Pathology of Head and Neck Cancer

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UNC Pathology and Laboratory Medicine
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Learning Objectives

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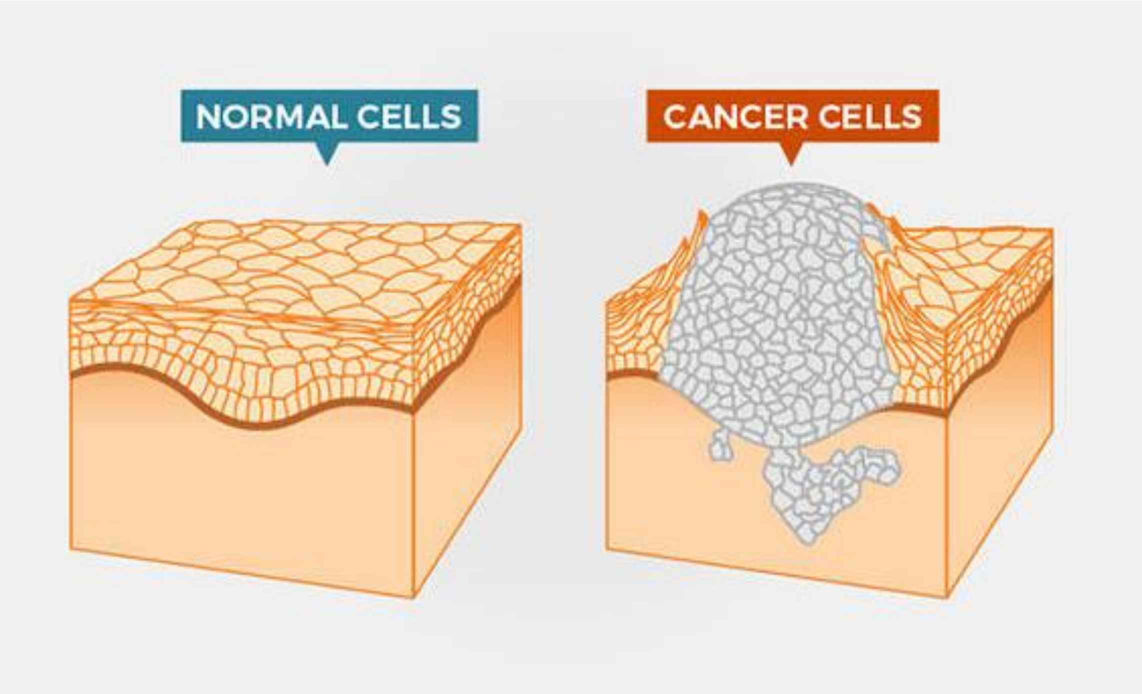
- Define cancer and some causes and risk factors for cancer
- Understand normal anatomy and histology of head and neck sites
- Describe the most common causes and risk factors for head and neck cancer (squamous cell carcinoma)
- Compare and contrast the characteristics of the two main types of squamous cell carcinoma
- Explain the method of immunohistochemistry
- Describe ways SCC is treated and could potentially be prevented

What is Cancer?

