


Introduction to Medical Oncology and Clinical Trials

Elizabeth Griffiths, MD
Assistant Professor of Medicine
Leukemia Section
Roswell Park Cancer Institute
elizabeth.griffiths@roswellpark.org

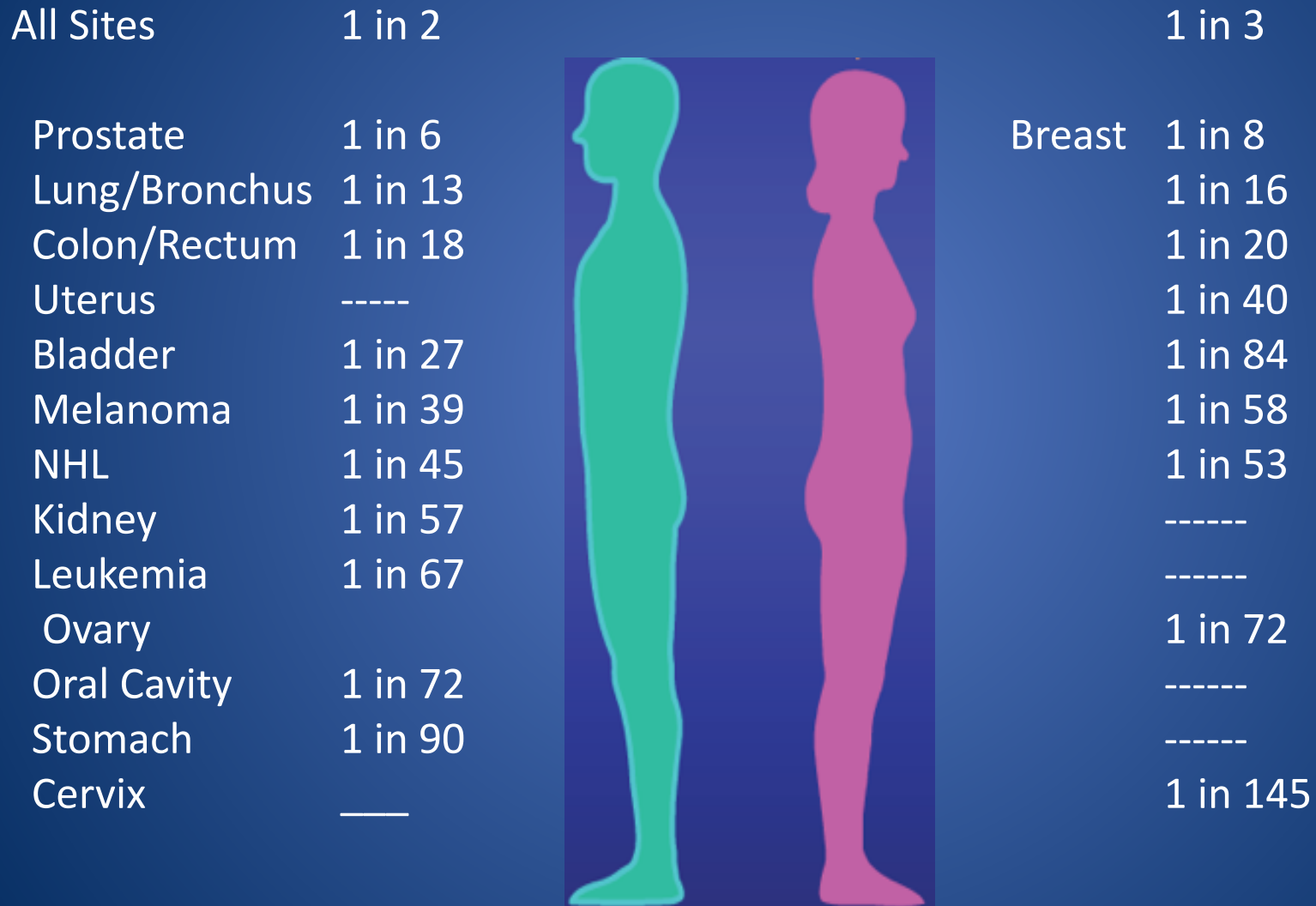
Outline

- Burden of Disease
- Modes of Treatment and Successes
- Medical Oncology/Hematology Training and Implementation
- Developmental Therapeutics and Testing

Definition and Burden of Disease

- Oncology: Study of malignant tumors of lethal potential
- Malignancies can arise in any tissue, at any age and spread by direct extension or lymphatic / vascular circulation
- Cancer is the 2nd leading cause of death in the USA (1/4 US deaths), 3rd worldwide (after  dz and infection)

