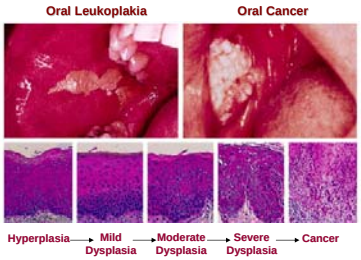
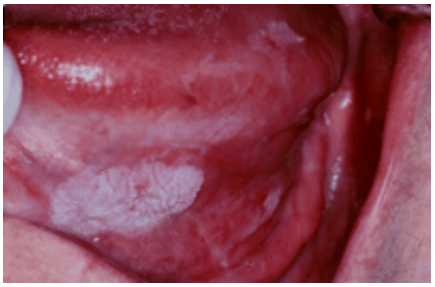
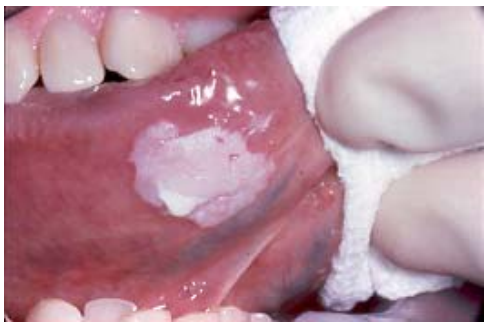
Progression From Leukoplakia to Oral Cancer

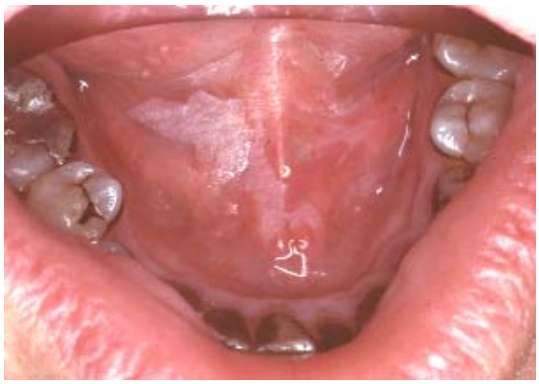


Oral Leukoplakia

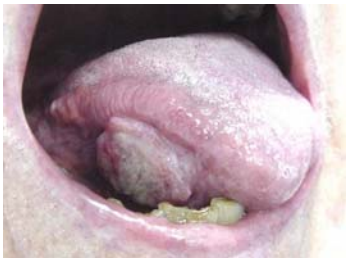


Idiopathic Leukoplakia

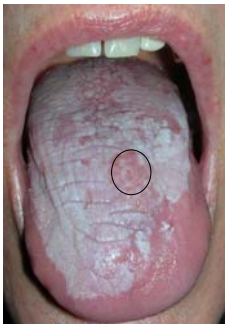


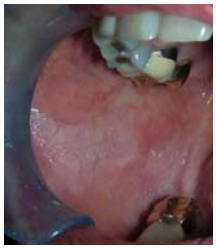


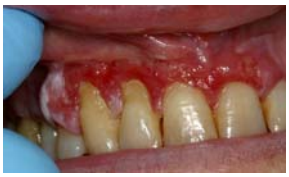
SCCA of Tongue

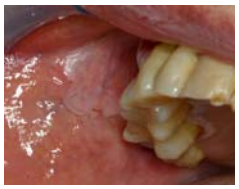


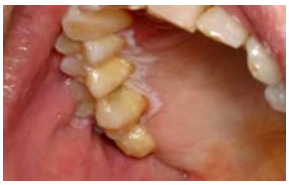
PROLIFERATIVE VERRUCOUS LEUKOPLAKIA (PVL)



