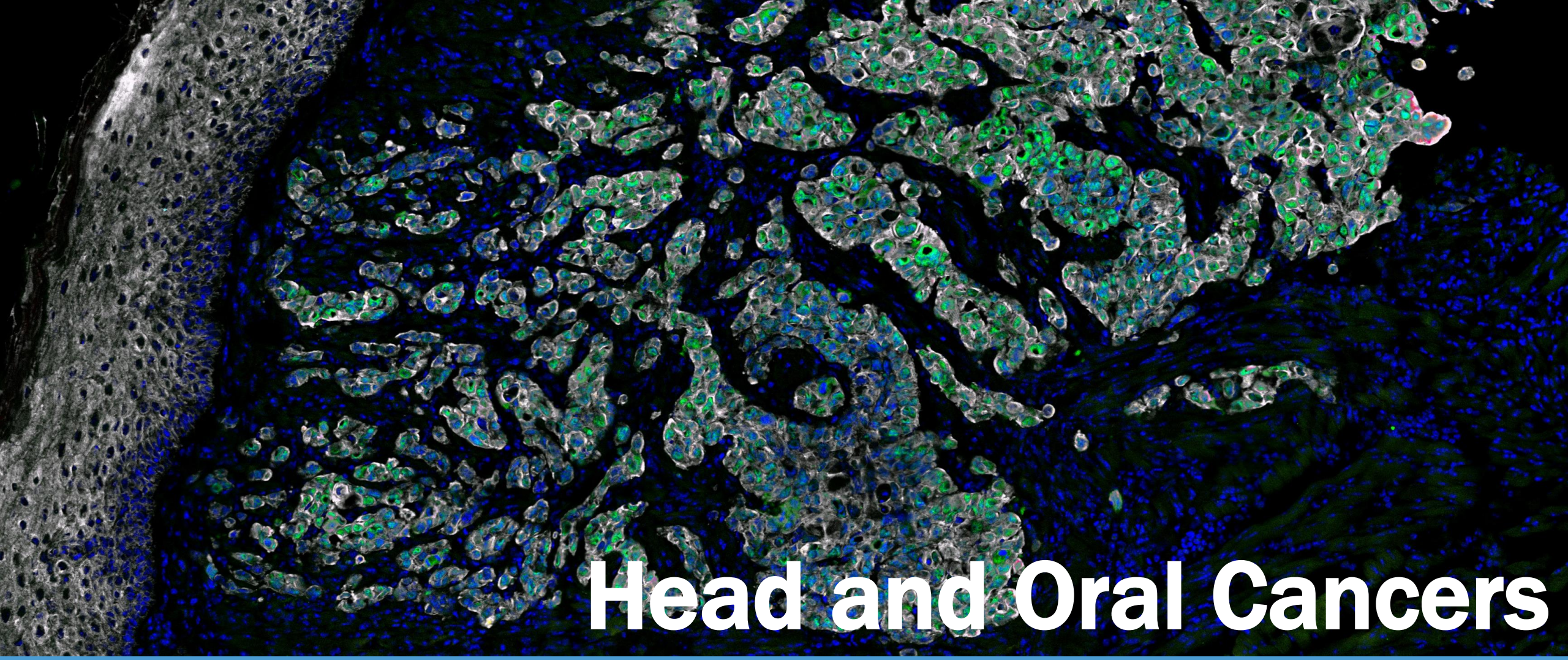


Head and Oral Cancers

UNC SCHOOL OF MEDICINE

Pathology of Disease course

November 9, 2021

Bethany Brown (bethany_brown@med.unc.edu)

Learning Objectives

UNC SCHOOL OF MEDICINE

Following today's lecture, students will be able to…

1. Compare and contrast HPV+ and HPV- head and oral cancers with respect to etiology, treatments, and prognosis
2. Outline how mutagens lead to carcinogenesis
3. Discuss therapeutic strategies for head and oral cancers

Learning objectives are what I use to make exam questions! ☺

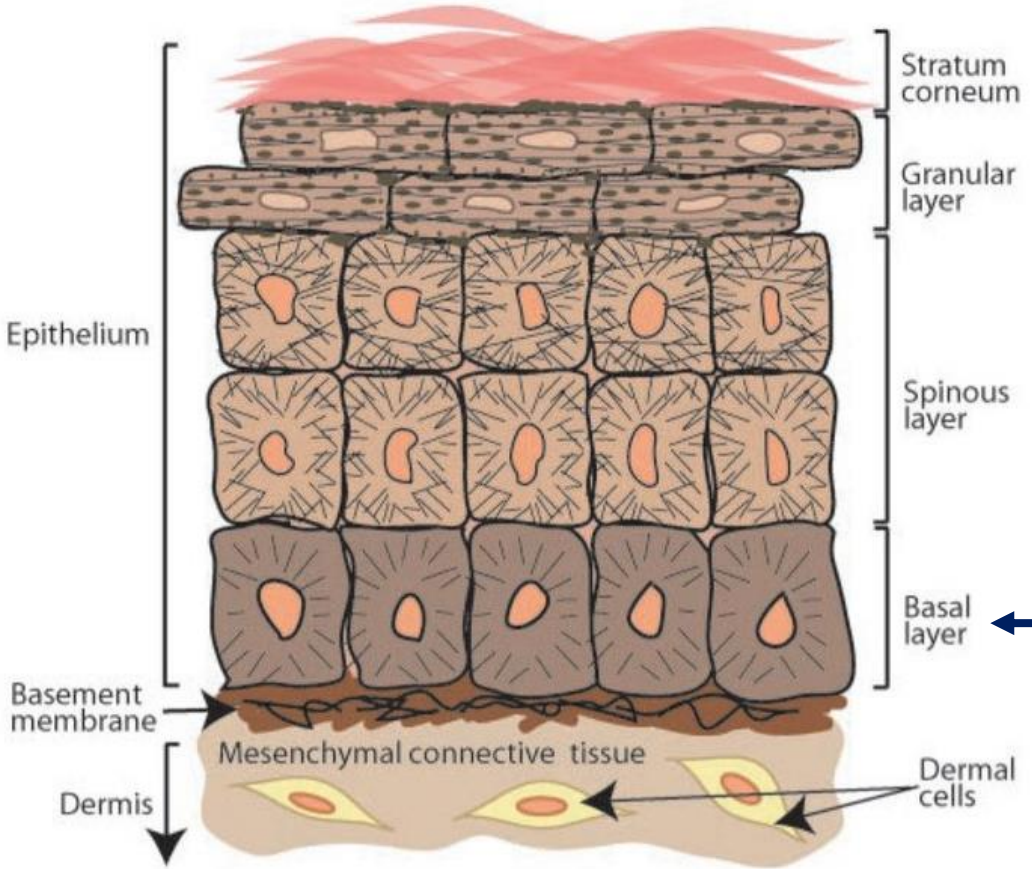
Lecture outline

UNC SCHOOL OF MEDICINE

- Intro to head and oral cavity anatomy, histology
- Mechanisms of carcinogenesis
- Types of head and oral cancers
- Therapies and opportunities
- Ongoing questions in the field
- Questions/Discussion
  - Please feel free to use the chat or unmute and ask questions throughout!

- My path to grad school

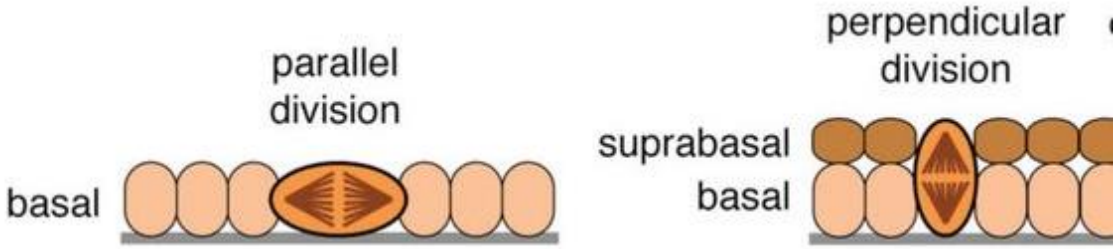
Stratified epithelia



What are some examples of stratified epithelia?

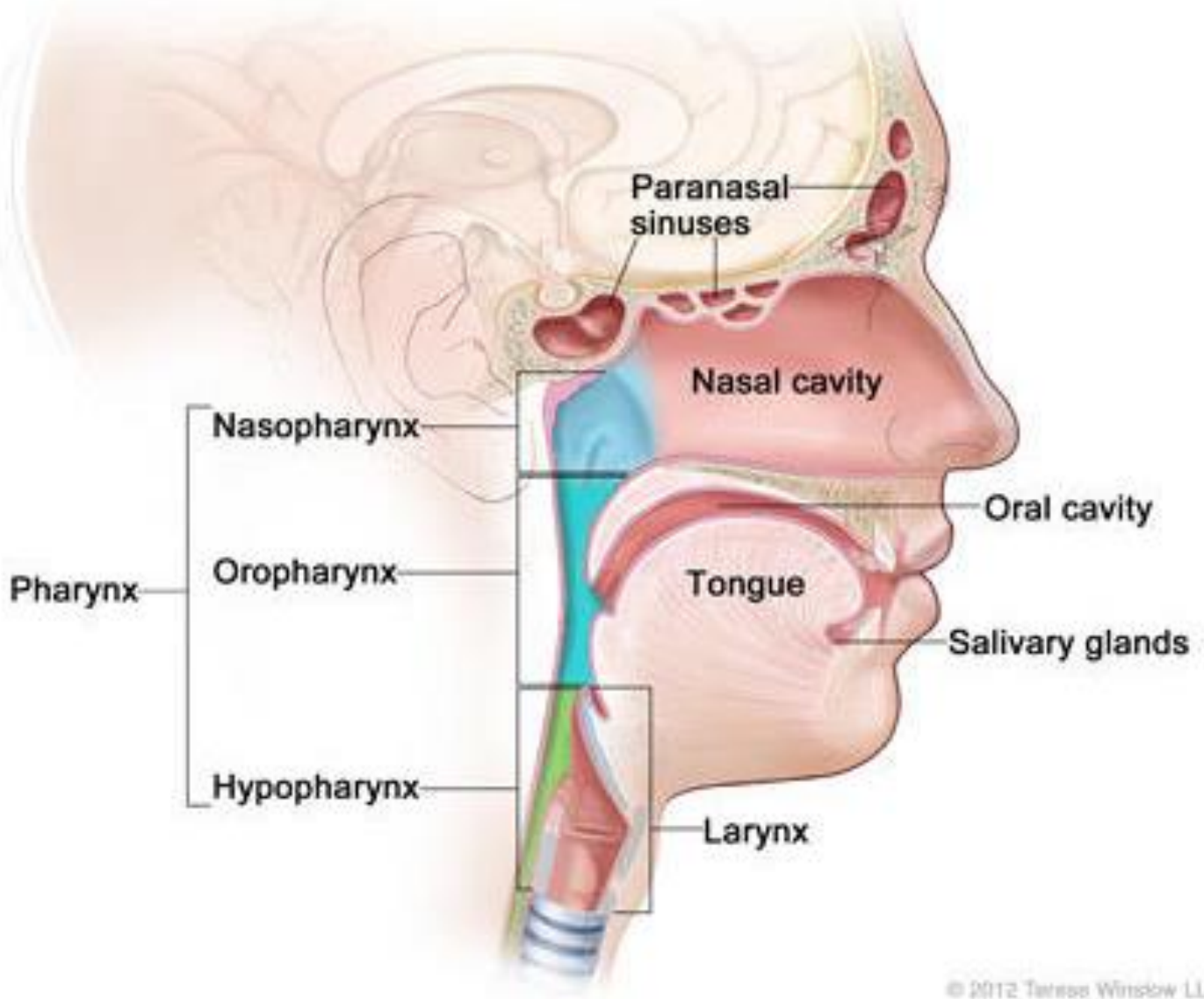
Type your answer in the chat but don't hit enter til I say go!

Proliferation happens here!