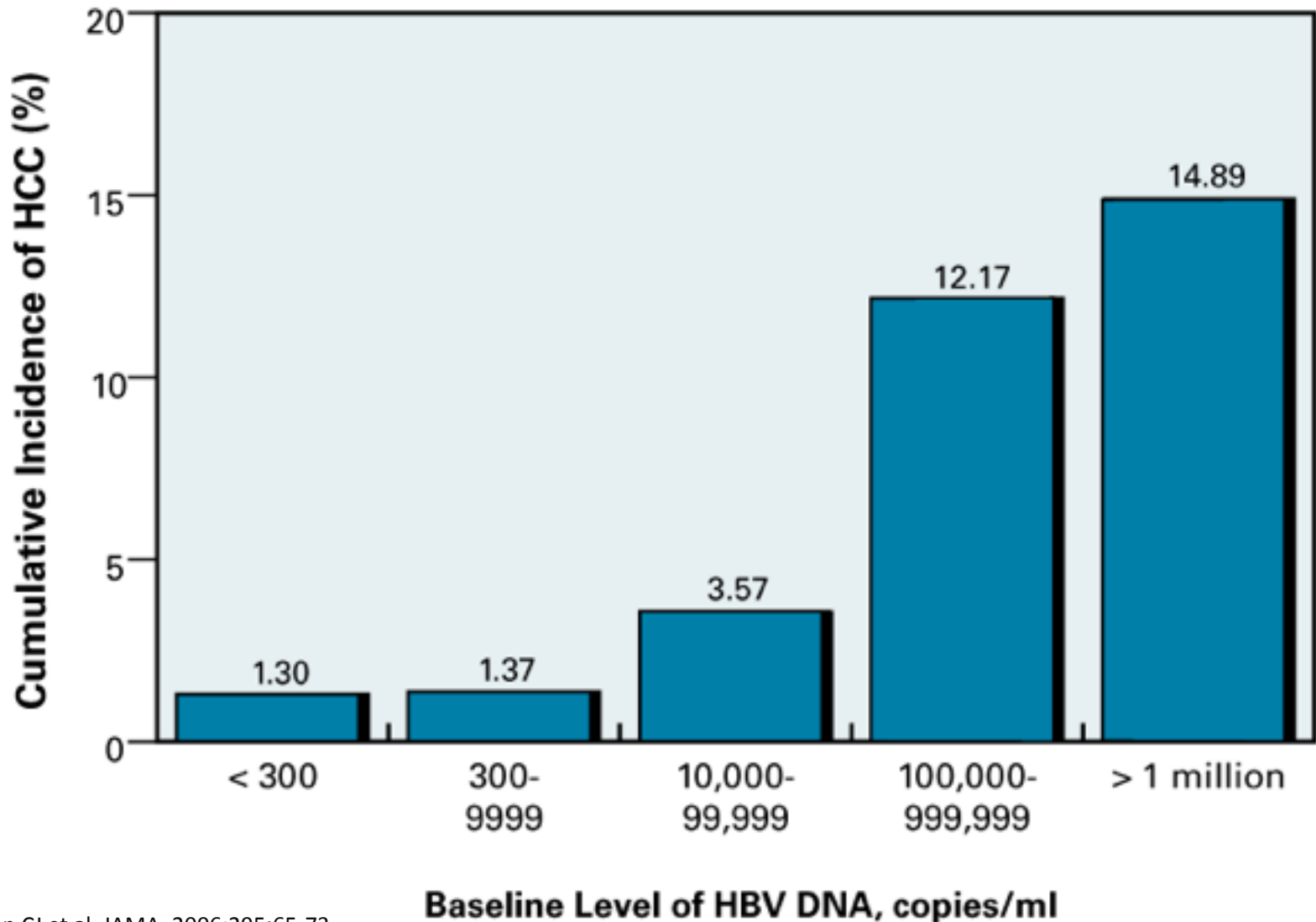
Lifetime Cancer Risk



Cancer Etiology

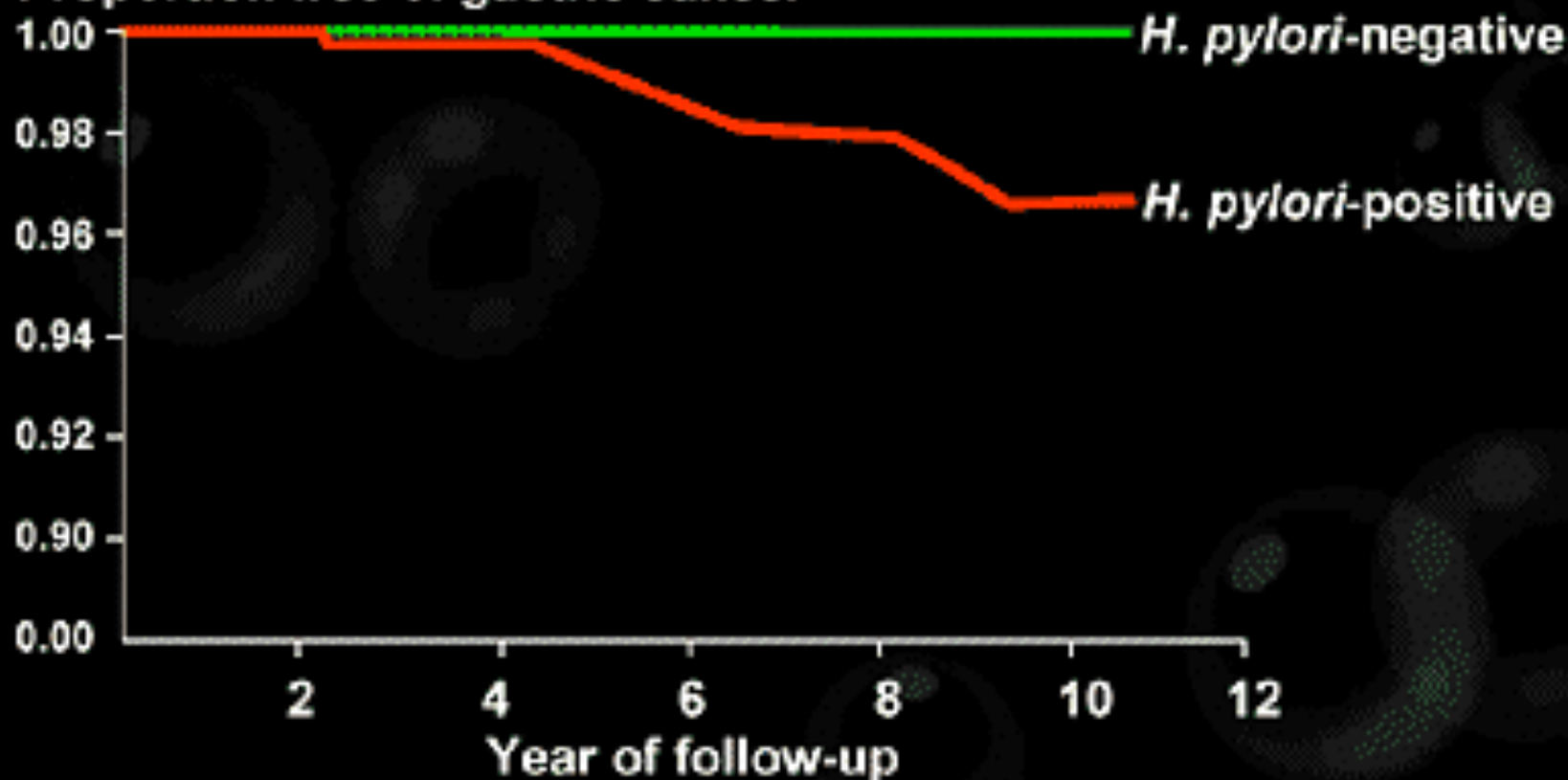
- Viral/Infectious Mechanisms (worldwide #1 cause , Hep B, HPV, EBV, HIV)
- Genetics
- Chemical carcinogens (tobacco, benzene etc)
- Environmental/Industrial Carcinogens
- Drug-induced cancers (eg secondary neoplasia)
- Radiation exposure (<1%)

