

as a result of increased occurrence of CRF (2). In 87 patients treated with cisplatin-bleomycin chemotherapy, major cardiac events were found in 5 (6%; age at time of event 30–42 y; 9–16 y after chemotherapy): 2 had a myocardial infarction (1 fatal) and 3 had angina pectoris with proven myocardial ischemia. An increased observed-to-expected ratio of 7.1 (95% CI 1.9–18.3) for coronary artery disease, as compared with the Dutch population, was found. Of the 87 patients, 62 were additionally evaluated for cardiac damage and CRF. Their cardiovascular risk profile was compared with that of 40 patients with comparable age and follow-up duration treated with orchidectomy only for stage I disease. Additional cardiovascular damage after chemotherapy was observed: subclinical dysfunction of the left ventricle, microalbuminuria, and a raise in markers of endothelial damage (2). Furthermore, we observed an unfavorable profile of CRF resembling syndrome-X (or metabolic syndrome) with insulin resistance, dyslipidemia, hypertension, and endothelial damage in ~30% of the cured TC patients (3). It remains unresolved whether the increased number of cardiac events and the observed cardiovascular damage are a direct toxic effect of the chemotherapy or whether they are a result of the increased incidence of CRF. One can hypothesize that endothelial damage caused by the bleomycin-cisplatin chemotherapy together with the consequences of subclinical hypogonadism are the main causes of the observed increase in CRF and cardiovascular disease (CVD). Microalbuminuria, present in about one-fourth of the patients who received this chemotherapy, has been identified as an independent risk factor for CVD in large trials and thus might contribute to the high cardiac event rate, because endothelial activation is an early event in atherogenesis. We recently found that in these TC survivors, circulating platinum levels are still detectable more than 20 y after cisplatin combination chemotherapy (4). Chronic exposition of endothelium to platinum may therefore play an additional role in the development of the CVD.

Long-term survivors of metastatic TC appear to have an increased risk for CVD that is accompanied by an unfavorable CRF profile and signs of persisting endothelial damage. When compared with the threat for secondary malignancies after chemotherapy for TC, the increased risk for CVD may perhaps represent even a bigger problem. Unraveling of the pathogenesis of CVD after chemotherapy for TC cancer is of great importance and is the focus of several cross-sectional and prospective studies in TC patients currently underway at our institution. These investigations will provide opportunities for tailoring potential toxic treatment and guiding primary and secondary prevention strategies for serious side effects of chemotherapy treatment.

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Second Primary Cancers: An Overview. Lois B. Travis. Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD.

As survival after a diagnosis of cancer improves, identification and quantification of the late effects of therapy become critical. The occurrence of second malignant neoplasms constitutes one of the most serious side effects of successful radiotherapy and chemotherapy. Although acute myeloid leukemia was the first observed carcinogenic effect of cancer treatment, solid tumors now represent the largest second cancer burden in some populations of survivors. Second primary cancers, however, do not necessarily represent an adverse effect of therapy but may reflect the operation of host determinants, shared etiologic influences, gene-environment interactions, and other factors. Critical to any assessment of second cancers is an evaluation of whether their occurrence exceeds the expectation and the size of the risk. Both cohort and case-control study designs have been used to quantify risk and will be described in the presentation. The characterization and estimation of second cancer risk is important in terms of patient management, enabling physicians to make informed decisions with regard to optimal therapy of the initial cancer, balancing efficacy against early and late toxicity. These investigations also provide a singular opportunity to study carcinogenesis because patients are exposed to measured amounts of potentially cancer-inducing agents, and dose-response relationships with radiation and chemotherapy can frequently be defined. The presentation will provide an overview of second primary cancers, focusing on selected highlights, with an emphasis on radiotherapy and chemotherapy in adults; areas for future research will also be summarized. Although cancer treatment is a double-edged sword, it should always be kept in mind that advances in therapy are largely responsible for the enormous improvements that have been observed in patient survival. Thus, the benefits of most cancer treatments far exceed any risk of developing a second cancer.

Molecular Epidemiology of Cancer. Fred F. Kadlubar. National Center for Toxicological Research, Jefferson, AR.

Molecular epidemiology not only provides us with the ability to predict interindividual differences in susceptibility to environmental exposures that lead to clinical disease, but also indicates effective prevention strategies. Biomarkers of susceptibility include polymorphisms in carcinogen and drug metabolism, DNA repair, and genes that control cell growth. Wide variations in carcinogen and drug metabolism are important determinants of individual cancer susceptibility. Such polymorphisms in carcinogen- and drug-metabolizing enzymes may be due to heritable or environmental factors, and the application of metabolic phenotyping and genotyping methods to epidemiologic studies has provided new insights into such gene-environment interactions. Polymorphisms in DNA repair or processing became evident from rare hereditary disorders involving defective repair or chromosomal stability. About 130 different genes are involved in DNA repair, and lower DNA repair proficiency or polymorphisms have recently been associated with increased susceptibility to cancers of the skin, brain, lung, stomach, breast, bladder, head and neck, and colon. Although over 100 genes have been identified that serve as positive or negative regulators of cell growth as well as of the cell cycle and apoptosis, these have been largely associated with rare hereditary disorders involving greatly increased human