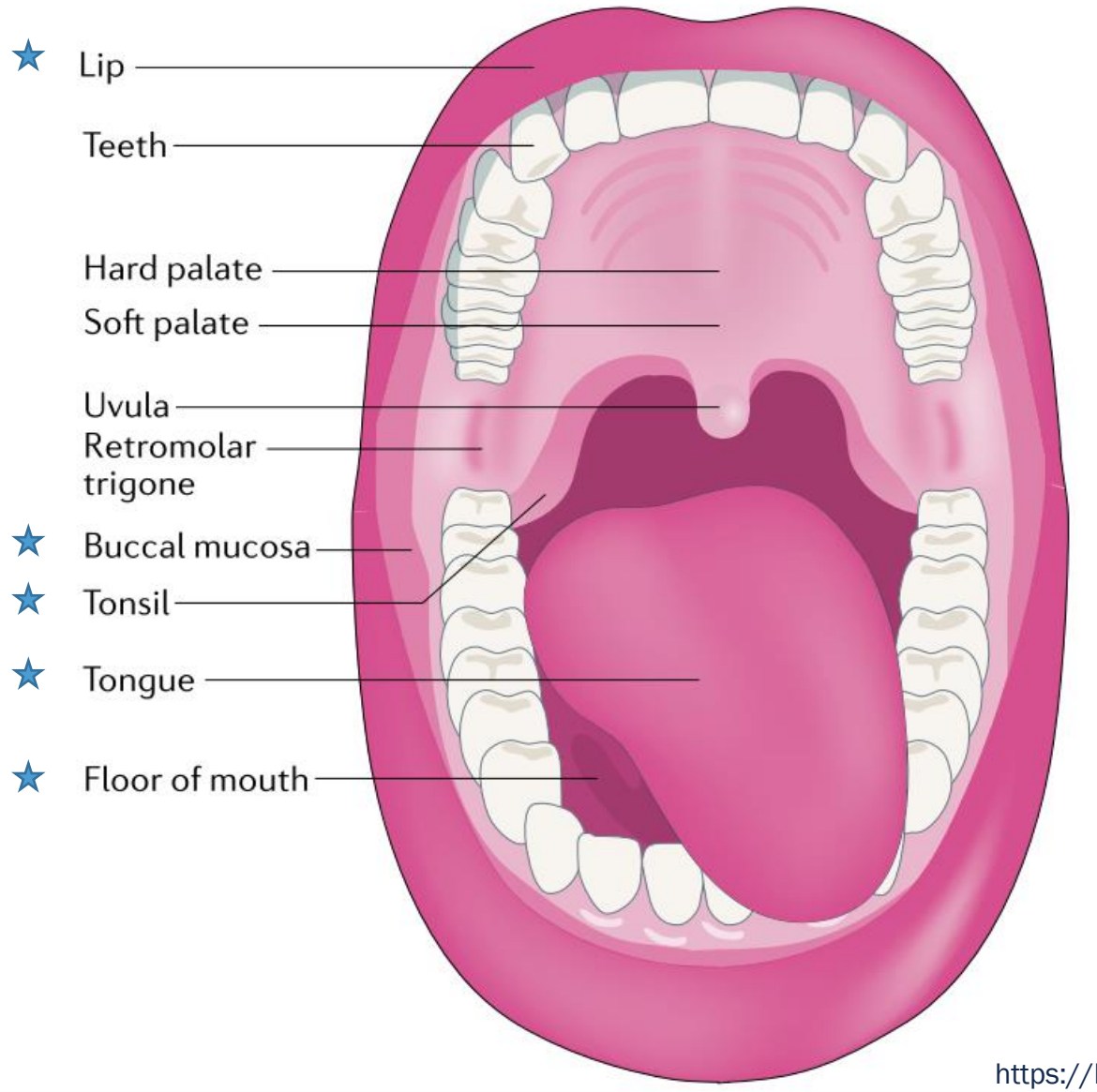


Head and oral cancer sites

UNC SCHOOL OF MEDICINE

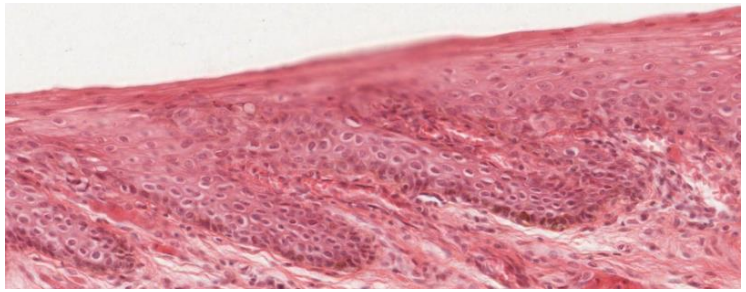


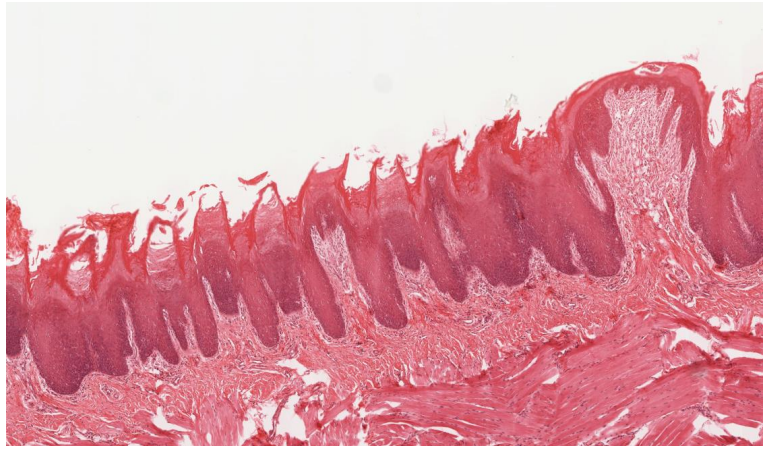
Anatomy of the oral cavity

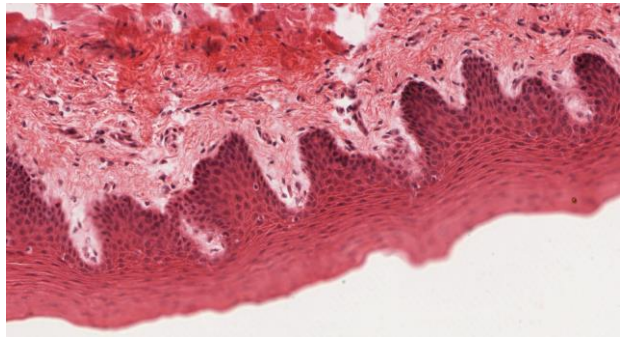


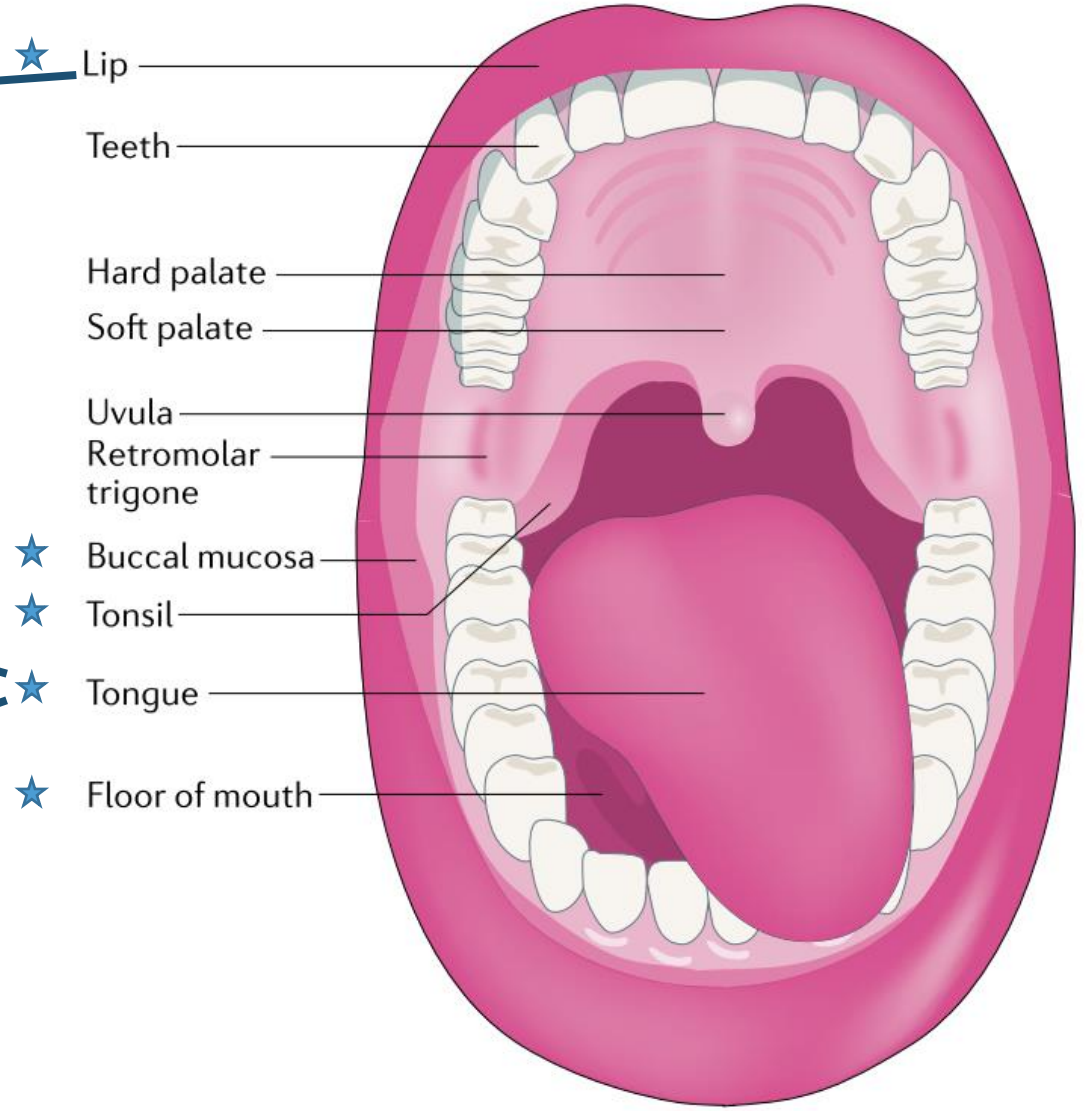
https://histology.medicine.umich.edu/resources/oral-cavity