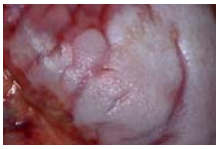


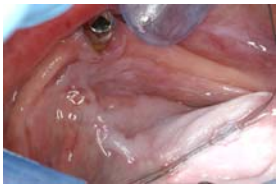


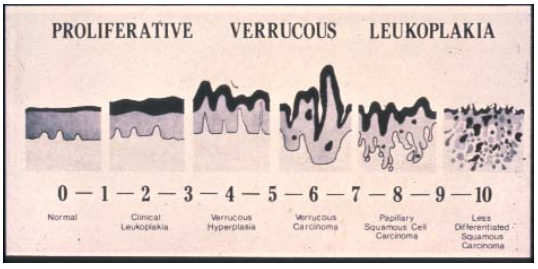




79 year old female



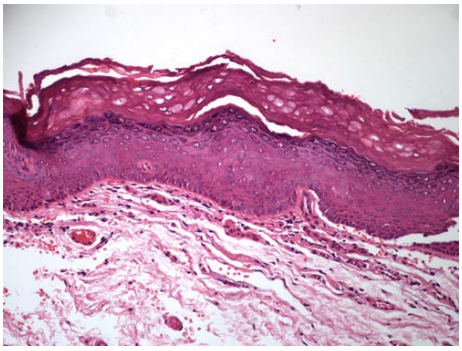


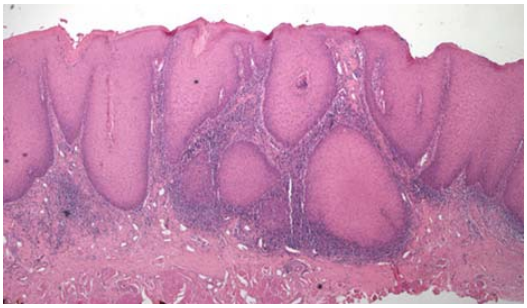


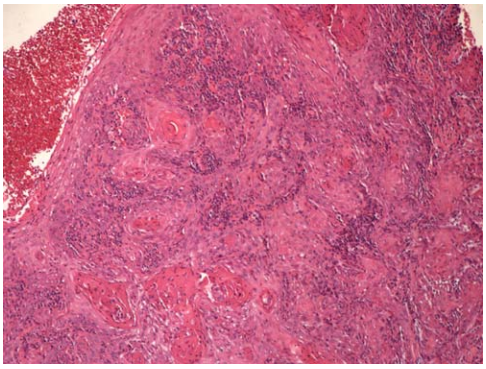
Oral Surg Oral Med Oral Pathol (1985) 60(3):285-298

PROLIFERATIVE VERRUCOUS LEUKOPLAKIA (PVL)

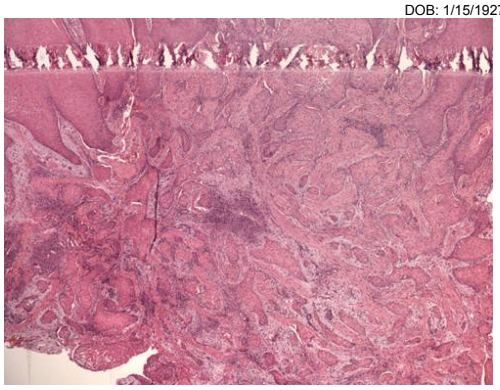
- No absolutely predictive histologic pattern
- No test available to prove likely progression
- Must be re-evaluated very frequently and totally removed if recurs