Hepatitis B and Hepatocellular Carcinoma



H. pylori eradication results in decreased risk of gastric cancer development

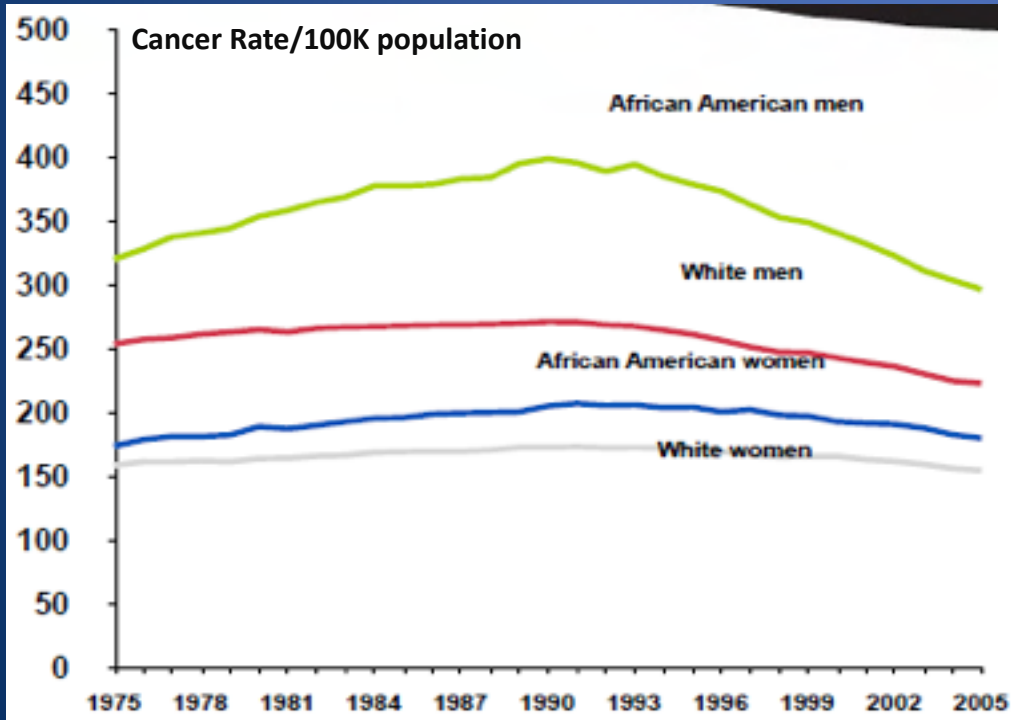
Proportion free of gastric cancer



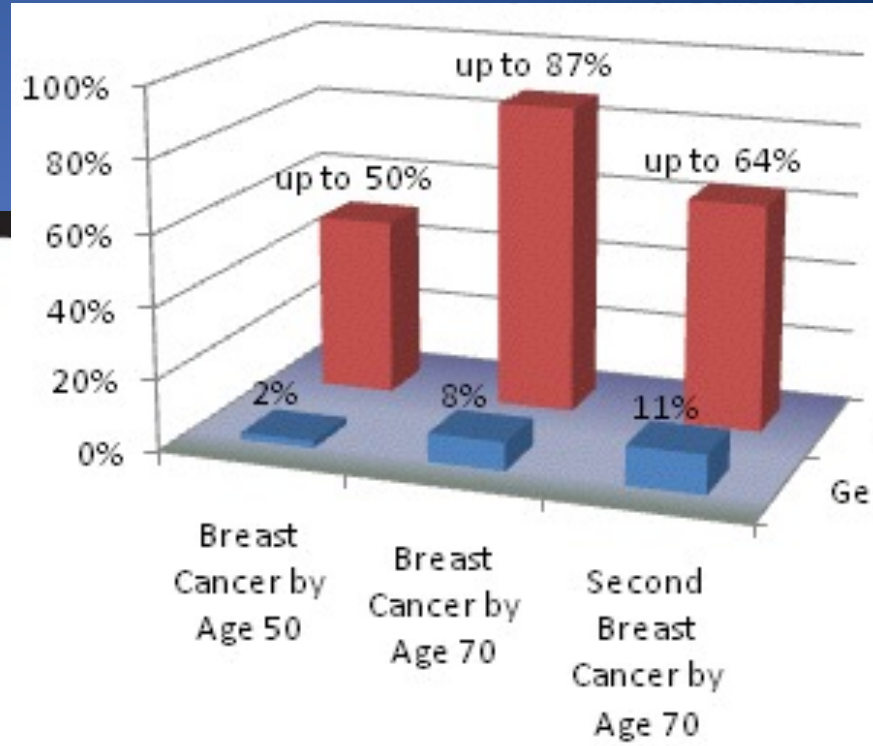
Uemura et al, *N Engl J Med* 2001; 345: 780