Anatomy of the oral cavity



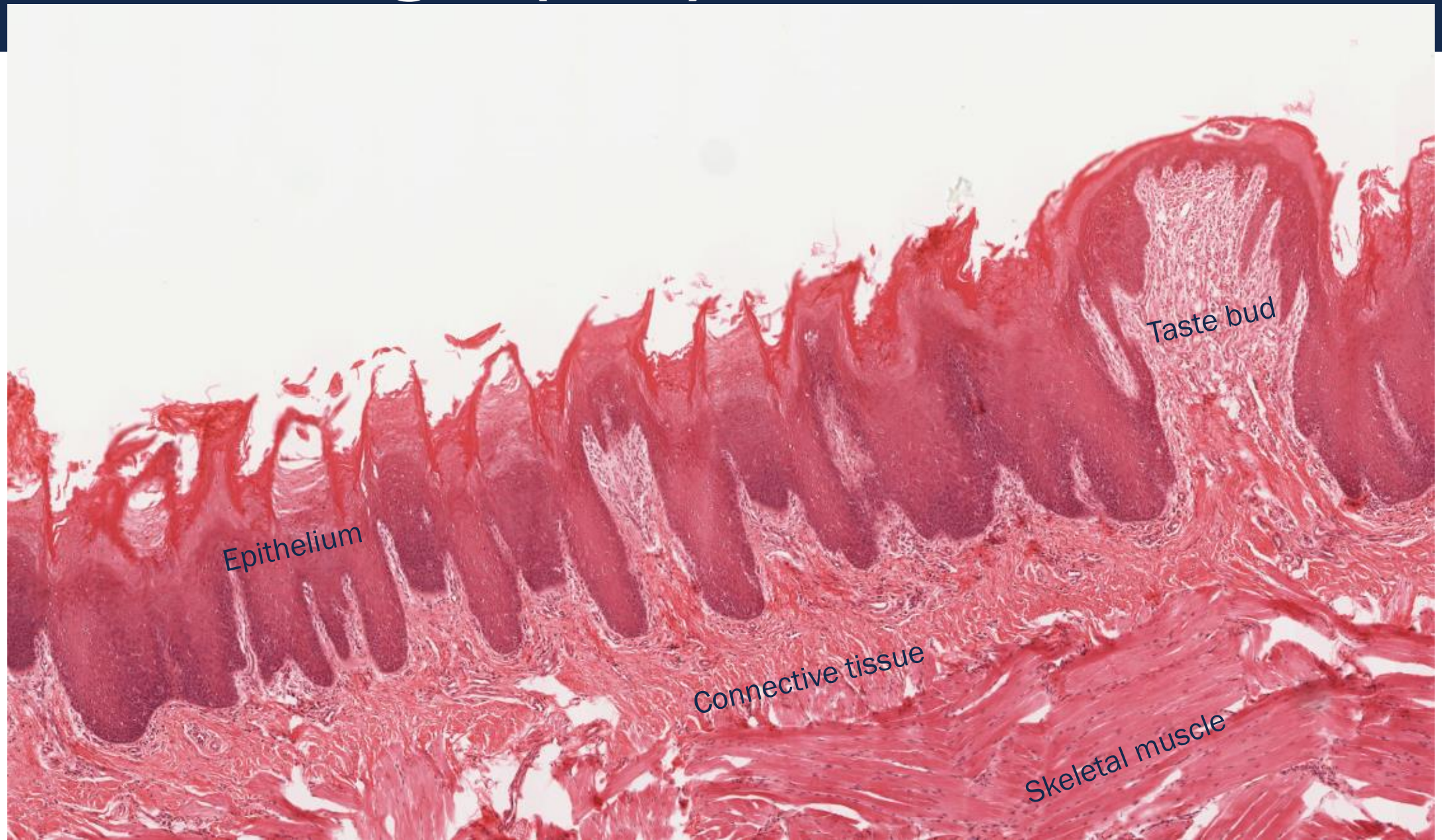




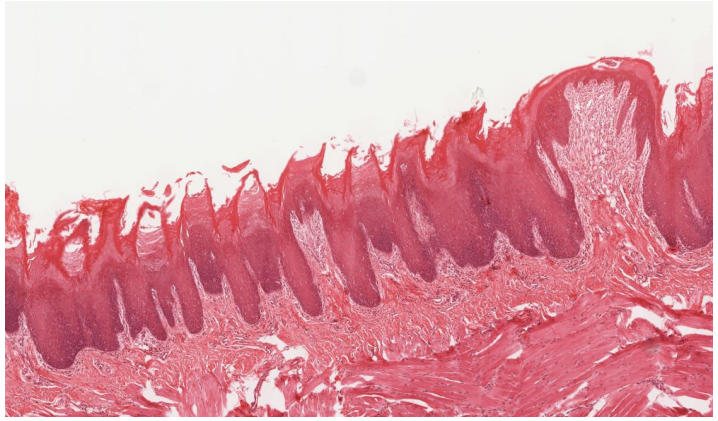


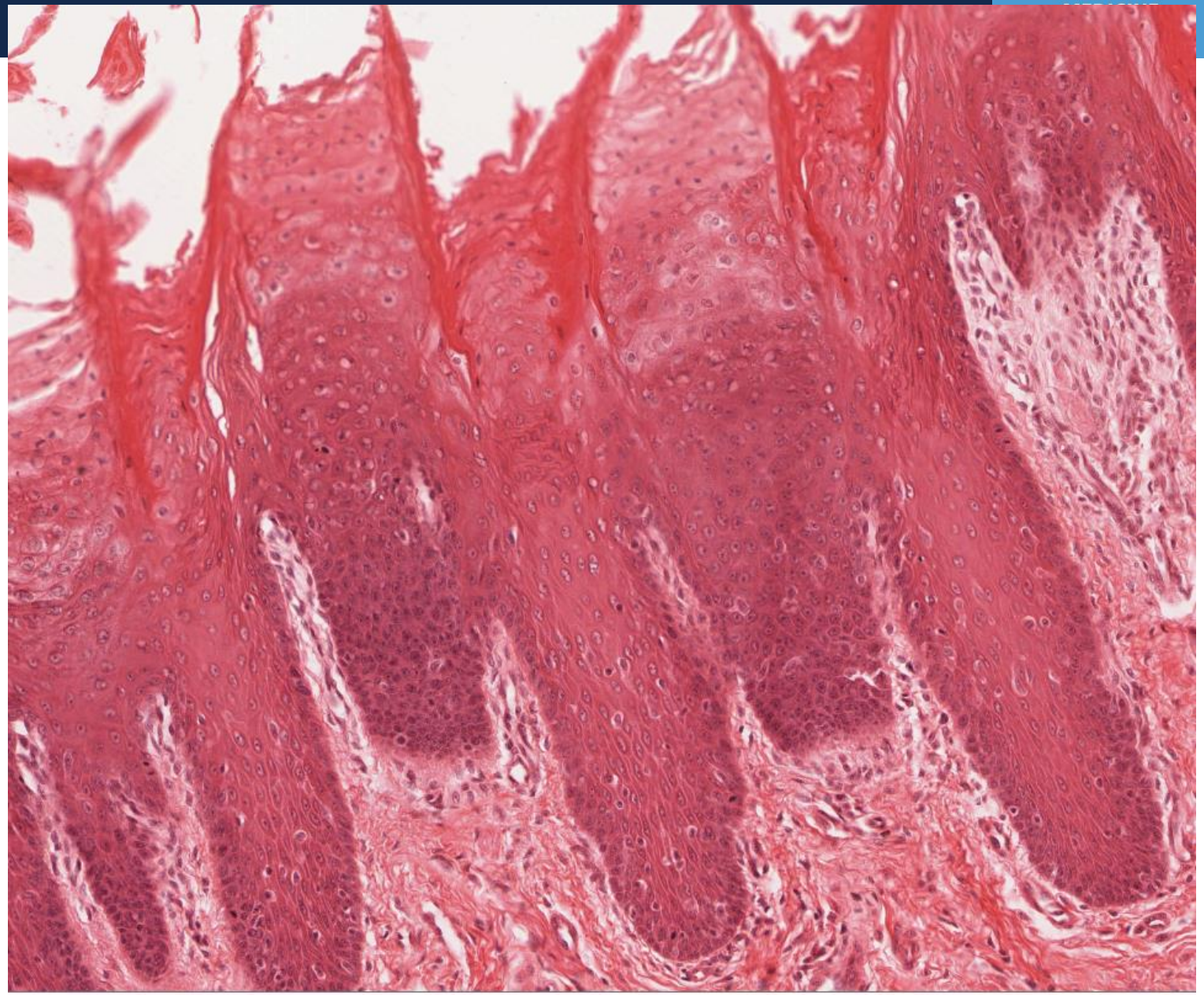
https://histology.medicine.umich.edu/resources/oral-cavity

Dorsal Tongue (H&E)



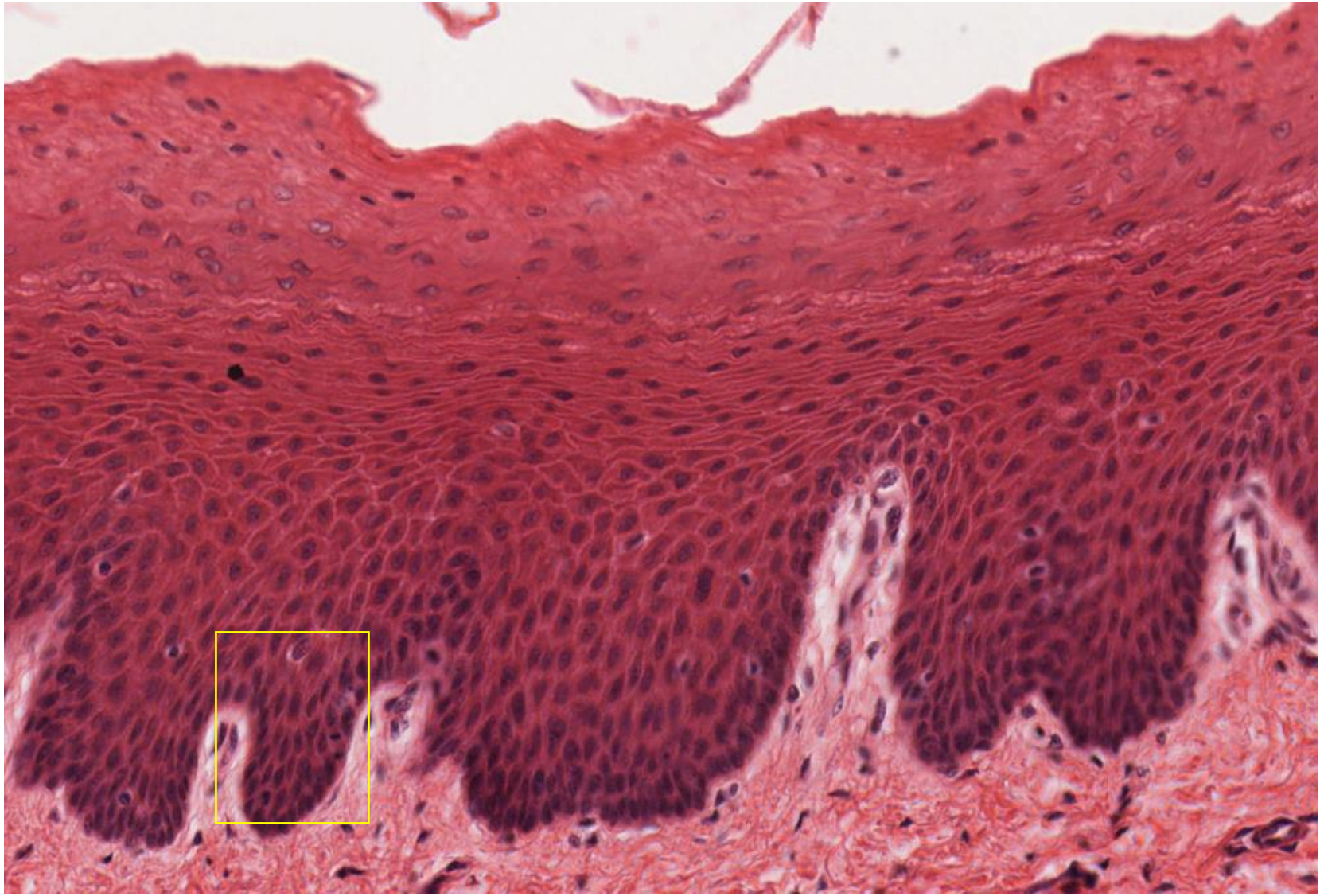
Dorsal Tongue (H&E)

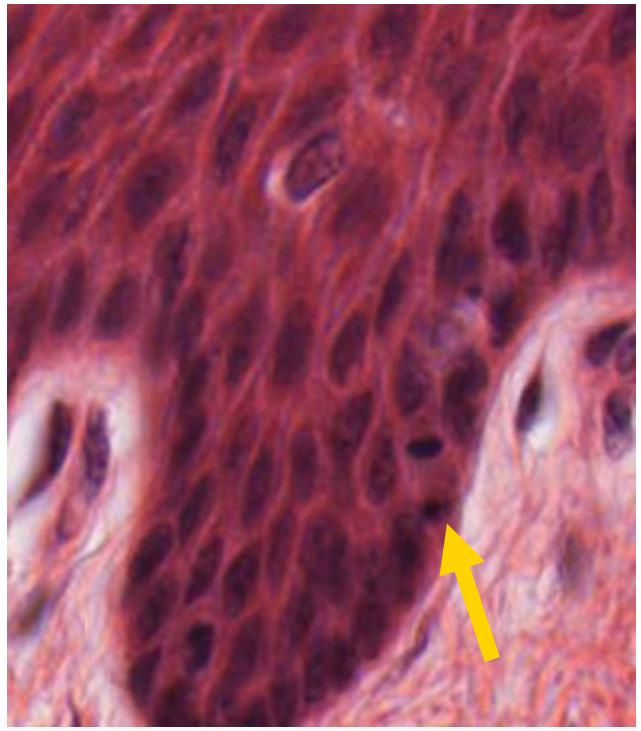




Ventral Tongue (H&E)

UNC SCHOOL OF MEDICINE

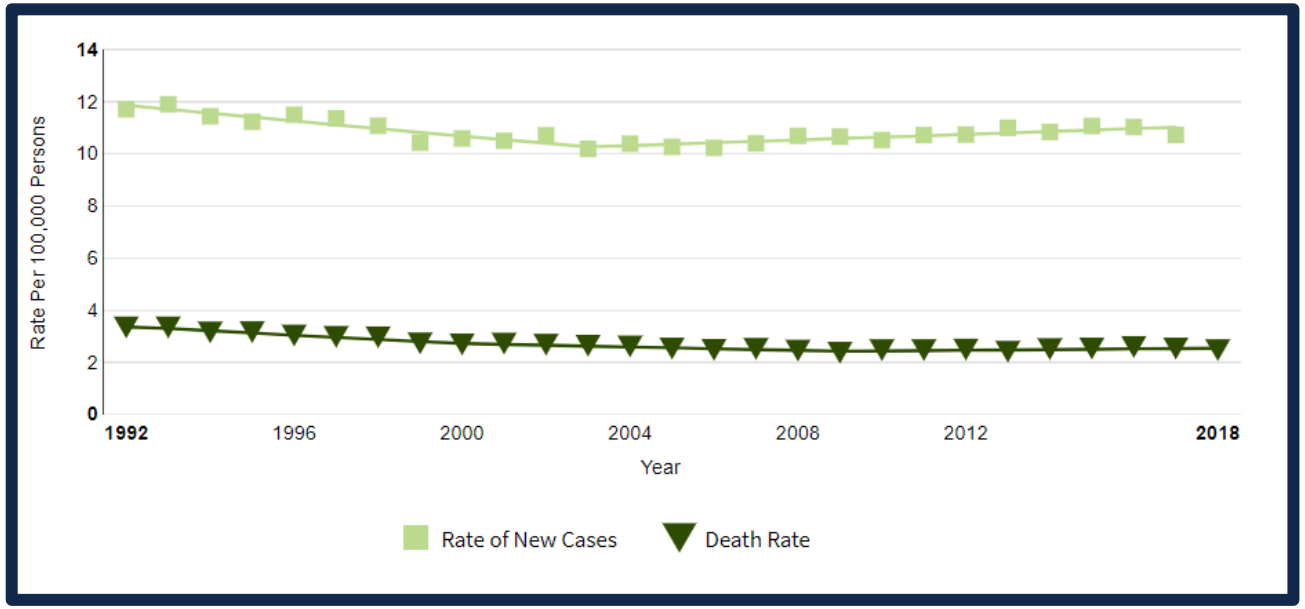


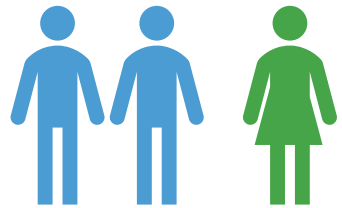


Statistics for head and neck cancers

UNC SCHOOL OF MEDICINE

- 7th most common cancer worldwide
- 4% of cancers in the USA
- 68,000 new cases per year with ~15,000 deaths in USA alone
- Globally, 900,000 cases and >400,000 deaths annually





2-4x more men than women

Diagnosing head and neck cancers

UNC SCHOOL OF MEDICINE

- 95% of oral cancers are Squamous Cell Carcinomas (SCC)
- Adenocarcinomas of the salivary glands are the 2nd most common

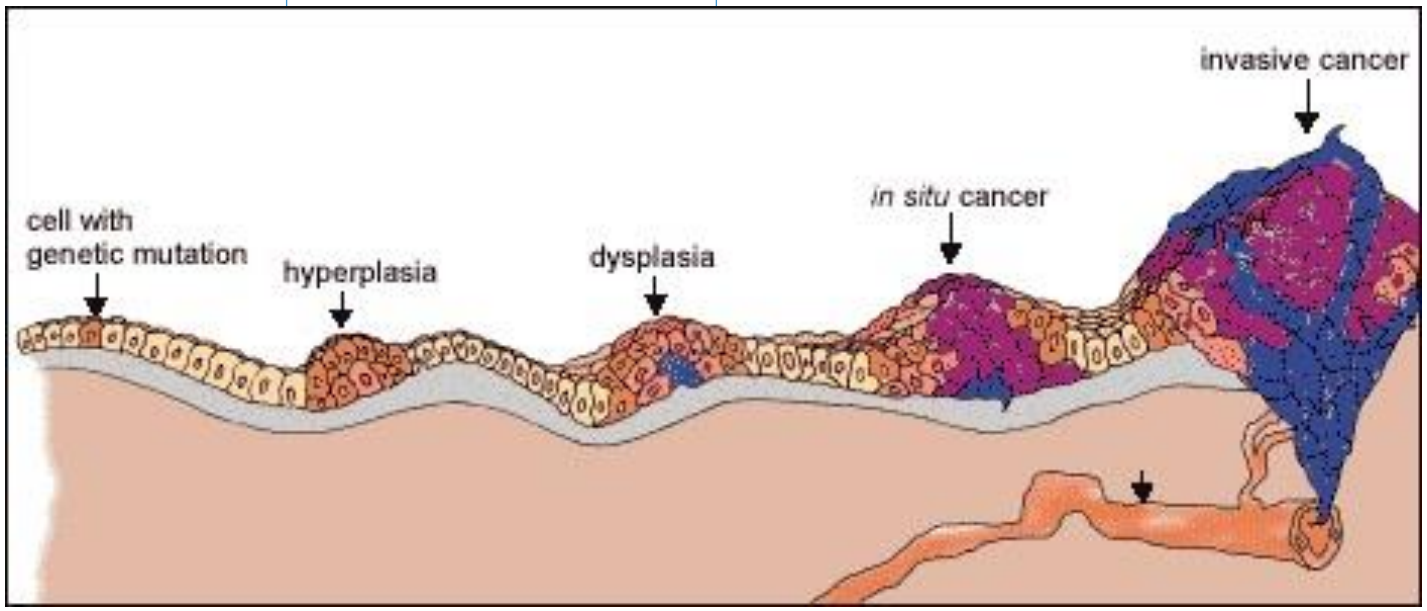
1. Patient self-identifies oral lesion or found by dentist
2. Fine needle aspiration biopsy
3. H&E staining (in combination with pancytokeratin staining)
4. HPV status determination by RT-PCR
5. Staging and defining treatment strategy

How does OSCC arise?