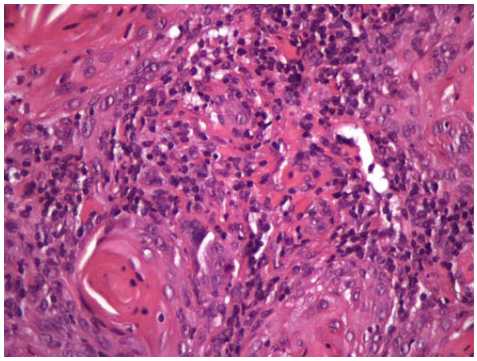




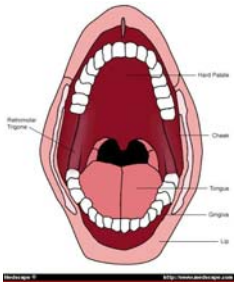


R.S.J
DOB: 1/15/1927



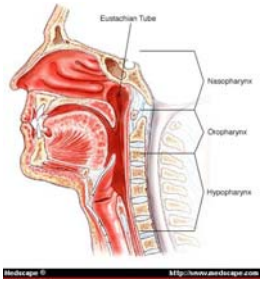


Anatomic Sites for Oral Cancer



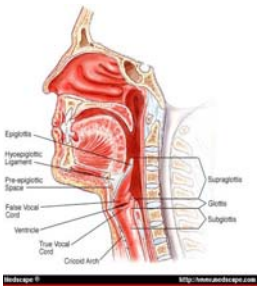
- Lip
- Buccal Mucosa
- Alveolar Ridge
- Retromolar Trigone
- **Floor of Mouth**
- Hard Palate
- **Tongue (Lateral border and ventral)**
- **Soft palate**

Pharynx: Anatomic Sites



- Nasophaynx
- Oropharynx
  - Base of Tongue
  - Soft Palate
  - Tonsillar Pillar and Fossa
- Hypopharynx
  - Pyriform sinus
  - Lateral/Posterior pharyngeal walls
  - Postcricoid area

Larynx: Anatomic Sites



- Supraglottis (30-35%)
  - False Cords
  - Arytenoids
  - Epiglottis
  - Arytenoepiglottic fold
- Glottis (60-65%)
- Subglottis (5%)

Risk Factors for Head/Neck Cancer

Environmental risk factors: (a) **Tobacco – smoking or chewing**
(b) Alcohol
(c) Areca nut

Radiation

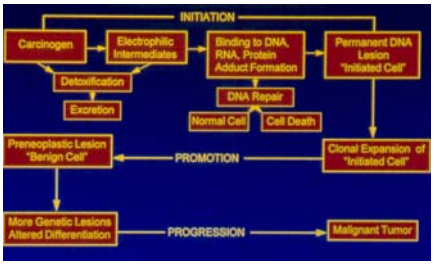
Viral: (a) HPV 16 and 18
(b) EBV (Epstein-Barr virus)

Iron and vitamin A deficiency

Oncogenes and tumor-suppressor genes

Familial and genetic predisposition

Mechanism of Chemical Carcinogenesis



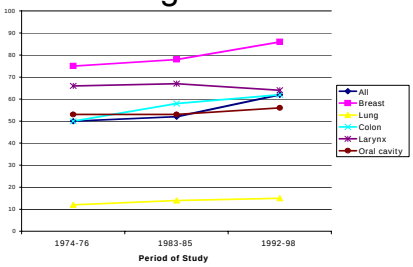
HNSCC Perspective: Predicted Incidence Among Other Cancers

- Breast cancer 212,600
- Lung cancer 171,900
- Colon cancer 105,500
- **Head/Neck 38,000**
- Leukemia 30,600
- Brain 18,300

HNSCC Incidence

- An estimated 38,000 patients in the United States will be diagnosed with HNSCC in 2003
- 11,000 deaths will occur in the United States due to this disease
- Oral cavity and pharynx 27,700
  - Tongue 26%
  - Mouth 33%
  - Pharynx 30%
  - Other oral cavity 11%
- Larynx 9,500

Trends in 5 Year Relative Survival Rates by Year of Diagnosis



Clinical Prognostic Factors

- Performance status and co-morbidities
- Primary site of disease
- Tumor stage
- Depth of invasion
- Nodal stage
- Total tumor burden
- Post-surgical margin
- Histologic grade
- Response to chemotherapy
- Pretreatment hemoglobin

Staging

- Stage at diagnosis is the single most predictive factor of survival.
- T stage: based on tumor size
  - Lip, oral cavity, oropharynx
- T stage: based on subsite involvement
  - Glottic and supraglottic larynx, nasopharynx.
- N and M staging is uniform for all sites

Early Diagnosis is Critical

- Overall survival falls by half from stage I/II to stage III/IV disease
- Some regions (base of tongue) often go undetected until late stage
- Public health efforts to incorporate oral cancer screening exam for routine dental visits
- Not uncommon scenario is for an adult with neck node to receive antibiotics often delaying diagnosis

HNSCC Treatment: Role of Chemotherapy

- Locally advanced disease
  - Induction chemotherapy followed by radiotherapy allows organ preservation without compromising survival
  - Concomitant chemo/radiation therapy improves local control and survival compared with radiation alone and allows organ preservation
  - Distant failure is emerging as local control rates improve
- Distant disease
  - Cisplatin based chemotherapy improves survival over best supportive care