Genetic Susceptibilities

Can be gene specific risk,
or population specific SNPs
conferring enhanced risk

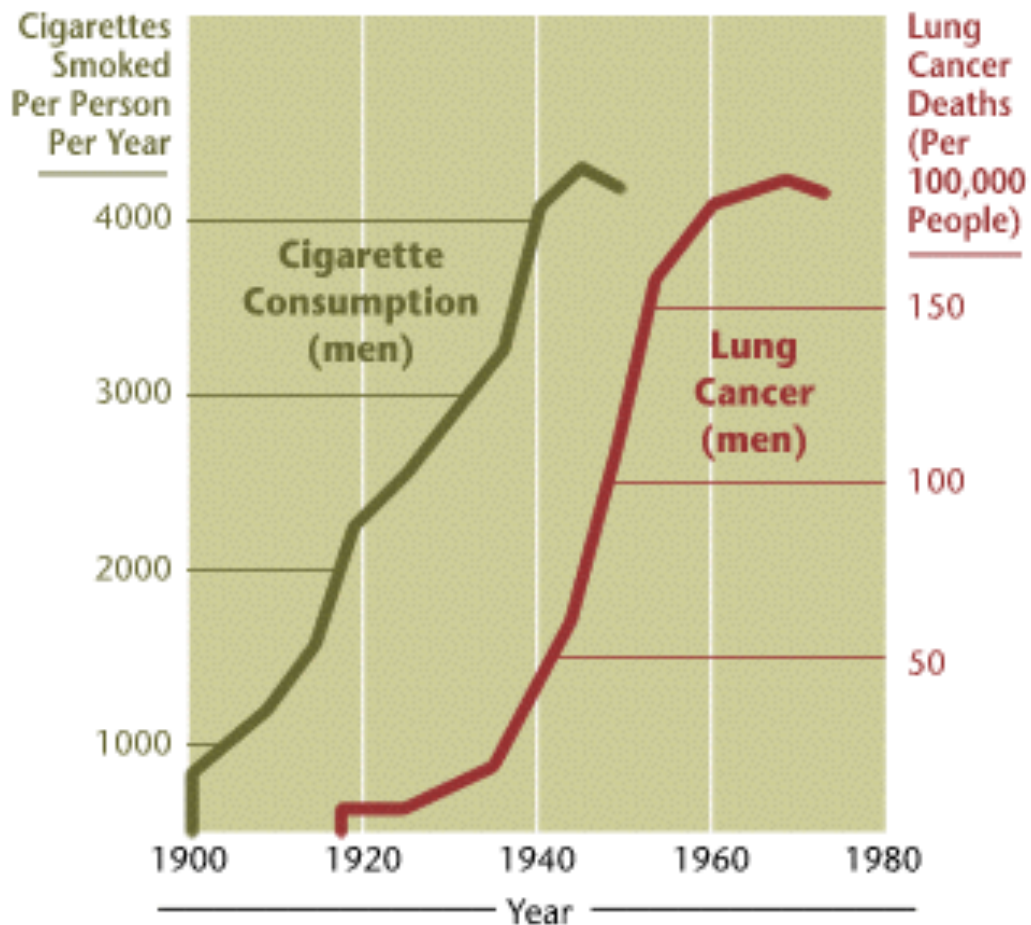


BRCA Mutation Carriers



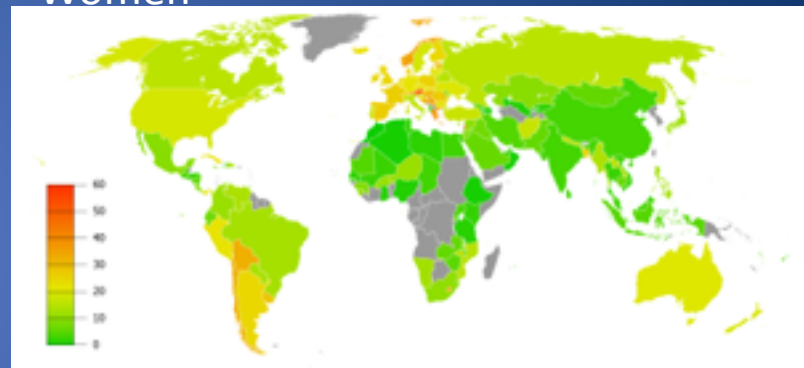
Smoking

20-Year Lag Time Between Smoking and Lung Cancer

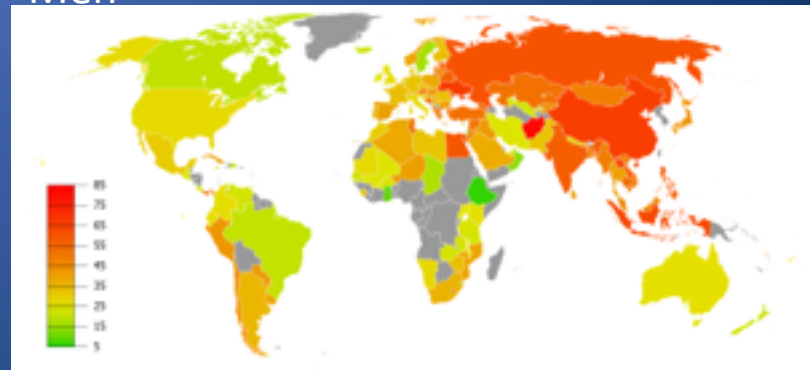


Worldwide Smoking Prevalence (%)