Hyperplasia → Dysplasia → Carcinoma in situ → Carcinoma → High grade Carcinoma

Accumulation of mutations aid in progression →

Thickening of epithelium Excessive proliferation Inhibition of apoptosis Normal morphology	Suprabasal mitoses Dedifferentiation Aberrant expression of basal markers suprabasally Abnormal and irregular morphology Increased cellular density Increased nuclear:cytoplasmic ratio	Dysplasia++ Can develop internal necrosis Technically cancer, but confined to epithelia	Invasion of the basement membrane Blood vessel recruitment (angiogenesis)	Ulcerations Potential to metastasize because of dedifferentiation



http://www.ndhealthfacts.org/wiki/Oncology_%28Cancer%29

Diagnostic criteria for OSCC

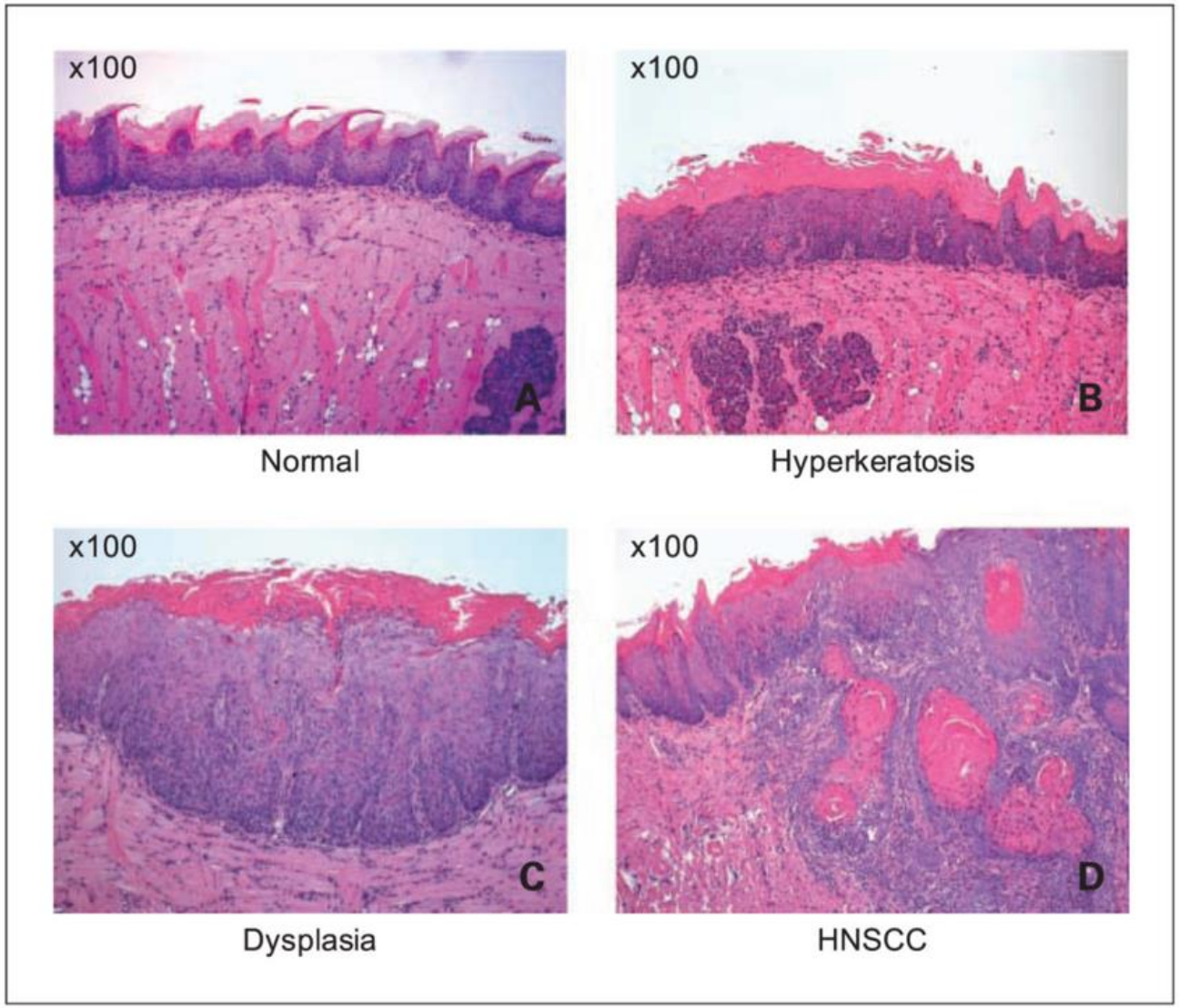
UNC SCHOOL OF MEDICINE

Signs it's Squamous

1. Keratin pearls
2. Excessive keratinization (early lesions)
3. Exists in epithelial tissue

Signs it's Cancer

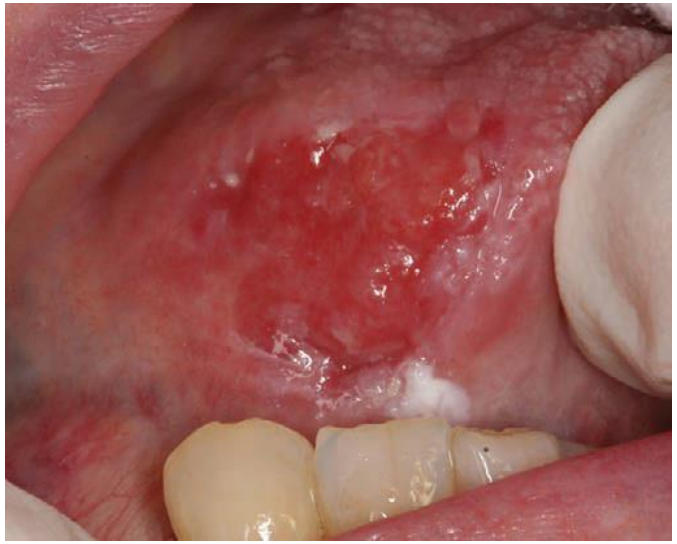
1. Excessive Ki67 staining (suprabasally)
2. Dedifferentiation of cells
3. Pleiomorphic nuclei

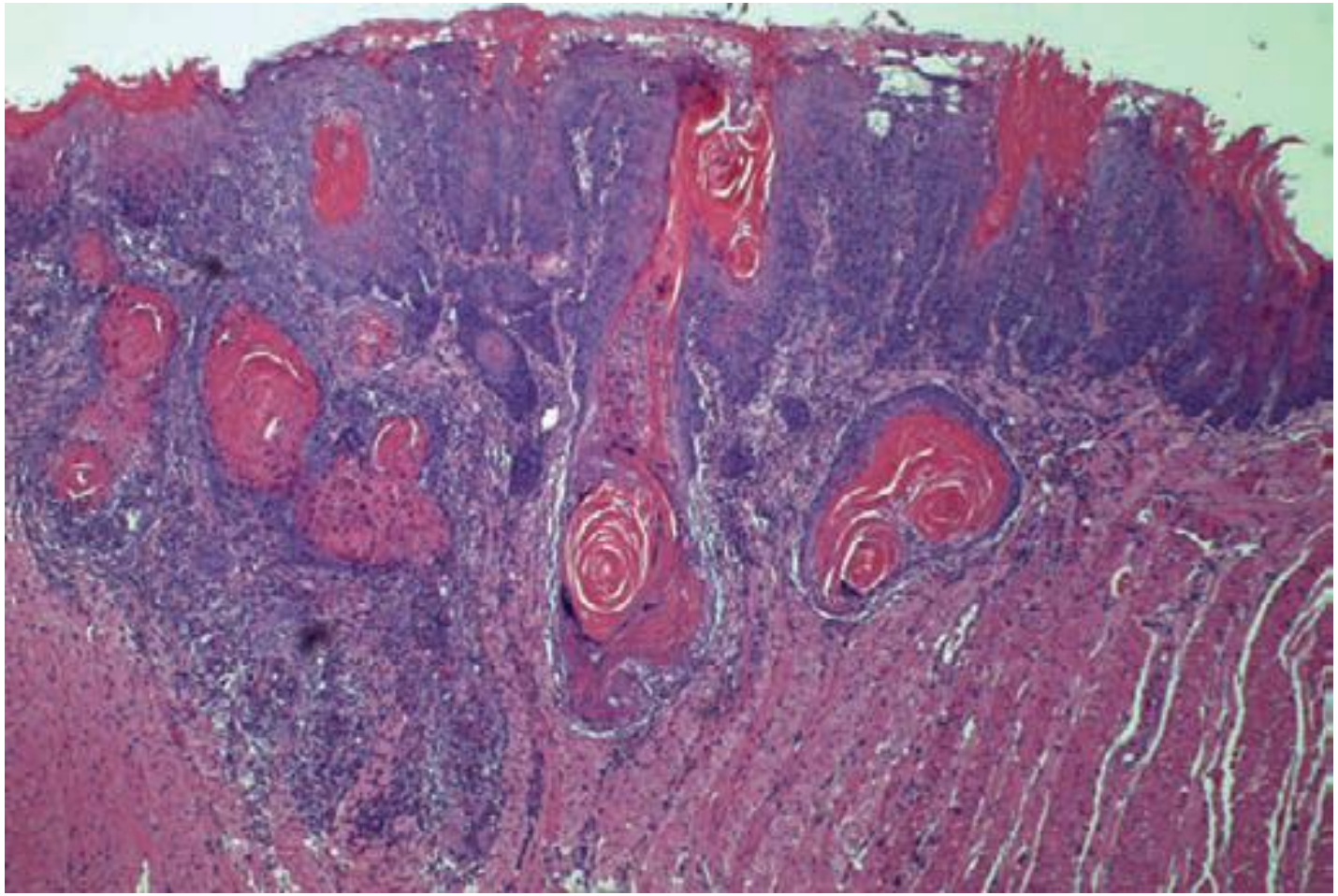


Hasina, Rifat & E Martin, Leslie & Kasza, Kristen & Doçi, Colleen & Jalil, Asif & Lingen, Mark. (2009). ABT-510 Is an Effective Chemopreventive Agent in the Mouse 4-Nitroquinoline 1-Oxide Model of Oral Carcinogenesis. Cancer prevention research (Philadelphia, Pa.). 2. 385-93. 10.1158/1940-6207.CAPR-08-0211.

Head and neck squamous cell carcinoma (HNSCC)

UNC SCHOOL OF MEDICINE





Can you find:

1) Keratin pearls
2) Invasion into the underlying tissue
3) Hyperkeratinization

Robbins, Basic Pathology Fig 14-4

How do you get HNSCC?

UNC SCHOOL OF MEDICINE

What are the main risk factors associated with HNSCC?

Type your answer in the Zoom chat but don't hit Enter til I say go

Learning Objectives

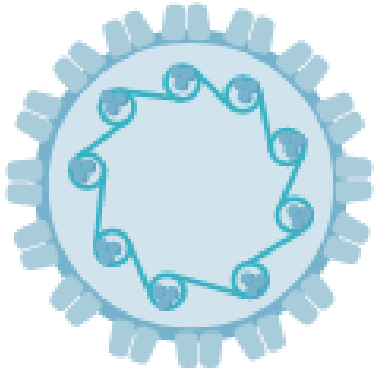
UNC SCHOOL OF MEDICINE

Following today's lecture, students will be able to…

1. Compare and contrast HPV+ and HPV- head and oral cancers with respect to etiology, treatments, and prognosis
2. Outline how mutagens lead to carcinogenesis
3. Discuss therapeutic strategies for head and oral cancers

Learning objectives are what I use to make exam questions! ☺

How do you get HNSCC?



Human papillomavirus (HPV)
Epstein-Barr virus (EBV)

- Low mutational burden
- Site-specificity
- Non-keratinized
- Younger patients (avg 53 years)
- Good prognosis
- *Preventable*!

Tobacco products of all kinds

- Also Paan/betel quid, occupational exposure, radiation exposure, some genetic predisposition
- High mutational burden
- Affects oral cavity, lungs, esophagus…
- Keratinized
- Older patients (avg 66 years)
- Poorer prognosis
- *Most are preventable*!

Oral HPV infection is common!

UNC SCHOOL OF MEDICINE

Figure 1. Prevalence of any oral HPV among adults aged 18–69, by race and Hispanic origin and sex: United States, 2011–2014.

