many pediatric leukemias are initiated in utero. Epidemiological studies have identified high birth weight, absence of early life infections, pesticides, and low maternal folic acid/vitamin supplementation as risk factors for childhood leukemia. Some relevant genetic polymorphisms, particularly in the folate pathway, have also been implicated. Further, leukemia-associated translocations (e.g., MLL/AF4, MLL/AF9, TEL-AML1, AML1-ETO) in neonatal blood spots have been observed in children who later developed ALL and AML. Unfortunately, primary reliance on the case-control approach and little integration across disciplines is hampering progress in understanding relationships. For example, geneticists have developed MLL/AF4 and MLL/AF9 knock-in mice that develop hematopoietic neoplasms, and TEL-AML1 and AML1-ETO transgenic mice that do not, but none has been used to explore suspected environmental risk factors. We are integrating novel approaches across several disciplines to investigate the causes of childhood leukemia. One initiative includes investigating the potential role of environmental exposures (e.g. maternal folic acid, pesticides) in murine models through tracking disease outcome and gene methylation and expression in appropriate target cells in offspring. In an initial effort to understand the mechanism by which maternal folic acid (FA) impacts the risk of childhood leukemia, we conducted a pilot study using a murine model that examines gene expression in B-lineage cells of the offspring of mothers randomized to low (0.3 mg/kg), control (2.0 mg/kg) and high (8.0 mg/kg) FA diets prior to conception through weaning. Thirty three genes were identified as differentially expressed between offspring of mothers assigned to different dietary groups. Five genes that were up or down regulated by at least 2-fold in the low or high FA groups compared to the control group have been selected for validation by comparative RT-PCR: CDH8, GHR, E2F3, NEU3, and HOXD9. The second initiative involves establishing a pregnancy cohort to investigate the functional relationship between specific exposures and their biomarkers (e.g. cytokines, folate, growth factors) in cord blood and neonatal blood spots in relation to relevant risk factors (e.g., infection, maternal vitamin supplementation, high birth weight) and genetic polymorphisms of interest. Data generated from these initiatives will inform future studies of childhood leukemia and will also be applicable to other cancers.

15-IS
Evaluating cumulative evidence in genomic epidemiology

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The evaluation of cumulative evidence in human genome epidemiology presents several challenges. With the advent of massive-testing high-throughput platforms, the amount and complexity of data is unprecedented. Moreover, the concept of sufficient replication has evolved over time and more stringent criteria are now required to claim that an association with robust credibility has been detected. This may reduce the problem of having too many associations proposed, of which only a trifle stand the test of time. Stringent and systematic criteria are needed to enhance our understanding of the rapidly evolving status of the field of human genome epidemiological associations and to place these associations in context. One interim effort has been the generation of the Venice criteria for grading the credibility of genetic associations (Ioannidis et al., International Journal of Epidemiology 2008). The Venice criteria have three axes on which the evidence is appraised: amount of evidence, replication consistency, and protection from bias. Each of the three axes is rated from A to C. There is also a composite grading across the three axes. Associations that get an A in all three axes are considered to have “strong” epidemiological credibility; those that get at least one B but not C are considered to have “moderate” epidemiological credibility; and those that get at least one C are graded as having “weak” credibility. The advent of large-scale evidence in large scale collaborative studies and in synopses of associations in whole fields has allowed the application of the Venice criteria in various settings. I will present several examples of the application of the criteria in associations on cancer and other fields and will highlight some of the remaining challenges. Further refinement and validation of the performance of these criteria would be useful.

16-IS
Transdisciplinary Science Approaches for Molecular Epidemiology

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To make further significant advances in cancer molecular epidemiologic research, a transdisciplinary science approach is needed that integrates the study of the biologic nature of cancer and its clinical applications with behavioral and social influences on cancer. Molecular epidemiology could be more integrated into a broader approach to solving cancer-related problems by seeking collaborative approaches that draw on other disciplines. This transdisciplinary approach may be a more effective way to apply the finding of molecular epidemiology for use in therapeutic, behavioral, and public health interventions to reduce the burden of cancer by taking into account the behavior and social determinants of cancer. Such an approach seeks to discover interactions between social, environmental, behavioral and biologic factors in cancer etiology. In this presentation I present 1) a brief historical perspective on the origins of transdisciplinary thinking in science, 2) a cross-disciplinary, multi-level framework for organizing cancer research along these lines, 3) some examples, and 4) a review some of the challenges in adopting this approach. The goal is to promote a more complete understanding of the causes of cancer that will lead to improved translation and implementation of the results of research.

17-IS
Abstract not received

18-IS
Future perspectives of molecular cancer epidemiology

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Our understanding of cancer is evolving rapidly through the application of “omic” technologies and the importance of epigenetic changes is becoming apparent. Genomics is being used to find genetic variants conferring susceptibility to cancer through genome-wide scans of >500K polymorphisms and high-throughput sequencing. High quality DNA is needed for this endeavor. Transcriptomics (gene expression profiling) is providing insights into carcinogenic mechanisms and is being used to sub-classify cancers. Methods that preserve and isolate all forms of RNA are critical. Proteomics and metabolomics are newer technologies that are likely to impact our understanding of cancer etiology in the near future. Proteomics holds special promise in understanding the histone code that controls gene expression. Metabolomic profiles are highly dependent upon diet and standardized collection procedures are key, but novel insights could be obtained through this approach. The epigenome has been less explored to date, but new microarrays that measure hundreds of microRNAs or the CpG promoter methylation status of hundreds of genes are now available. Cell heterogeneity poses the same problem for epigenomics as it does for mutation analysis. The mutations or epigenetic changes of importance are usually present in only a small number of clonal cells. Fortunately, lab-on-a-chip technologies have now advanced to the point that single cell genetic analysis is feasible. However, intact cells or nuclei will be needed for these assays, again posing a problem to the epidemiologist. Finally, advances in nanotechnology should allow for multiplexed immunoassays of protein adducts, cytokines and antibodies in very small quantities of human material, such as pieces of dried blood spots and a few microliters of serum. At last, some good news for epidemiologists, as these nano-immunoassays can be combined with microfluidics on lab-on-a-chip microdevices so that they are applicable in large-scale cohort studies and in samples collected in low-resource environments such as developing countries. Lab-on-a-chip microdevices therefore hold promise in revolutionizing molecular cancer epidemiology in the not-too-distant future through the emerging field of exposure biology.

Proffered papers – Abstracts

1-PP
Serologic response to HPV and the risk of head and neck cancer

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Introduction: Head and neck squamous cell carcinomas (HNSCC) are frequent cancers in Latin America. Tobacco and alcohol are the main risk factors, although recent studies support a role for human papillomavirus (HPV) in a subgroup of HNSCC. **Objectives:** To evaluate the association between serologic response to HPV infection and HNSCC in a Latin-American population. **Methods:** A hospital-based case-control study was conducted in three countries from Latin America (Argentina, Brazil, and Cuba) to evaluate risk factors for HNSCC. Using multiplex serology, serum