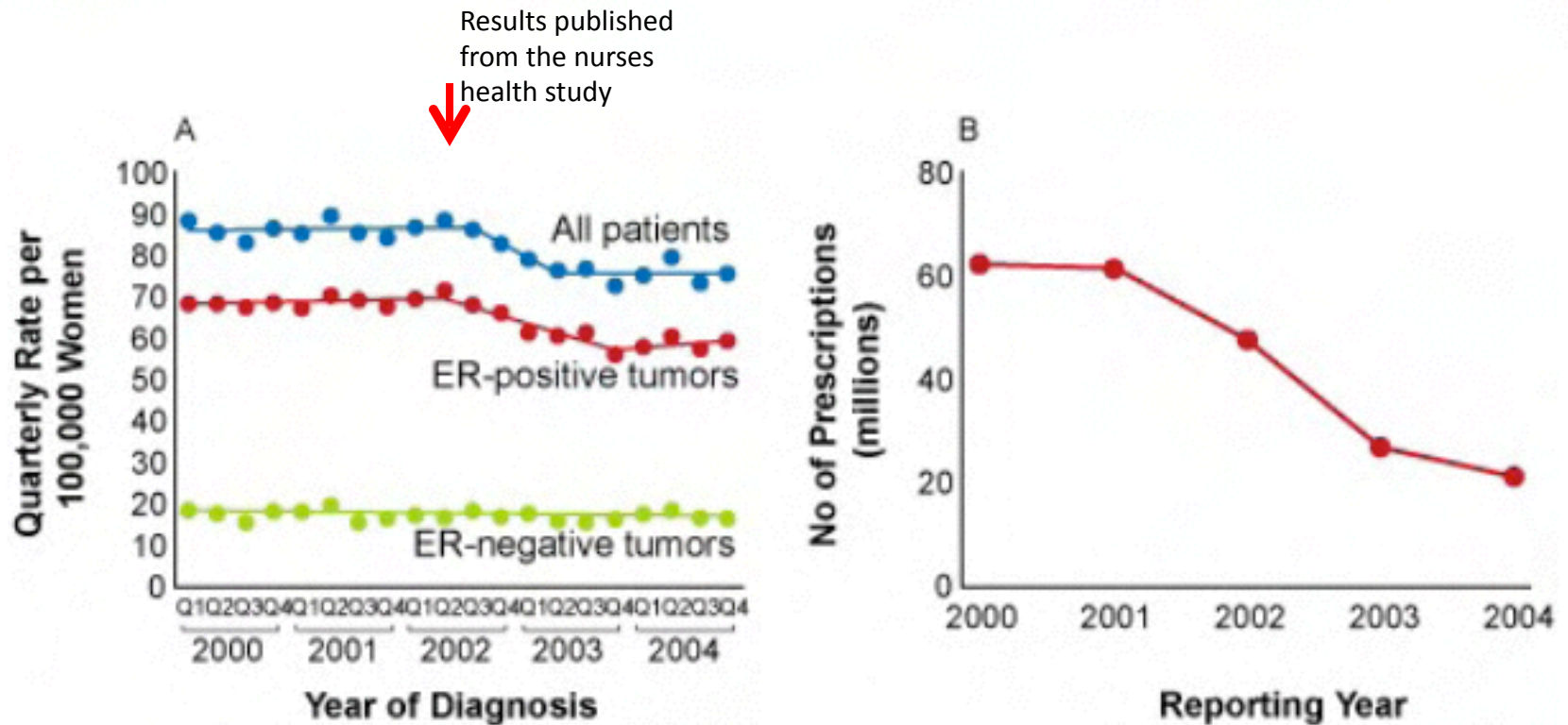
Women



Men

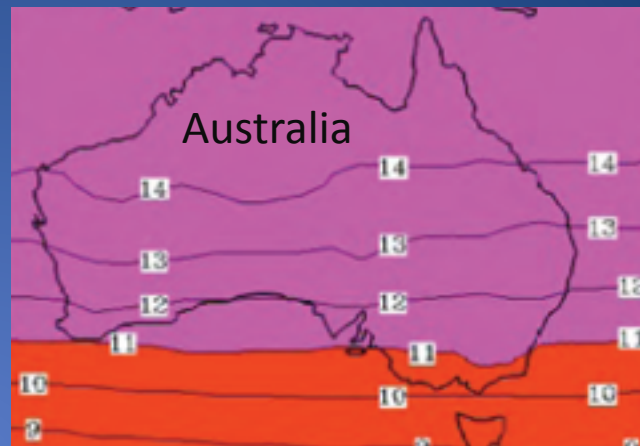


Hormone Replacement Therapy



Ravdin et al NEJM 2007; Womens' Health Initiative JAMA 2002.

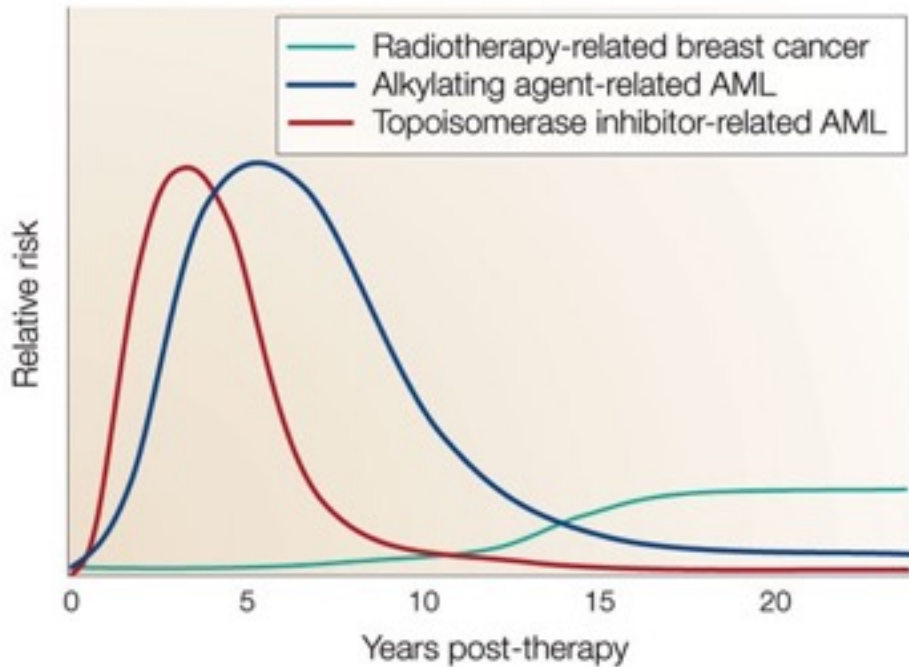
Geography and Sun Exposure



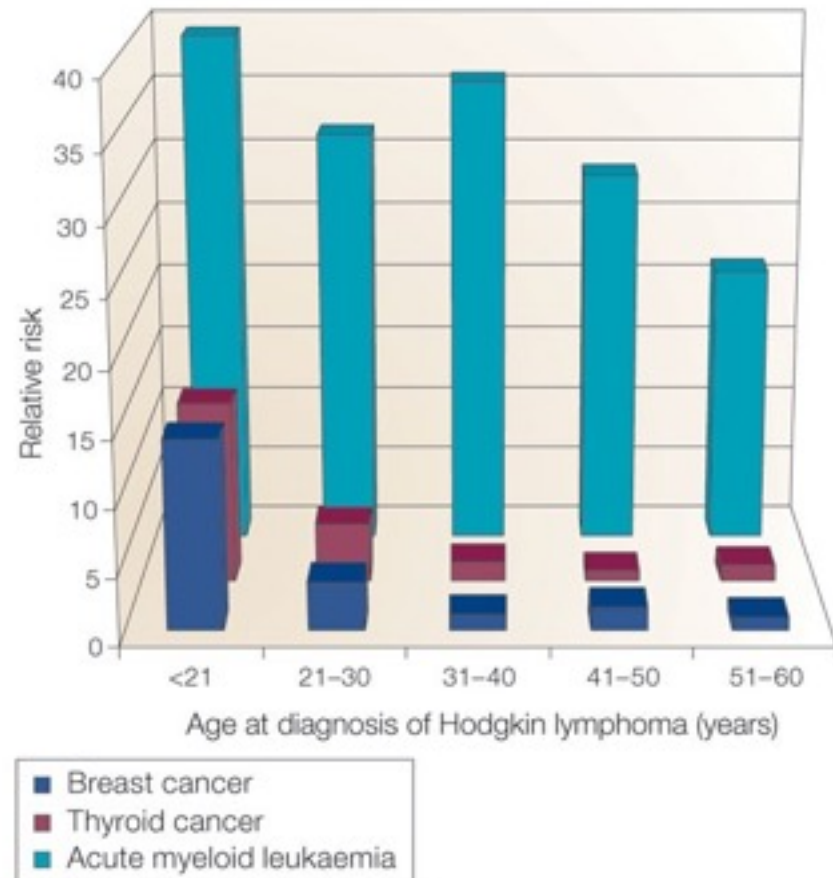
Site	USA	Australia
ALL	1 in 2	1 in 3
Prostate	1 in 6	1 in 5
Lung/Bronchus	1 in 13	1 in 12
Colon/Rectum	1 in 18	1 in 10
Bladder	1 in 27	1 in 39
Melanoma	1 in 39	1 in 14
Stomach	1 in 90	1 in 55