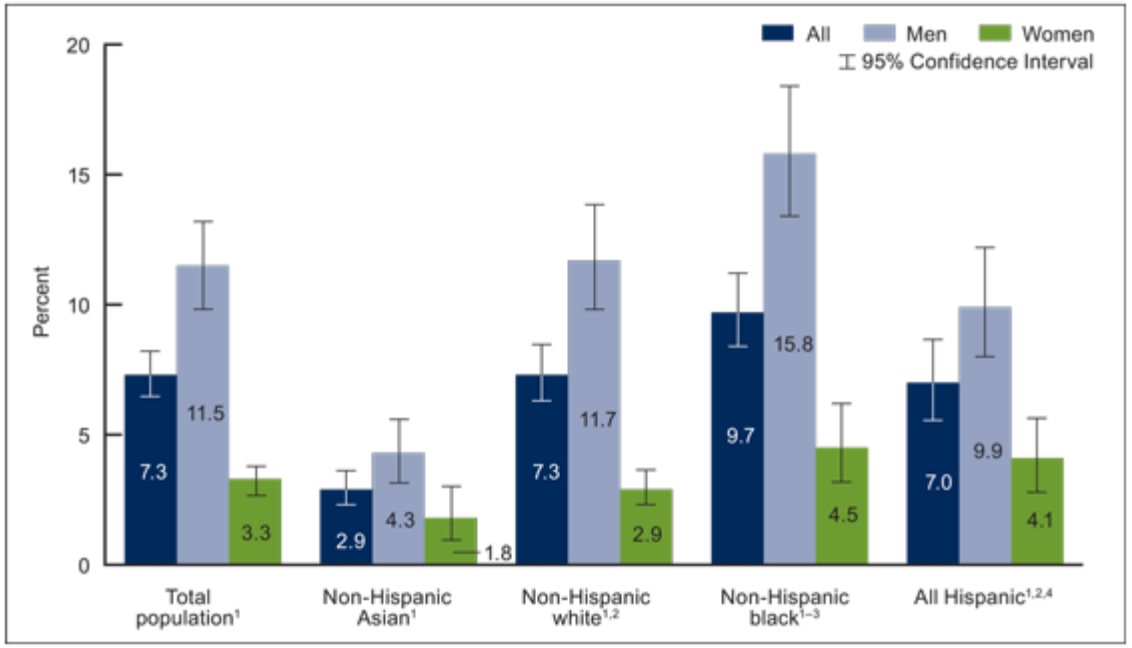
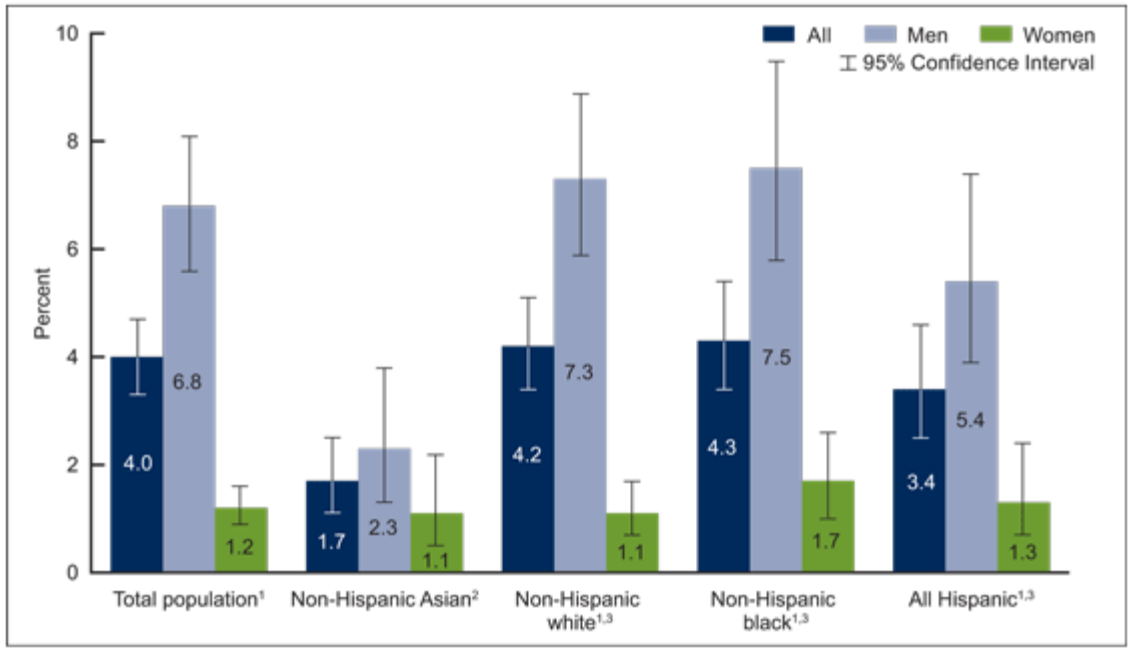


Figure 2. Prevalence of high-risk oral HPV among adults aged 18–69, by race and Hispanic origin and sex: United States, 2011–2014

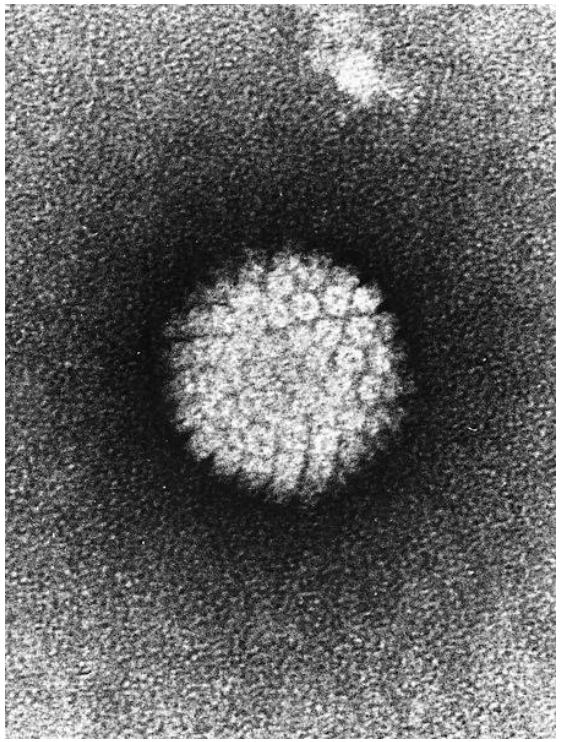


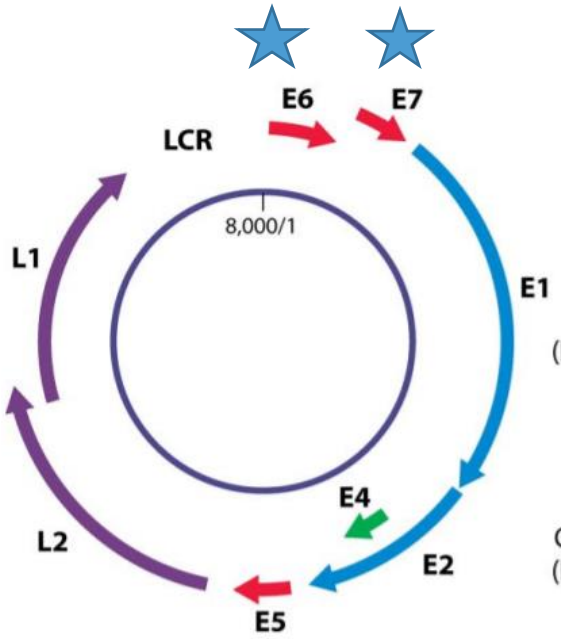
https://www.cdc.gov/nchs/products/databriefs/db280.htm

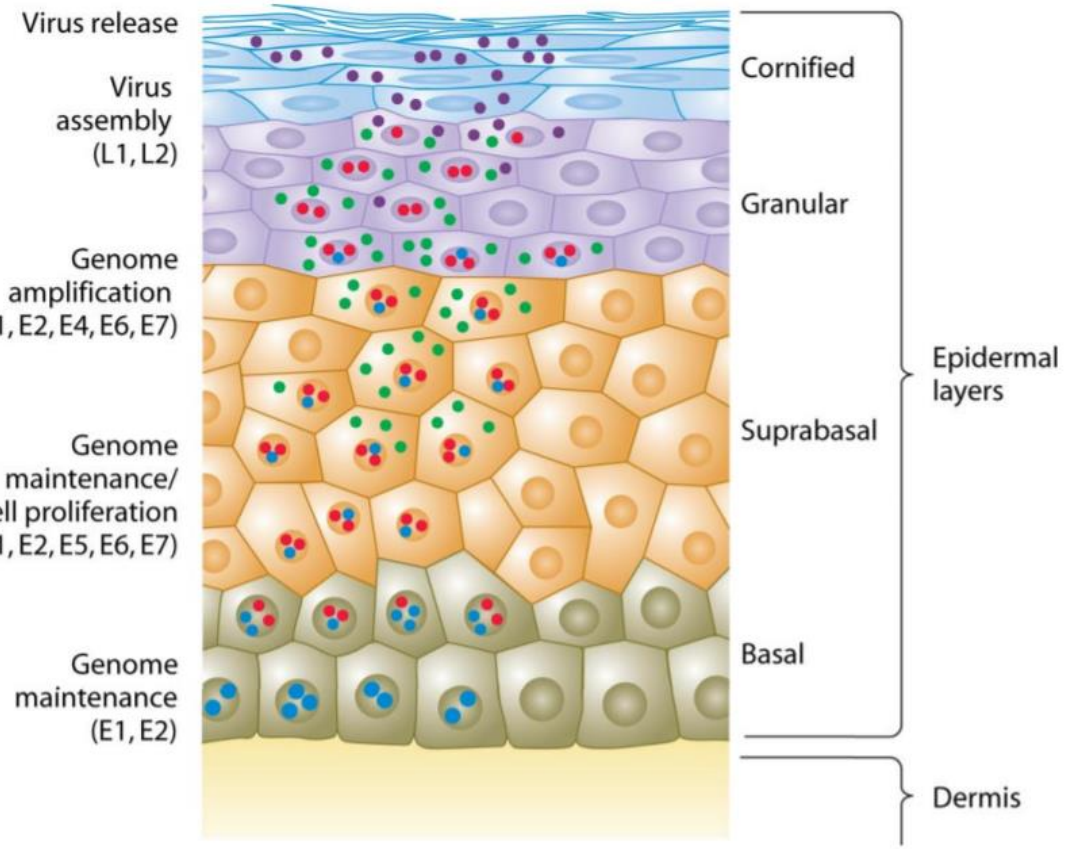
High-risk HPV Infection

UNC SCHOOL OF MEDICINE

Regions most often affected:
Tonsils
Oropharynx (non-keratinized)
Base of tongue







High risk HPV infection

UNC SCHOOL OF MEDICINE

- HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 68, 69, and 73 are classified as high-risk HPV

- Gardasil (HPV vaccine) *prevents infection!!!* from HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58