HNSCC Treatment: Historical Perspective

- Stage I/II
  - Surgery
  - Radiation therapy
  - 60-80% 5 yr survival with either modality
- Stage III/IV
  - Resectable
    - 30% 5 year survival
  - Unresectable
    - 6-12 month median survival
  - Failure of local control is most frequent cause of death

Radiotherapy

- Primary and gross adenopathy require a total of 70 Gy in 2 Gy/day fractions
- Altered fractionation schemes under study
  - Accelerated fractionation
  - Hyperfractionation
- Brachytherapy

Surgical Principles: Lymph Node Dissection

- Comprehensive
  - Removes all lymph node groups
  - May or may not remove the sternocleidomastoid muscle, jugular vein and spinal accessory nerve.
- Selective
  - Removes nodes based on anatomic drainage patterns
  - Supraomohyoid, Lateral

Surgical Principles: Resectable vs. Unresectable

- No formal definition exists
- Surgeon's experience, reconstructive surgeons, prosthodontists
- In general - Unresectable disease:
  - Cervical vertebrae
  - Brachial plexus
  - Deep muscles of the neck
  - Carotid artery

Three Major Problems in the Pathogenesis of Oral and Head/neck Cancer

1. What are the chances for an individual at high risk to develop oral premalignant lesion or oral cancer?
2. How can we predict if a particular oral premalignant lesion will progress to oral cancer?
3. How can we effectively monitor and thus prevent the development of recurrence or second primary malignancy in a treated individual? or undergoing cancer chemoprevention?

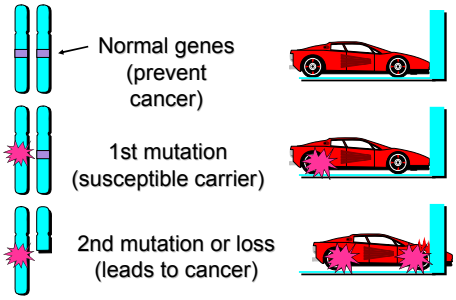
Genes Associated With Cancer Predisposition

Tumor suppressor genes
- The cell's brake for tumor growth
- Cancer arises when both brakes fail

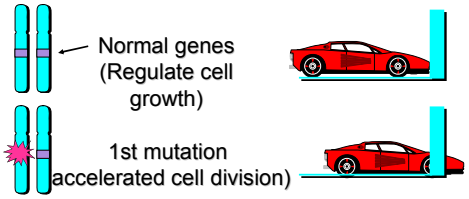
Oncogenes
- Accelerates cell division
- Cancer arises when stuck in "on" mode

DNA damage-response genes
- The repair mechanics for DNA
- Cancer arises when both genes fail, speeding the accumulation of mutations in other critical genes

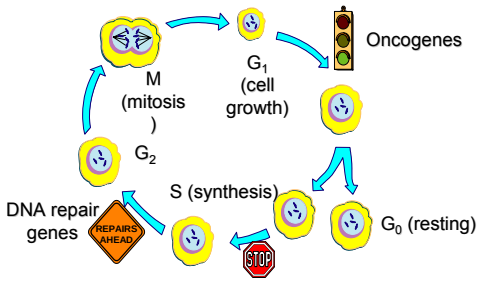
Tumor Suppressor Genes



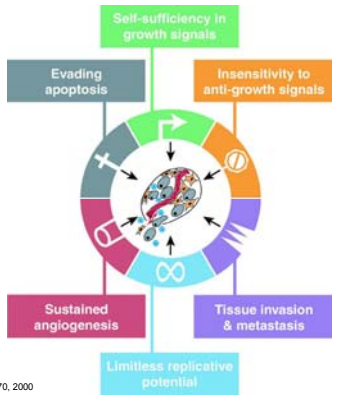
Oncogenes



The Cell Cycle



The Hallmarks of Cancer



Hanahan, D and Weinberg, R.A. Cell 100, 57-70, 2000

Molecular Genetics

- p53
- Rb
- Cyclin dependent kinase inhibitors
  - p16, p21, p27
- Cyclin D1 amplification
- Epidermal Growth Factor Receptor
- STAT 3 expression