sun
H. pylori

Drug and Radiation Induced Cancers



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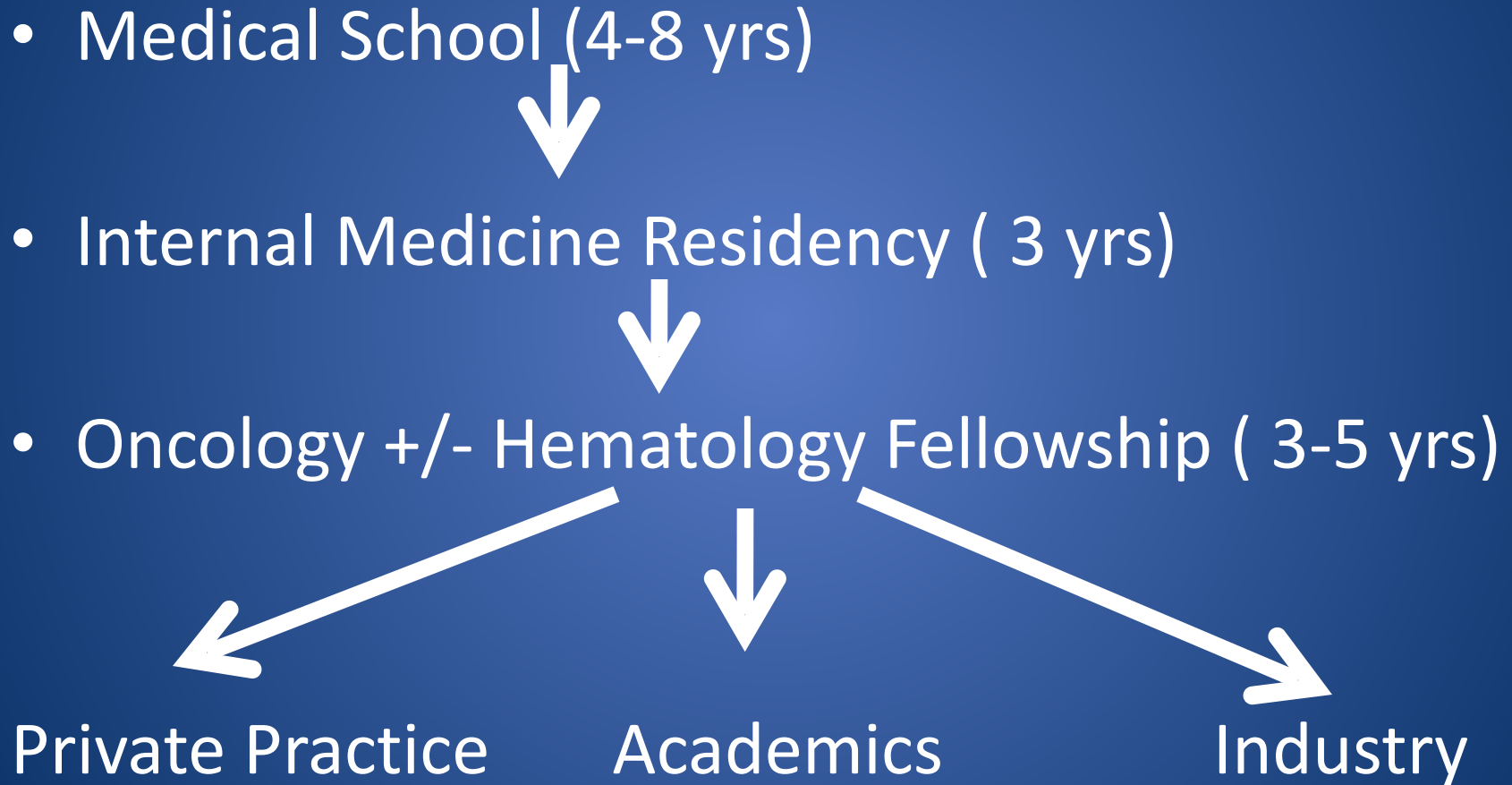
Strategies in Cancer Management

- Primary Prevention-
 - Tobacco, alcohol, dietary changes, environmental management, vaccination, antibiotics
- Screening programs (early detection/2^e prevention)
 - Mammography, PSA/DRE, Pap Smears, Colonoscopy
- Treatment-
 - Surgery for local control
 - Radiation for loco-regional management
 - Oncology which includes cytotoxic, hormonal, immunological, targeted and supportive therapies
- Palliation

What is Medical Oncology?

- Medical Oncologist
- Doctor who specializes in diagnosing and treating cancer using chemotherapy, hormone therapy or biological therapy
 - Often the main health care provider for someone with Cancer
 - Provides supportive care and coordinates treatment by other specialists

Medical Oncology Training



Role in Cancer Prevention

- Recognition of social, occupational, nutritional, sexual practices that contribute to neoplasia
- Education of the general public in cancer prevention
- Smoking is the most common correctable risk factor for cancer (worldwide also vaccination for HBV, HPV, prevention of HIV)
- Evaluate and screen appropriately populations at increased genetic cancer risk (BRCA, HNPCC, APC, p53, Rb families)

Cancer Diagnosis

- Requires histologic proof on at least one occasion
- New symptoms in a patient with a prior history of cancer need extensive/exhaustive evaluation
- No symptoms should be attributed to cancer without biopsy evidence, BUT cancer should always be on the differential
- Cancer patients can also have other symptomatic diseases

“Chemotherapy”

- Chemicals (usually gene-toxins, but now more targeted therapy as well) used to treat or control cancer
- Oncologist responsible for appropriate drug and dose combination
- Drug (s) used depend on cancer type, stage, patient age and comorbidities
- Management of side effects

Principles of Treatment

- Where is the tumor? What effect does it have on normal organ structure/function?
- How toxic is the treatment to surrounding/systemic normal tissues
- Is treatment potentially CURATIVE? Or is it PALLIATIVE (decreased sx, improved QOL)

Laws of Therapeutics

I- if it is working, keep it up

- *Primum non nocere*- subject to constant reassessment in oncology. Curative and sub-curative strategies are almost always toxic, how much risk is worth it?

II- If it isn't helping, stop doing it.

III- if you don't know what to do, do nothing.

- Ask your colleagues, go to tumor board.

IV- The treatment shouldn't be worse than the disease

Principles of Chemotherapy

Therapeutic Approaches

- Local/Regional
 - Surgery
 - Radiation, PDT
 - Chemotherapy (eg intravesical, intrathecal, topical, hepatic arterial chemoembolization)
- Systemic
 - Chemotherapy (cytotoxic, hormonal, immunologic, tyrosine kinase inhibitors)
 - Supportive Care (anti-emetics, growth factors, narcotics)

Combined Therapies

Neo-Adjuvant

- Chemotherapy and/or radiation given before surgery
 - Idea is to shrink the tumor to allow smaller resections or organ preservation (eg for head and neck, breast, pancreas cancers or sarcomas)
 - Response to treatment gives an *in vivo* test of chemosensitivity/resistance (sarcomas) and can provide prognostic information in some cases
 - May enhance the efficacy of radiation so as to avoid the need for surgery.