HPV status affects mutational burden

UNC SCHOOL OF MEDICINE

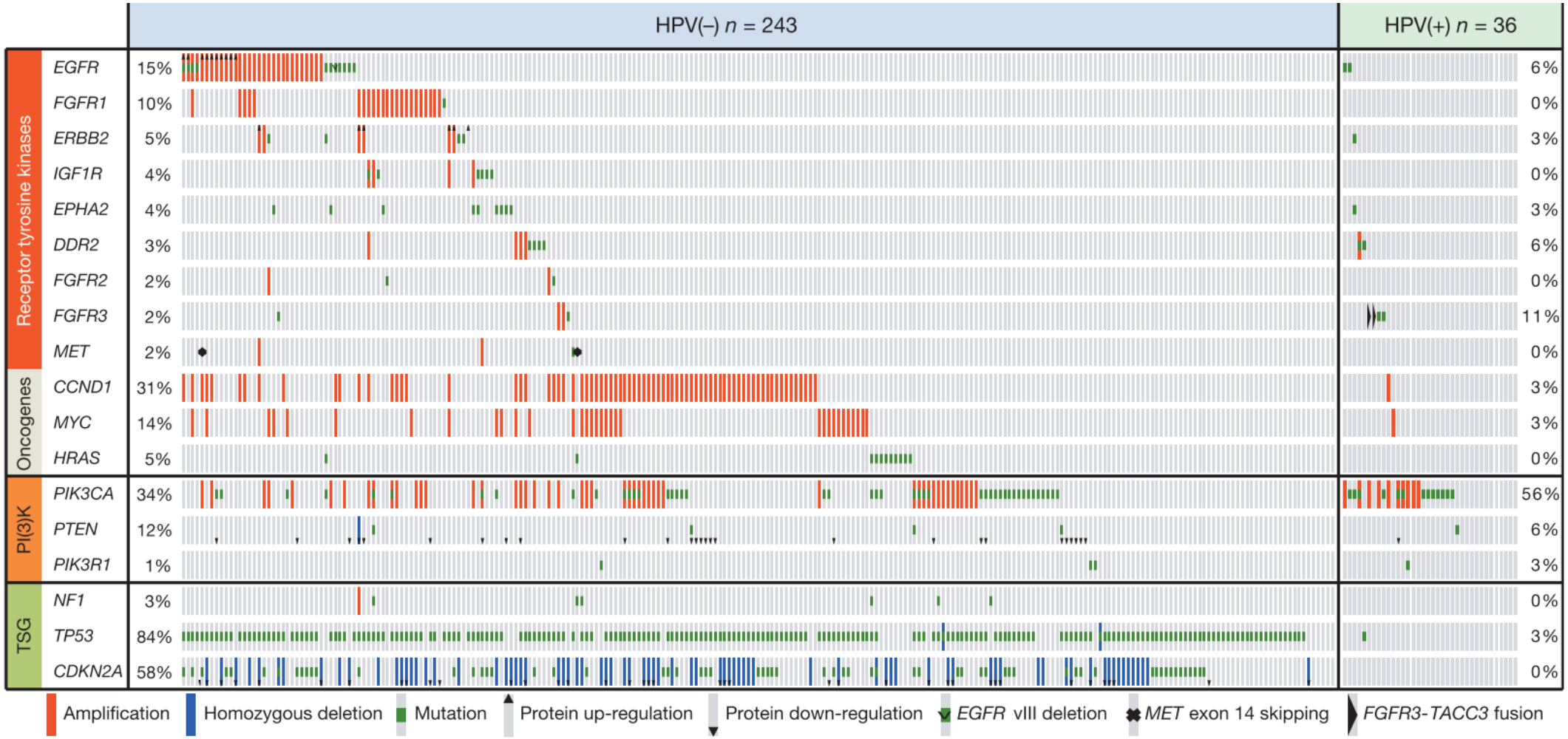


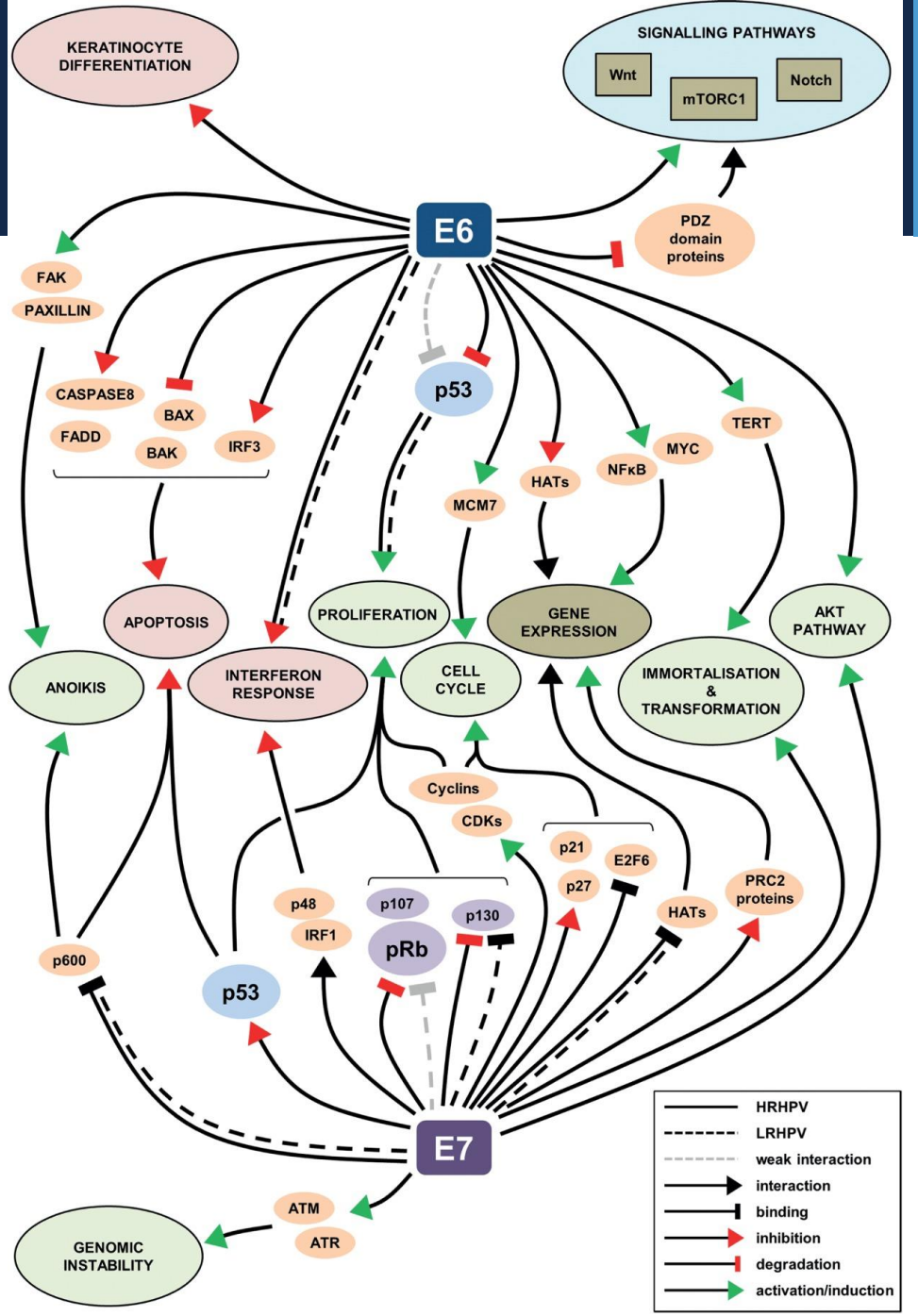
Figure 3 | Candidate therapeutic targets and driver oncogenic events. Alteration events for key genes are displayed by sample ($n = 279$). TSG, tumour suppressor gene.

The Cancer Genome Atlas Network (2015). "Comprehensive genomic characterization of head and neck squamous cell carcinomas." Nature **517**(7536): 576-582.

HPV pathogenesis

Why do you think most HPV+ HNSCCs lack mutations in p53?

Type your answer in the chat but don't hit enter til I say go!



Groves, I.J., Coleman, N., 2015. Pathogenesis of human papillomavirus-associated mucosal disease. The Journal of Pathology 235, 527–538.. doi:10.1002/path.4496

Learning Objectives

UNC SCHOOL OF MEDICINE

Following today's lecture, students will be able to…

1. Compare and contrast HPV+ and HPV- head and oral cancers with respect to etiology, treatments, and prognosis
2. Outline how mutagens lead to carcinogenesis
3. Discuss therapeutic strategies for head and oral cancers

Learning objectives are what I use to make exam questions! ☺

Two types of mutations

UNC SCHOOL OF MEDICINE

Germline mutations

- Occur in a gamete, passing from parent to child
- Cause inherited cancers
- 5-20% of all cancers

Acquired mutations

- Damage to genes in a particular cell or subset of cells
- Not heritable
- Mutagens/carcinogens are often responsible
- May be acquired through aging

Types of genes associated with cancers

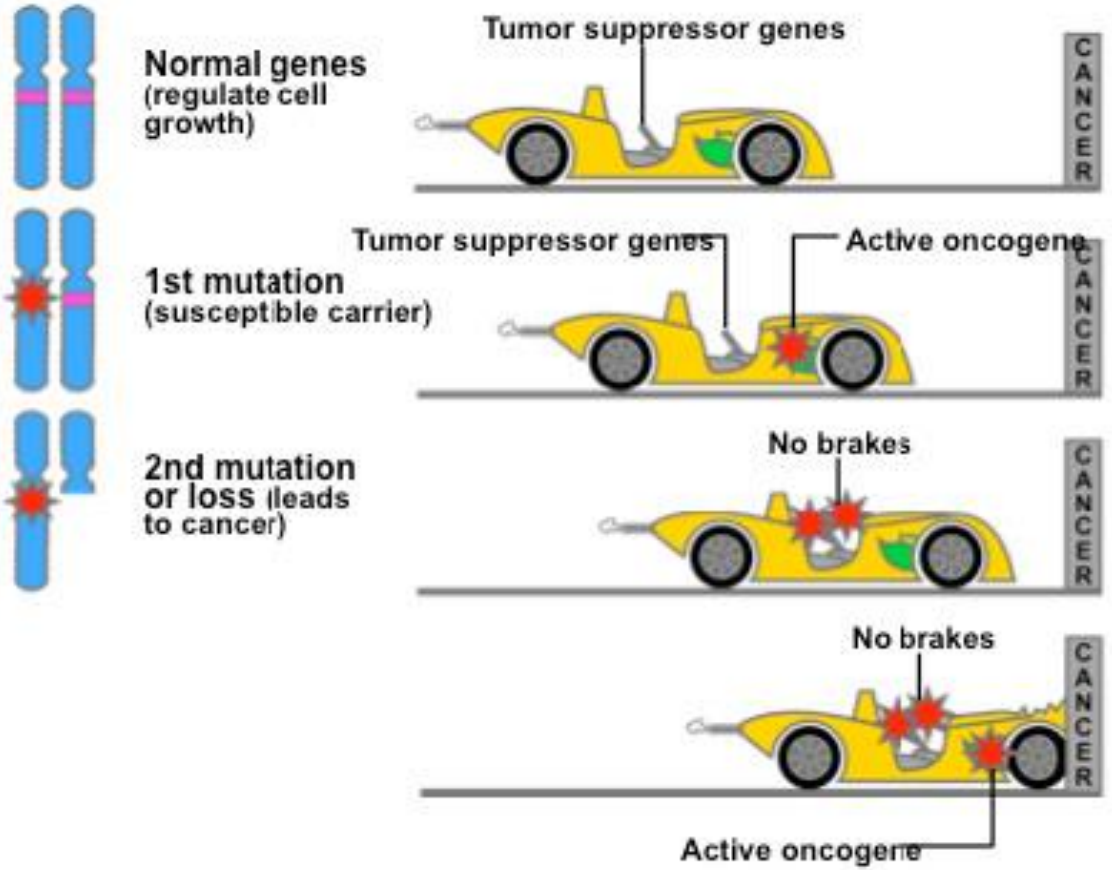
UNC SCHOOL OF MEDICINE

Tumor suppressor genes

- Normally protective
- Regulate cell cycle, repair DNA damage, control cell death
- Ex. *BRCA1/2*, *TP53*

Oncogenes

- "Driver mutations"
- Control cancer growth and spread, involved in cellular communication
- Ex. *HER2, RAS*



https://cisncancer.org/research/what_we_know/advances/oncogenes.html

HPV status affects mutational burden

UNC SCHOOL OF MEDICINE

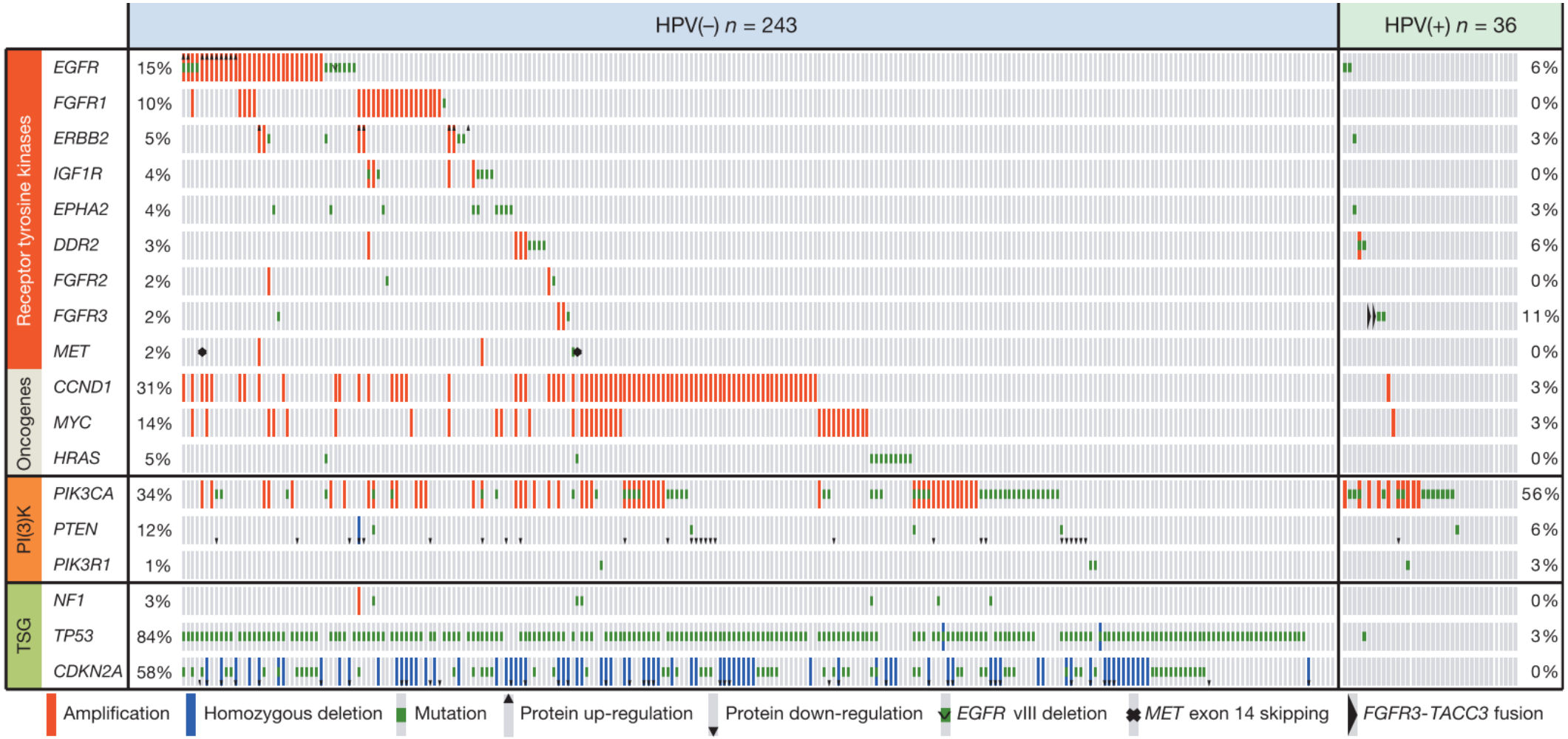
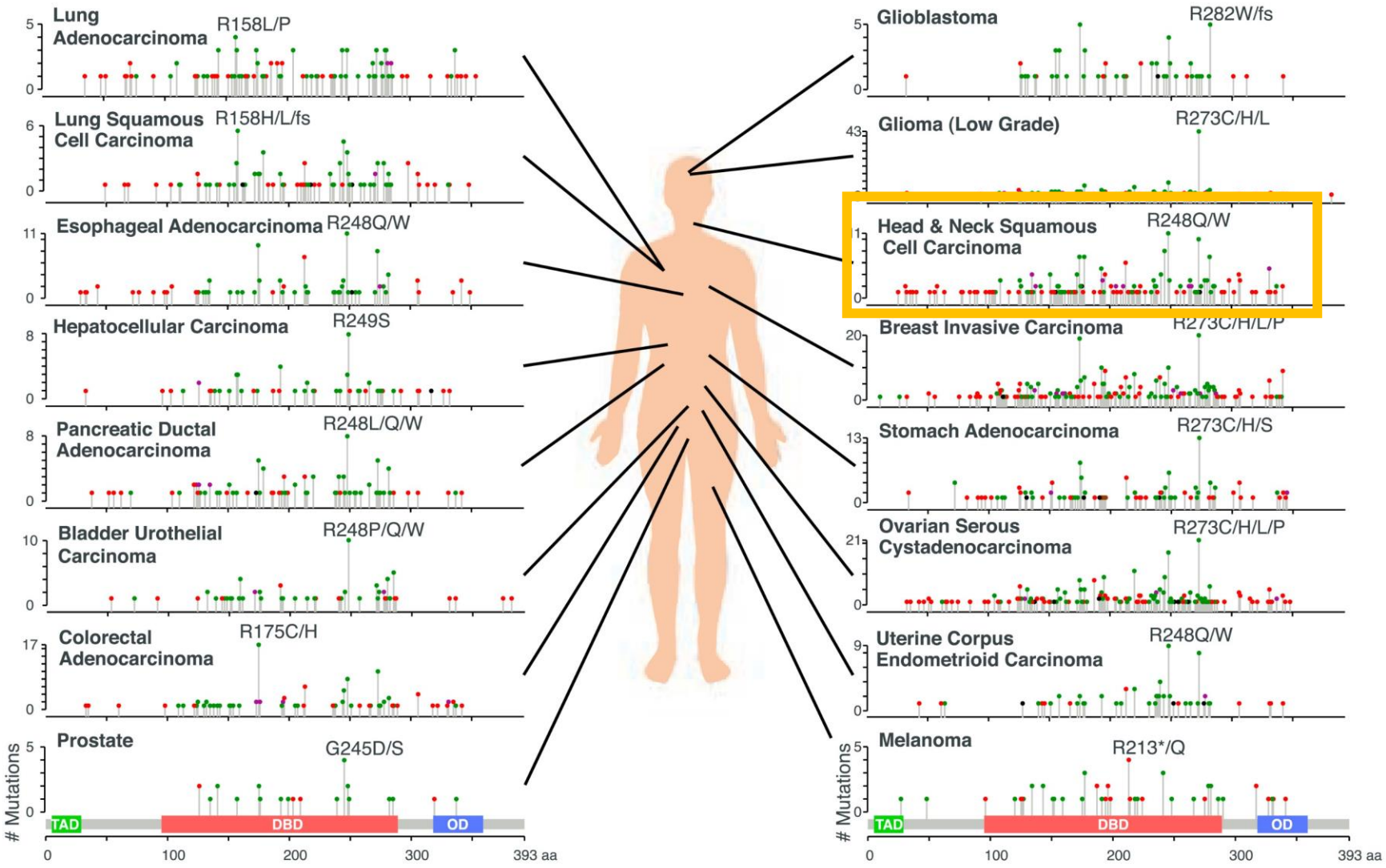