cancer susceptibility. The common polymorphisms in these genes have not yet received much attention, but studies indicate that these may be associated with breast, endometrial, ovarian, bladder, colon, lung, thyroid, gastric, nasopharyngeal, esophageal, multiple myeloma, and head and neck cancer. It should be emphasized that although these common genetic polymorphisms do not alone confer high individual cancer risk (low penetrance), they involve a large proportion of the population (high prevalence). Thus, their attributable risk can be high because it can affect a larger number of people in comparison with those rare defects (low prevalence) that greatly increase disease risk (high penetrance) but in much fewer individuals (low attributable risk). The combination of several high risk alleles in a single individual (gene-gene interactions) can result in further increases in relative risk. When increased relative risk is combined with carcinogen exposure, the probability of developing cancer becomes quite high. Examples of such multigene-environment interactions from our ongoing molecular epidemiologic studies of colon, breast, and prostate cancer will be presented.

Intraepithelial Neoplasia: Target for Prevention. Bernard Levin. Division of Cancer Prevention, University of Texas M.D. Anderson Cancer Center, Houston, TX.

Carcinogenesis is characterized by progressive disorganization at the molecular, cellular, and tissue levels. This process may be lengthy—sometimes up to several decades. Our understanding of carcinogenesis has been advanced by the concept of intraepithelial neoplasia (IEN). IEN usually occurs in most epithelial tissues as “moderate to severe dysplasia, is on the causal pathway leading from normal tissue to cancer and is close in stage of progression to cancer (invasive neoplasia)” (1). It is often multifocal and multiclonal. Subjects with IEN, particularly if severe, are at increased risk for developing invasive cancer in affected tissues. IEN may be detectable by familiar methods (e.g., use of endoscopy to locate adenomas in familial adenomatous polyposis) or discernible at a very early stage of development by using novel genomic, imaging, or proteomic techniques. The management of intraepithelial neoplasia requires an understanding of the natural history of specific lesions. Interventions may depend on the site or severity of the condition and the potential effect on quality of life. Interventions may include surgical removal of the IEN (e.g., severely dysplastic Barrett’s esophagus), colonoscopic polypectomy (sporadic adenomas), or medical approaches (chemoprevention). Chemoprevention is the use of specific chemical compounds to prevent, inhibit, or reverse carcinogenesis before the development of invasive disease (2,3). Trials of chemopreventive agents are often large, lengthy, and expensive. The design and successful execution of chemopreventive trials often involves a complex set of partners including individuals at risk, the pharmaceutical industry, and federal agencies such as the National Cancer Institute and the Food and Drug Administration. To date, only 5 compounds have been approved for the treatment of IEN: topical 5-FU and topical diclofenac for multiple actinic-keratoses; intravesical bacillus Calmette-Guérin for bladder carcinoma in situ; tamoxifen for diffuse carcinoma in situ after lumpectomy and breast radiotherapy; celecoxib for adenomatous polyps in patients with familial adenomatous polyposis. In addition to defining molecular targets for chemopreventive intervention, genomic and pro-

teomic techniques may help to refine entry criteria for trials aimed at eradication or control of IEN as well as enhance correlations with the outcome of such interventions.

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The Influence of Prenatal and Childhood Nutrition on the Development of Cancer. David Gunnell,* George Davey Smith,* Jeff Holly.† *Department of Social Medicine and †Division of Surgery, University of Bristol, Bristol, UK.

An individual’s risk of developing cancer is determined by genetic predisposition together with the accumulation of adverse and protective exposures occurring from conception through to adulthood. Migrant studies, secular trends in incidence, and international variations point to the importance of environmental exposures in cancer etiology. There is growing recognition that patterns of nutrition in utero and throughout childhood influence risk of breast, prostate, colorectal, hematopoietic, and some other cancers. Indirect evidence for this comes from studies showing that anthropometric markers of prenatal and childhood growth—such as birthweight (growth in utero), leg length (prepubertal growth), and height (growth throughout childhood)—are positively associated with risk of a number of common malignancies. Intriguingly, in some studies low birthweight infants (<2500 g) also appear to be at increased risk. More direct evidence for the role of specific aspects of childhood diet comes from the relatively few studies with measures of diet recorded in childhood that are of sufficient size and duration of follow-up to investigate diet-cancer associations. Analysis of the Boyd Orr cohort—a 60-y follow-up of ~5000 subjects with detailed contemporaneously recorded childhood (family) diet—suggests that low energy and high fruit intake in childhood are associated with lower cancer risk. Recent epidemiologic research suggests that nutritional influences on circulating levels of insulin-like growth factor-I (IGF-I) provide a plausible explanation for patterns of cancer risk in relation to diet, low and high birthweight, childhood height, and leg length. High levels of IGF-I promote cell turnover and reduce apoptosis; high levels are associated with raised birthweight and greater childhood height. High levels of energy, milk, dairy products and animal protein intake are associated with raised IGF-I. There is some evidence that vegetable intake is associated with low IGF-I levels but these aspects of diet may operate through other pathways, such as by reducing oxidative damage to DNA. Although raised IGF-I levels are associated with increased risk of prostate, colorectal, and premenopausal breast cancer, they may protect against other chronic diseases such as heart disease and neurodegeneration. Public health policies aimed at modifying circulating levels of IGFs should therefore be carefully tailored to optimize overall population health.