Adjuvant Therapy

- Post-Surgical Chemotherapy and/or Radiation
 - Given AFTER the surgery to improve local control, decrease risk of metastatic disease and prolong survival
 - Can offer cure for some tumors where surgery alone has a low cure rate (ie Wilms' Tumor, Osteosarcomas)
 - Prolongs disease free interval for stage II or III breast cancer, Stage III ovarian cancers and Stage (II)/III Colon Cancers, Pancreatic Cancers all stages, Lung Cancers Ib, II, III post surgery

Targeted Therapies

- “medications which block the growth of cancer cells by interfering with specific molecular targets needed for carcinogenesis/growth/metastases, rather than by genotoxic stress”
- More effective/less harmful to normal cells
- New Paradigms- trial design, stability vs remission
 - Monoclonal Antibodies
 - Tyrosine Kinase Inhibitors
 - Vaccines

Upfront Chemotherapy

- For diseases which are not treatable with local measures
- For most solid tumors the goal is usually prolongation of survival rather than cure
 - systemically administered drugs to slow the growth of tumor cells, decrease the burden of metastatic disease
- BUT: Some Cancers are curable with Chemotherapy alone

Cancers Treatable/Curable with Chemotherapy Alone

- Acute Lymphoblastic Leukemia/Lymphoma in children
- Seminomas
- Hodgkin Lymphoma
- Classical Burkitt Leukemia/Lymphoma
- Promyelocytic Leukemia
- Diffuse large B cell Lymphoma
- Hairy Cell Leukemia
- Chronic Myelogenous Leukemia

Curable with Combined Modality (Chemo+XRT or Surgery/Chemo/XRT)

- Non-Metastatic Carcinomas
 - Some early Stage lung cancers
 - Head and neck cancers
 - Early Stage Gastric or esophageal cancers
 - Breast Cancer (maybe)
 - Prostate Cancer (maybe)
 - Ovarian Cancers (maybe)
 - Sarcomas (some, as long as they are small)

What about the Rest??

- Bottom line:
 - Metastatic cancer is rarely curable
 - Even cancers treated at early stage sometimes have micrometastases which show up later
 - Cancers that relapse are often difficult to treat due to acquisition of resistance to chemotherapy
- SO:
 - We try high dose therapy (i.e. auto-transplant for breast cancer)
 - Give growth factors to try and allow higher doses of chemo, more frequently (Dose Density)
 - Combine different drugs given sequentially to decrease toxicity and avoid resistance (PROmaceCYTABOM, CHOP, hyperCVAD)
 - Try new drugs/drug combinations (CLINICAL TRIALS)

Cancer Drug Development

Steps

- Novel Compound Identification (pre-clinical)
- Production and Formulation
- Toxicology evaluation *in vivo*
- Phase I Clinical Trials
- Phase II Clinical Trials
- Phase III Clinical Trials
- General Medical Use / Phase IV Clinical Trials

Development of Anti-Cancer Compounds

- Traditionally: Cancer Chemotherapy National Service Center established by the NCI in 1955 in order to screen compounds submitted by external institutions and companies for anti-cancer activity.
 - Example is taxol (extracted from the bark of the Pacific yew tree, *Taxus brevifolia*)
 - Identification based on EFFICACY, mechanism interrogated after the fact
 - analogues developed and synthesized
- Modern: drug development is based upon the idea of “Rational Drug Design”
 - The TARGET is known, medicinal chemistry allows the development of compounds which are predicted to bind the target of interest.

NCI Drug Screen

- Preliminary: compound incubated *in vitro* with 3 different tumor cell lines at a single concentration for 48 hours

If ANY activity →

- In vitro screen in 60 human tumor cell lines at 5 different doses for 48 hours

If promising →

- Hollow Fiber Technique: 12 target tumor cell lines grown in hollow fibers at two doses for 4 days

And →

- In vivo testing using xenografts: Human tumors injected sq in mice treated with various doses of compound for 30 days

Rational Drug Design

- Target Identified and recognized as the *sine qua non* of the cancer of interest (eg *BCR-ABL* tyrosine kinase mutation gene product in CML)
- Use of high-throughput screening of chemical libraries to identify molecules that bind/inhibit the activity of the TK (identification of 2-phenylaminopyrimidine)
- Compound tested and modified by addition of methyl and benzamide groups to improve binding to the target, solubility (imatinib)
- Pre-clinical testing in animal models and against human cell lines
- Clinical Trials demonstrate efficacy (IRIS trial, NEJM)

Production, Formulation and Toxicology

- Drug metabolism
- Chemical formulation (issues of solubility, protein binding, absorption)
- Dose, frequency, route
- Toxicology in at least two animal species
- Large-scale production plan

Investigational New Drug Applications (IND)

- Required for studies involving a new agent of unproven activity
- There are three IND types:
 - Investigator IND submitted by a physician for a trial. A research IND proposes studying an unapproved drug, or an approved drug for a new indication or a new patient population.
 - Emergency Use IND allows the FDA to authorize an experimental drug in an emergency situation. Used for pts who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
 - Treatment IND submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

INDs (Cont'd)

- Submitted either by Commercial or Research Entities
- IND Application must contain information in three broad areas:
 - Animal Pharmacology and Toxicology Studies - establish safety for initial testing in humans. Includes previous experience w/ drug in humans.
 - Manufacturing Information - provide info on composition, manufacture, stability. To assure adequate production and supply of consistent drug.
 - Clinical Protocols and Investigator Information
 - Detailed protocols for proposed clinical studies to assess safety/risk.
 - Info on the qualifications of the clinical investigators.
 - Commitment to obtain informed consent from the research subjects, review by IRB, and adherence to IND regulations.
- Once submitted, sponsor must wait 30 days before initiating any trials. FDA will review the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

Clinical Protocols

- May be designed by
 - Independent investigator
 - Pharmaceutical company
 - Multicenter cooperative groups
- Cooperative Groups includes general hospitals and cancer centers based on
 - Specific disease areas or treatment modalities (NSABP, RTOG)
 - Patient populations (POG)
 - Variety of cancer types (CALGB, ECOG, SWOG)

Clinical Protocols

- Designed to ensure uniformity and reproducibility of procedures and research design
- Avoids omissions, stipulates times for specific procedures and ensures standard doses, thresholds and end points
- All personnel should have access to a written protocol specifying the regimen, inclusion criteria, stopping parameters etc
- Pharmacists and oncology nurses serve as additional checks in the system.