Figure 3 | Candidate therapeutic targets and driver oncogenic events. Alteration events for key genes are displayed by sample ($n = 279$). TSG, tumour suppressor gene.

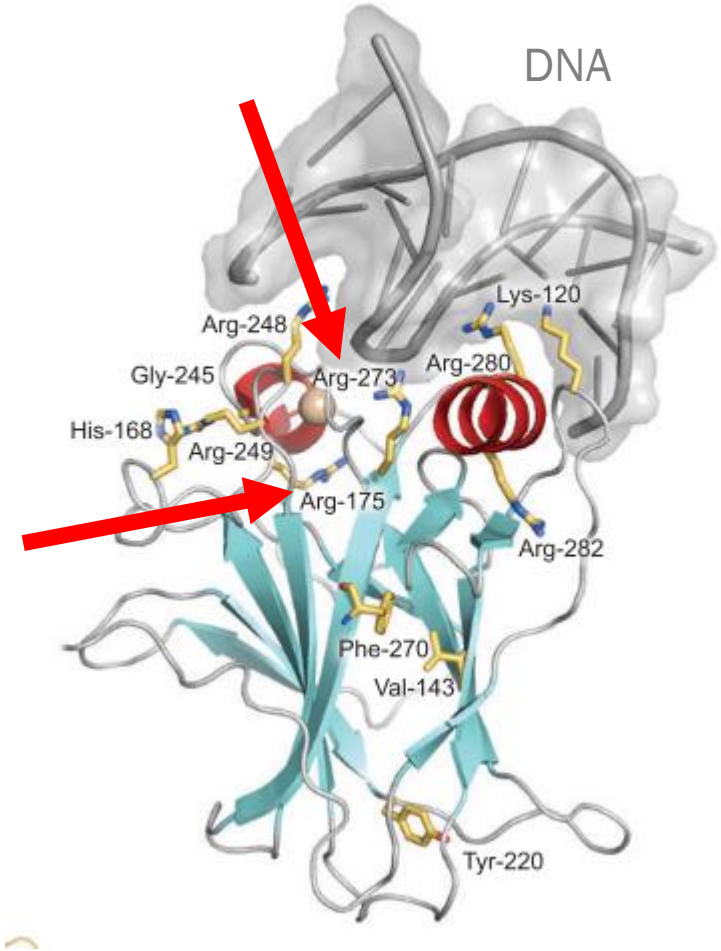
The Cancer Genome Atlas Network (2015). "Comprehensive genomic characterization of head and neck squamous cell carcinomas." Nature **517**(7536): 576-582.

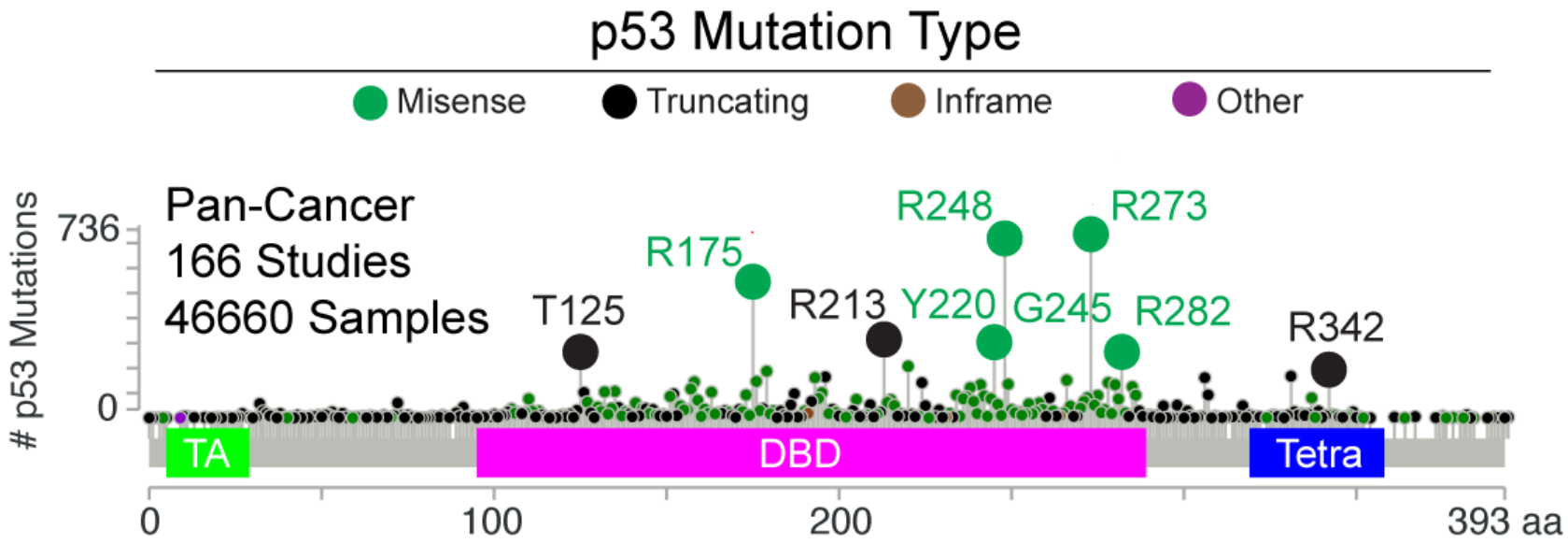
p53 is the most frequently mutated gene across all cancers



Edward R. Kastenhuber, Scott W. Lowe, Putting p53 in Context, Cell, Volume 170, Issue 6, 2017, Pages 1062-1078, ISSN 0092-8674, https://doi.org/10.1016/j.cell.2017.08.028.

p53 mutations in HNSCC occur in *hotspots* within the DNA binding domain





Two types of hotspot mutants –
Contact (R248, R273) and
Structural (R175, G245, R249, R282)

A.C. Joerger, A.R. Fersht, Structural biology of the tumor suppressor p53, Annu Rev Biochem 77 (2008) 557-82

Tumor-Node-Metastasis Classification

UNC SCHOOL OF MEDICINE

Table 1. Tumor–Node–Metastasis Classification of Human Papillomavirus (HPV)–Positive and HPV-Negative Oropharyngeal Cancer.*

Classification	HPV-Positive Oropharyngeal Cancer	HPV-Negative Oropharyngeal Cancer
Tumor		
TX	Primary tumor cannot be assessed	Primary tumor cannot be assessed
Tis	Carcinoma in situ	Carcinoma in situ
T0	No tumor identified	No tumor identified
T1	Tumor <2 cm in greatest dimension	Tumor <2 cm in greatest dimension
T2	Tumor >2 cm but <4 cm in greatest dimension	Tumor >2 cm but <4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension or extension to lingual surface of epiglottis	Tumor >4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced local disease; tumor invades larynx, extrinsic muscle of tongue, medial pterygoid muscle, hard palate or mandible, or beyond†	
T4a		Moderately advanced local disease; tumor invades larynx, extrinsic muscle of tongue, medial pterygoid muscle, hard palate, or mandible†
T4b		Very advanced local disease; tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

Node		
Nx	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
N0	No regional lymph-node metastases	No regional lymph-node metastases
N1	Metastases to 1 or more ipsilateral lymph nodes, none >6 cm in greatest dimension	Metastasis to a single ipsilateral lymph node, ≤3 cm in greatest dimension, without extranodal extension
N2	Metastases to contralateral or bilateral lymph nodes, none >6 cm in greatest dimension	
N2a		Metastasis to a single ipsilateral node, >3 cm but <6 cm in greatest dimension, without extranodal extension
N2b		Metastases to multiple ipsilateral lymph nodes, none >6 cm in greatest dimension, without extranodal extension
N2c		Metastases to bilateral or contralateral lymph nodes, none >6 cm in greatest dimension, without extra-nodal extension
N3	Metastases to one or more lymph nodes, >6 cm in greatest dimension	
N3a		Metastasis to a lymph node, >6 cm in greatest dimension, without extranodal extension
N3b		Metastases to one or more lymph nodes, with clinically overt extranodal extension
Metastasis		
M0	No distant metastases	No distant metastases
M1	Distant metastases	Distant metastases

Staging cancers based on TNM class

UNC SCHOOL OF MEDICINE

Table 2. Prognostic Stages According to the TNM Classification.*

Stage	HPV-Positive Oropharyngeal Cancer			HPV-Negative Oropharyngeal Cancer		
	Tumor	Node	Metastasis	Tumor	Node	Metastasis
0	Tis	N0	M0	Tis	N0	M0
I	T0, T1, or T2	N0 or N1	M0	T1	N0	M0
II	T0, T1, or T2	N2	M0	T2	N0	M0
	T3	N0, N1, or N2	M0			
III	T0, T1, T2, T3, or T4	N3	M0	T1, T2, or T3	N1	M0
	T4	N0, N1, N2, or N3	M0			
IV	Any T	Any N	M1			
IVA				T4a	N0 or N1	M0
				T1, T2, T3, or T4a	N2	M0
IVB				Any T	N3	M0
				T4b	Any N	M0
IVC				Any T	Any N	M1

Learning Objectives

UNC SCHOOL OF MEDICINE

Following today's lecture, students will be able to…

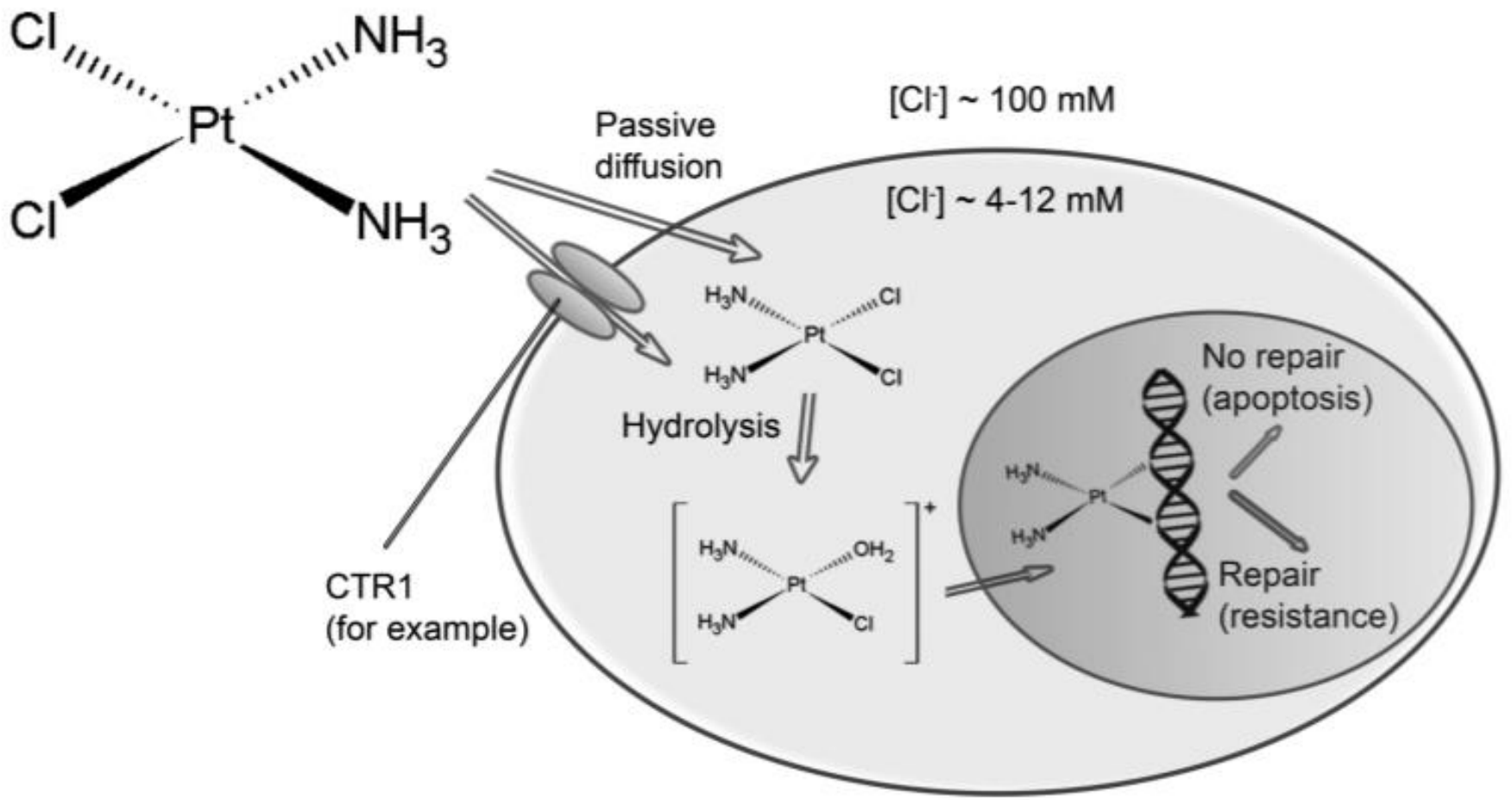
1. Compare and contrast HPV+ and HPV- head and oral cancers with respect to etiology, treatments, and prognosis
2. Outline how mutagens lead to carcinogenesis
3. Discuss therapeutic strategies for head and oral cancers

