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