Topics Covered in a Protocol

- Cover sheet- names and contacts for PI/study nurse
- Schema and Synopsis
- Background and rationale
- Objectives
- Patient selection
- Treatment plan w/dose adjustments
- Registration/randomization info, stratification and data management/submission
- Required data at entry on study and at every evaluation
- Expected toxicity and management
- Criteria for response, progression and relapse
- Removal of patients from therapy
- Drug formulation, availability, preparation
- Adverse event/reaction reporting
- Ancillary Therapy
- Statistical considerations
- References
- Model consent form

Phase I Trials

- Toxicology → IND application/approval → Phase I
- Patients → often refractory, pretreated, many different cancer types
- Goal is identification of TOXICITY
 - Dose limiting toxicity(DLT) is irreversible grade 3 or any grade 4 toxicity
 - Maximum tolerated dose (MTD) is highest dose at which DLT is seen in less than 33% of patients at a given dose level
 - Starting dose is 10% of the LD₁₀ in the most sensitive non-human species (sometimes problematic in targeted rxs)

Phase I Trials (cont)

- Patients are treated in “cohorts” of 3-6 people
- Medication Dose escalated after 3 patients are treated without DLT
- Medication dose is escalated using a modified Fibonacci sequence:
 - Initial increase 100%, then 67%, then 50%, 40% then 33% each further increase
- Lack of response in a phase I trial should not, in theory, stop further drug development

Phase Ib Trials

- Expansion Cohorts
 - Evaluate pharmacokinetics/pharmacodynamics at recommended phase II dose
 - Solid tumor biopsies add complexity to implementation
 - Evaluate further tolerability at selected dose
 - May limit to certain tumor types to preview efficacy
 - eg her2neu antibody (herceptin) tested in Her2 over-expressing breast cancers

Phase II Trials

- Endpoint is RESPONSE within specific tumor type
- Candidates should not be heavily pre treated
- No response in 14pts suggests drug ineffective
 - If ≥ 1 response observed, trial expanded to up to 30pts
 - 20% response rate suggests possible clinical utility
- BUT: effective drugs can be falsely rejected (due to incorrect dose/route, heavy prior exposure, poor patient PS)

Phase III Trials

- Endpoint is **ACTIVITY AND TOXICITY** relative to current standard of care
 - Requires equipoise w.r.t. likelihood of response between the two arms
- Size of the trial based on expected difference in endpoints between the new treatment and the standard of care.
- “**POWER**” is the number of patients needed to show statistically significant differences in response.
 - If a new treatment has response of 60% and standard has response of 40% to have a 90% chance of seeing differences with $p < 0.05$ you need 139 patients in each arm

Phase IV Studies

- Phase III studies determine STANDARDS OF CARE
- Further investigation of efficacy and safety of an approved regimen or treatment or treatment in new and different setting
- Post marketing studies of safety

Review of Clinical Trials

- Phase I: Establishes toxicity and dose-schedule
- Phase II: Identifies promising therapies
- Phase III:
 - Effect of treatment relative to natural history of disease (for diseases without current standard)
 - Effect of treatment relative to current standard
 - Toxicity of treatment relative to standard of care

Once Drug has Proven Efficacy

- New Drug Application(NDA) submitted to the FDA
 - Provide data on safety and efficacy of proposed use
 - Animal Studies, clinical info on PK/PD information
 - Appropriateness of proposed labeling (package insert)
 - Methods in manufacturing and quality control
- Biologic License Application(BLA) submitted to the FDA
 - Monoclonal antibodies for in vivo use
 - Cytokines, growth factors, enzymes, immunomod drugs, thrombolytics
 - Proteins for therapeutic use extracted from animals or microorganisms
 - Non-vaccine therapeutic immunotherapies

FDA Approval

- FDA approves a new drug or treatment based on “Clinical Benefit.” Usually data from Phase II or Phase III trials for specific indications
 - e.g. taxol approved for use in advanced ovarian cancer, metastatic breast cancer, and node positive breast cancer, but not for lung cancer (where it is also used)
- Determination of efficacy based on response rates or survival but can also be based on QOL measures
 - e.g. gemcitabine approval for pancreatic cancer

FDA Approval

- Once drug approved by the FDA it can be used outside it's approved indication. (e.g. taxol used for met lung cancer)
- Insurers will usually reimburse for drugs used outside labeled indications as long as phase II data exists demonstrating efficacy in that disease area.

Differences in Developmental Paradigms

- Cytotoxics (Taxol)
- ID and Development
 - Brute force screening of 1000s of molecules
 - Based on ability to kill cancer cell lines with less toxicity to normal cells
 - Phase I- identify MTD
 - Phase II-IV similar
- Mechanisms of Action
 - Inhibition of pathways for cell division
 - Often effective for multiple malignancies
- TOXICITY
 - Any rapidly dividing cells
- Targeted Inhibitors (Imatinib)
- Rational Design-
 - Specific Targets in mind
- High throughput screening for small molecules that hit the target
 - Phase I- Identify the Biologically Effective Dose
 - Phase II-IV similar
- Mechanism known in advance, specific targets identify possible usefulness
 - Target malignancies w/ the target
 - Inhibits without killing normal cells
- TOXICITY
 - Idiosyncratic
 - Often less severe

QUESTIONS?

elizabeth.griffiths@Roswellpark.org

716.845.3996

2010 Estimated US Cancer Cases



TOTAL	789,620 (100%)
Prostate	217,730 (28%)
Lung & Bronchus	116,750 (15%)
Colon & Rectum	72,090 (9%)
Bladder	52,760 (7%)
Melanoma	38,870 (5%)
NHL	35,380 (4%)
Kidney	35,370 (4%)
Oral/Pharynx	25,420 (3%)
Leukemia	24,690 (3%)
Pancreas	21,370 (3%)
Other	149,190 (19%)

Breast	207,090 (28%)
	105,770 (14%)
	70,480 (10%)
Uterine	43,470 (6%)
Thyroid	33,930 (5%)
NHL	30,160 (4%)
Melanoma	29,260 (4%)
Kidney	22,870 (3%)
Ovary	21,880 (3%)
	21,770 (3%)
	153,260 (21%)

2010 Estimated US Cancer Deaths

Mortality