Learning objectives are what I use to make exam questions! ☺

Therapeutic interventions

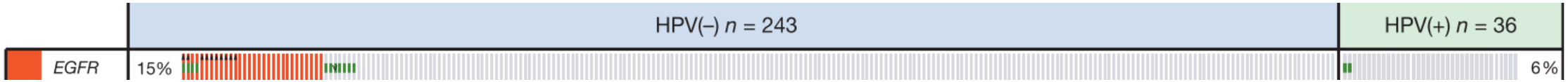
- Surgery, radiotherapy, and chemotherapy are the most common treatment strategies (chemoradiotherapy/ CRT)
- EGFR monoclonal antibody cetuximab
- Immune checkpoint inhibitors pembrolizumab and nivolumab for recurrent disease

Platinum-based chemotherapy



Cisplatin (shown)
Carboplatin

Cetuximab



- Only ~15% of HPV- HNSCC patients have EGFR mutations but over 80% of tumors have overexpression
- Cetuximab works as a radiation sensitizer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck

James A. Bonner, M.D., Paul M. Harari, M.D., Jordi Giralt, M.D., Nozar Azarnia, Ph.D., Dong M. Shin, M.D., Roger B. Cohen, M.D., Christopher U. Jones, M.D., Ranjan Sur, M.D., Ph.D., David Raben, M.D., Jacek Jassem, M.D., Ph.D., Roger Ove, M.D., Ph.D., Merrill S. Kies, M.D., Jose Baselga, M.D., Hagop Youssoufian, M.D., Nadia Amellal, M.D., Eric K. Rowinsky, M.D., and K. Kian Ang, M.D., Ph.D.*

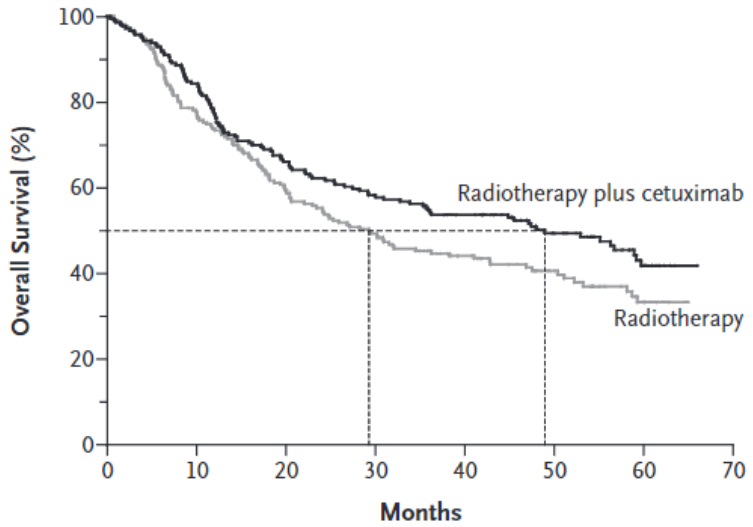
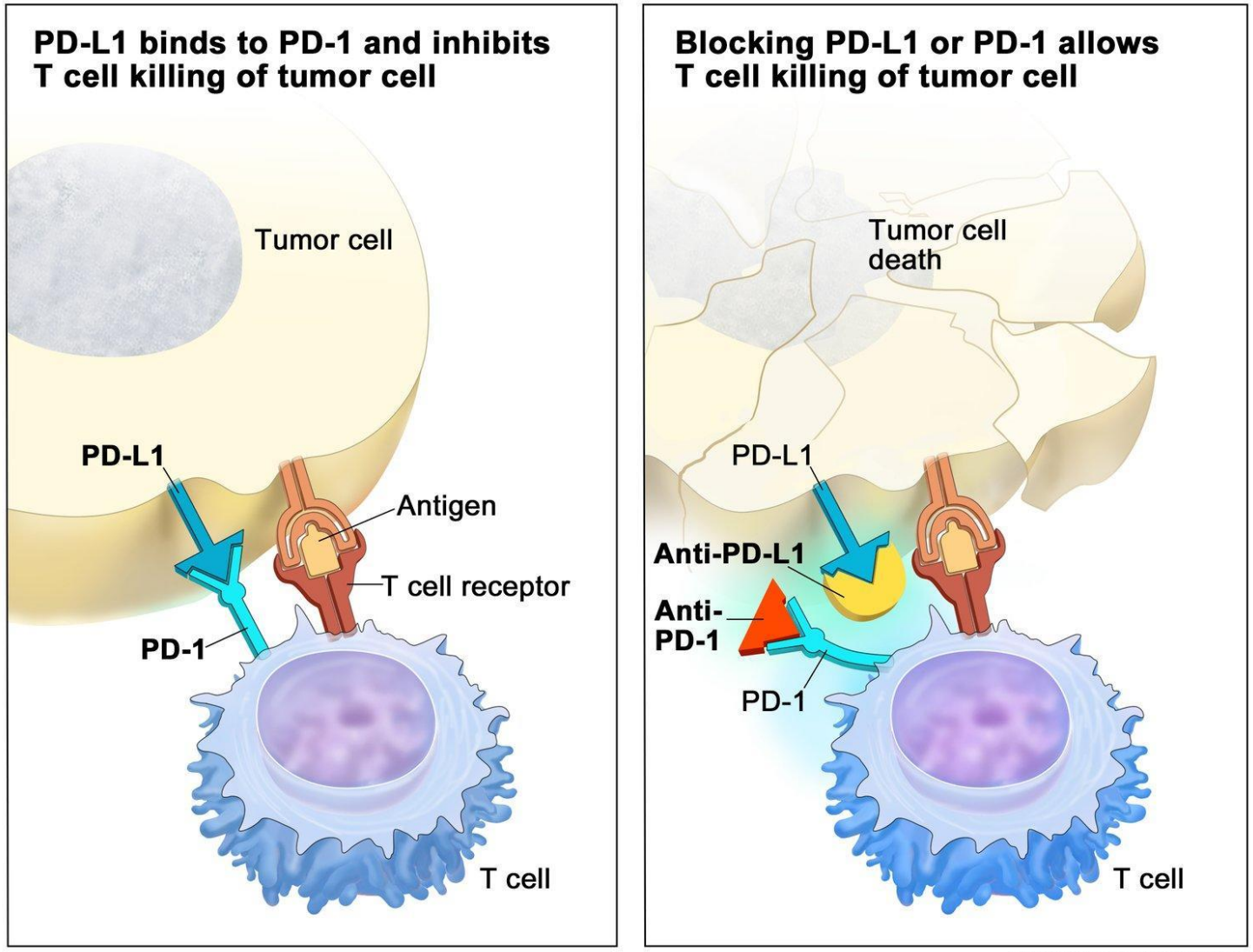


Figure 2. Kaplan–Meier Estimates of Overall Survival among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.

The hazard ratio for death in the radiotherapy-plus-cetuximab group as compared with the radiotherapy-only group was 0.74 (95 percent confidence interval, 0.57 to 0.97; P=0.03 by the log-rank test). The dotted lines indicate the median survival times.

Immune checkpoint inhibitors

pembrolizumab and nivolumab



https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/checkpoint-inhibitors

Ongoing research in the field

UNC SCHOOL OF MEDICINE

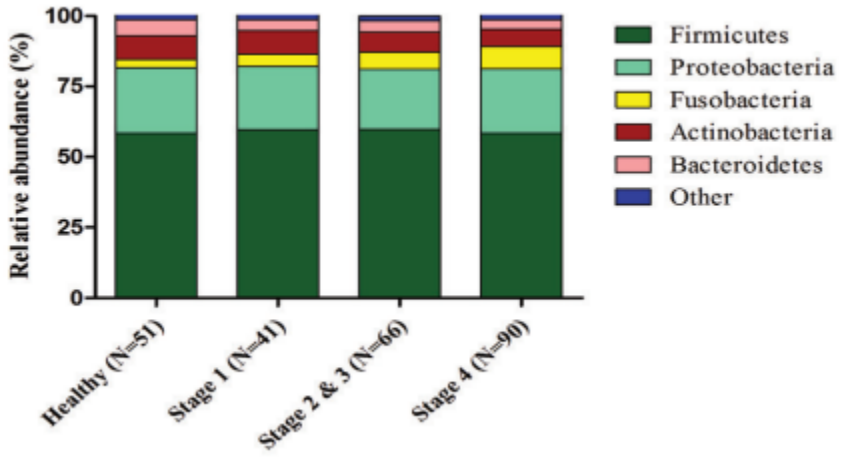
- Genomic instability
  - How do tumors tolerate such a high mutational burden?
- Tumor microenvironment and immunophenotypes
  - What immune cells are present?
  - What are cancer-associated fibroblasts doing?
- Oral microbiome's influence on HNSCC progression
  - Do certain bacteria and fungi can predispose patients to cancer development and worse outcomes?

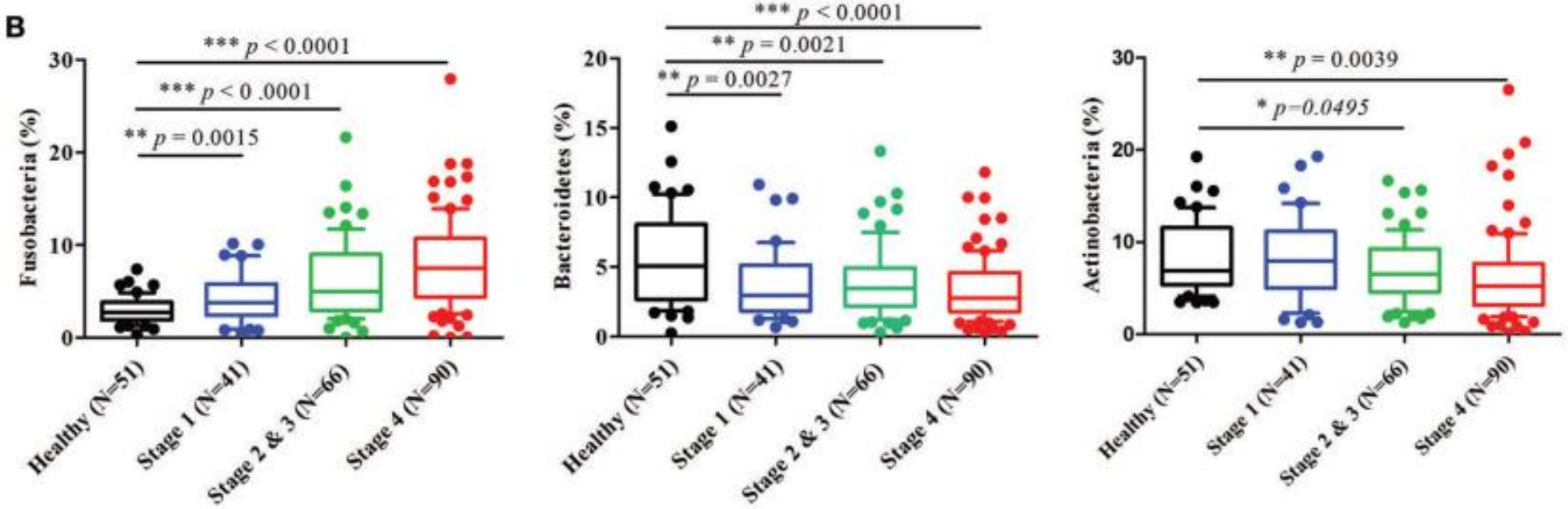
Microbiome and OSCC

UNC SCHOOL OF MEDICINE

Oral Microbiota Community Dynamics Associated With Oral Squamous Cell Carcinoma Staging

Chia-Yu Yang[1,2,3,4], Yuan-Ming Yeh[3,5], Hai-Ying Yu[6], Chia-Yin Chin[3], Chia-Wei Hsu[3], Hsuan Liu[2,3,4,7], Po-Jung Huang[2,3,5,8], Song-Nian Hu[6], Chun-Ta Liao[9], Kai-Ping Chang[3,9] and Yu-Liang Chang[10*]*





Conclusions

UNC SCHOOL OF MEDICINE

- HNSCC accounts for 95% of head and oral cancers
- The number of new cases is rising!
- It’s a public health issue that is largely preventable
- HPV infection and tobacco exposure are the main instigators and the two etiologies have different patient outcomes and genetic drivers
- Treatment strategies for HNSCC have not improved much so patient outcomes have also not improved

UNC SCHOOL OF MEDICINE

Questions?

My path to Path

UNC SCHOOL OF MEDICINE

- BS in Biology from Davidson College, entered as premed
- Applied for research funding to work on fruit fly genetics

- Research opportunities for undergrads and recent grads:
  - https://www.davidson.edu/academic-departments/biology/research/research-and-grant-opportunities

My path to Path

UNC SCHOOL OF MEDICINE

- Applied for Research Technician (lab assistant/tech) positions
- Jacks Lab at MIT for ~2 years
- Applied to 6 graduate schools, interviewed at 4
- Unexpectedly liked UNC-BBSP
- Interested in development and human disease

- Hybrid research/teaching postdoc position → STEM teaching faculty