EGFR Signaling - 101

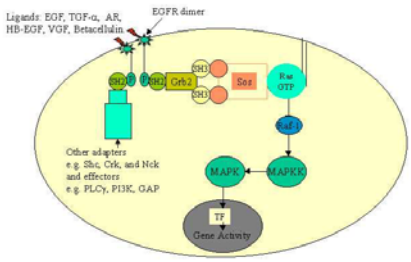
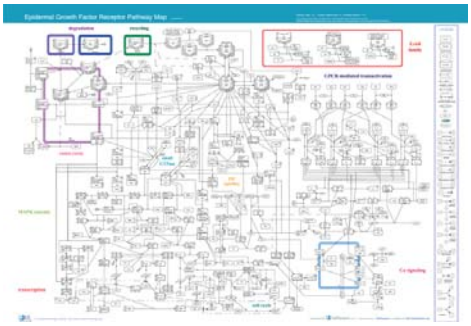
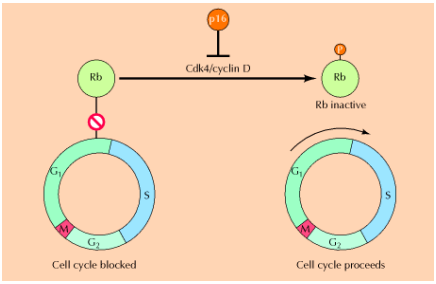


Fig 2. Schematic representation of EGFR mediated signal transduction after activation by its ligands.

Epidermal Growth Factor Receptor Drives Cell Growth



Cyclin D, p16 and Rb Regulate the Cell Cycle



p53 is the Guardian of the Genome

NORMAL MUTATED

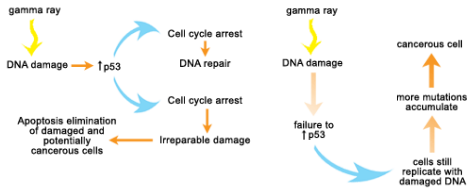


Table 2. Common Oncogene Alterations Identified in Primary Head and Neck Squamous-Cell Carcinoma.*

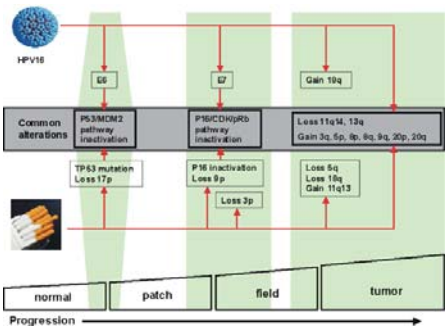
Gene	Frequency (%)†	Function
Tumor-suppressor genes		
p16INK4A	80	Senescence, cell-cycle progression
p53	50	Cell-cycle regulation, cell survival‡
PTEN	10	Signaling, migration
Rb	<10	Cell-cycle regulation, apoptosis
Proto-oncogenes		
Cyclin D1	30	Cell-cycle regulation
p63 (p40/p51/AIS)	30	Unknown§
Epidermal growth factor receptor	<10	Cell proliferation, growth

*Genes listed include those inactivated in tumors by deletion, point mutation, or promoter hypermethylation (tumor-suppressor genes) and those activated by amplification (proto-oncogenes).

†Frequency refers to the inactivation of tumor-suppressor genes or to the activation of proto-oncogenes.

‡The *p53* gene is activated in response to cellular stress.

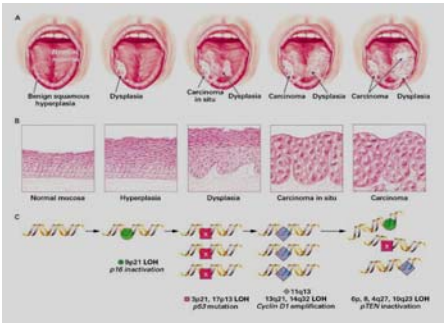
§The *p63* gene leads to increased tumor growth when it is overexpressed and is critical for keratinocyte proliferation.[58]



Smeets, S.J., et al. Oncogene (2006) **25,** 2558-2564.

Chromosomal Gains and Losses in HNSCC

HNSCC Progression



Forastiere, et al. NEJM 345 (26), 1890-1900, 2001

HNSCC Gene Expression Profiling Study

- Samples
  - 41 Squamous cell carcinoma (SCCA)
    - All collected at surgical resection
    - Flash frozen within 30 min of devascularization
    - Clinical data abstracted from the FUMC medical record
  - 13 Normal oral mucosa samples

Oligonucleotide Microarrays

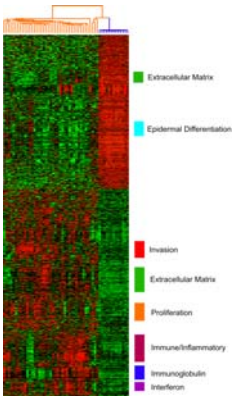
- Affymetrix U133A Human GeneChip
- ~22,200 Features
- ~18,000 Unique human genes
- All named genes
- Many ESTs

Data Analysis Methods

- Pre-processing
  - Gradient adjustments using GeneData Refiner
  - Intensity values derived by MAS 5.0 algorithm
  - Quantile-quantile normalized
- Filtering
  - HNSCC
    - Parametric T test adjusted for unequal variance
    - P value < 0.001
    - Difference in mean expression ≥ 100
    - Fold Change in mean expression ≥ 2 or ≤ 0.5
- Data Visualization
  - Hierarchical clustering (Pearson correlation or K-means)

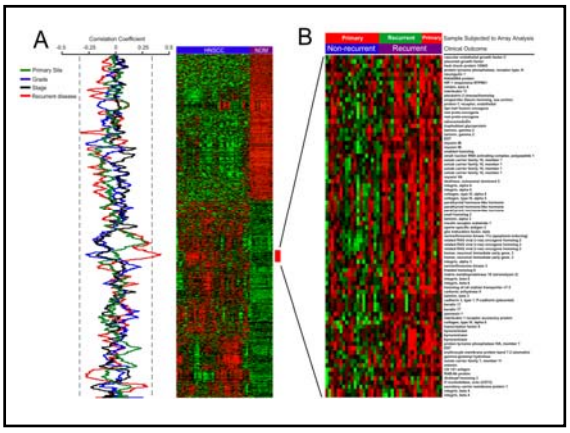
SCCA vs Normal: Class Comparison

- Genes selected by T test
  - P value < 0.001
- Total of 2,890 genes meet criteria
- Some signatures have been identified in other datasets
  - Proliferation



Correlating Gene Expression Signatures with Clinic Data

- Calculate correlation coefficients between gene expression values and clinical parameters:
  - Primary site
  - Stage
  - Grade (well, moderate, poor)
  - Presence of recurrent disease
- Permute class labels 5000 times to determine levels of significance



Areas Where Genomic Approaches May Help

- Biomarker Development
  - Who is at highest risk of treatment failure?
    - 20-40% of stage I/II patients suffer recurrence
  - Who is at highest risk of developing invasive carcinoma?
    - 10-20% of oral leukoplakia lesions with transform to invasive cancer
  - Who will have refractory disease?
  - Who has clinically occult disease?
    - Can the peripheral blood be used as a sentinal?
  - Assignment of unknown primary disease
- Novel Gene and Pathway Discovery

Future Challenges

- Despite recent advances in the treatment and biology of HNSCC and the promise of new therapies, we still need:
  - Accurate and sensitive biomarkers of disease response and progression
  - A more comprehensive view of the range of molecular defects

Conclusions

HNSCC remains a clinically important disease resulting in significant morbidity and mortality

HNSCC results from a constellation of complex genetic changes that impact cellular growth and death pathways

- Chromosomal gains and losses
- Specific oncogenes and tumor suppressor genes

Efforts to improve patient outcome should be directed at early detection of high risk patients and patients presenting with late stage disease

Genomic approaches hold substantial promise for the development of prognostic biomarkers and development of new therapeutic targets