- Uncontrolled division of abnormal cells



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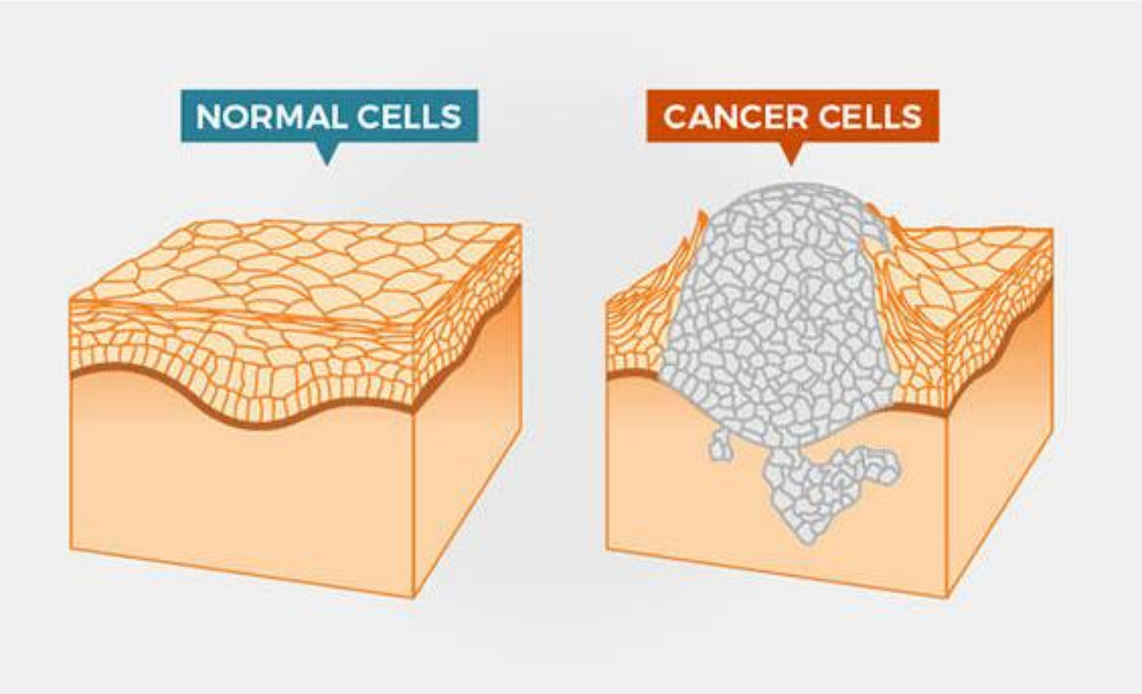

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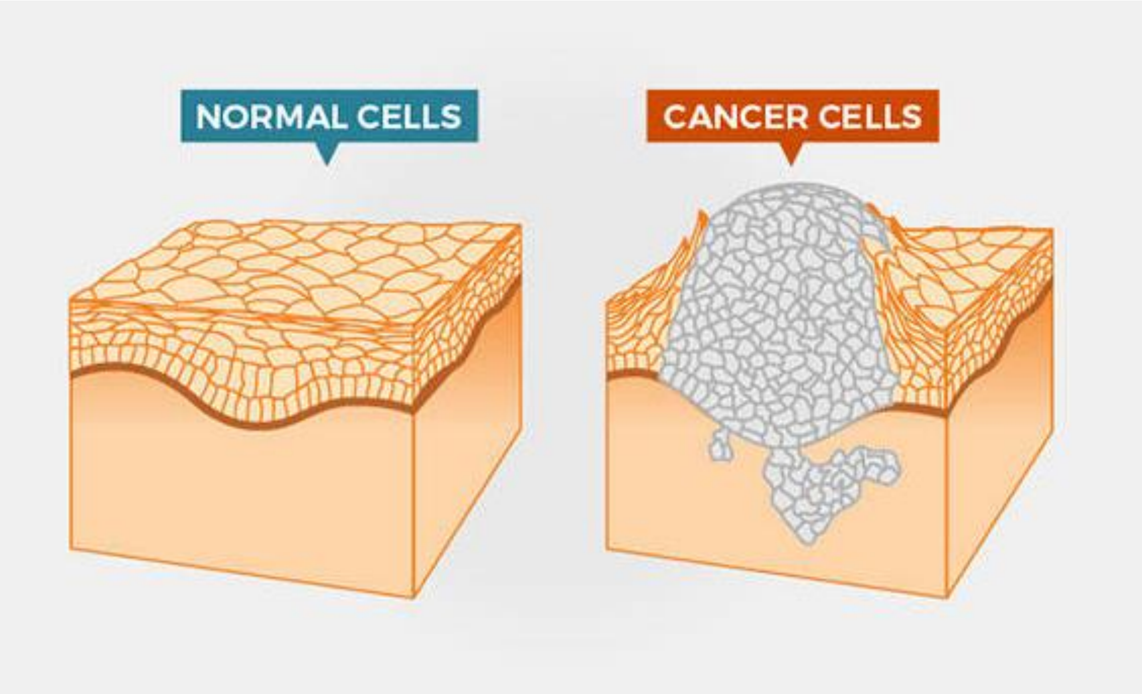

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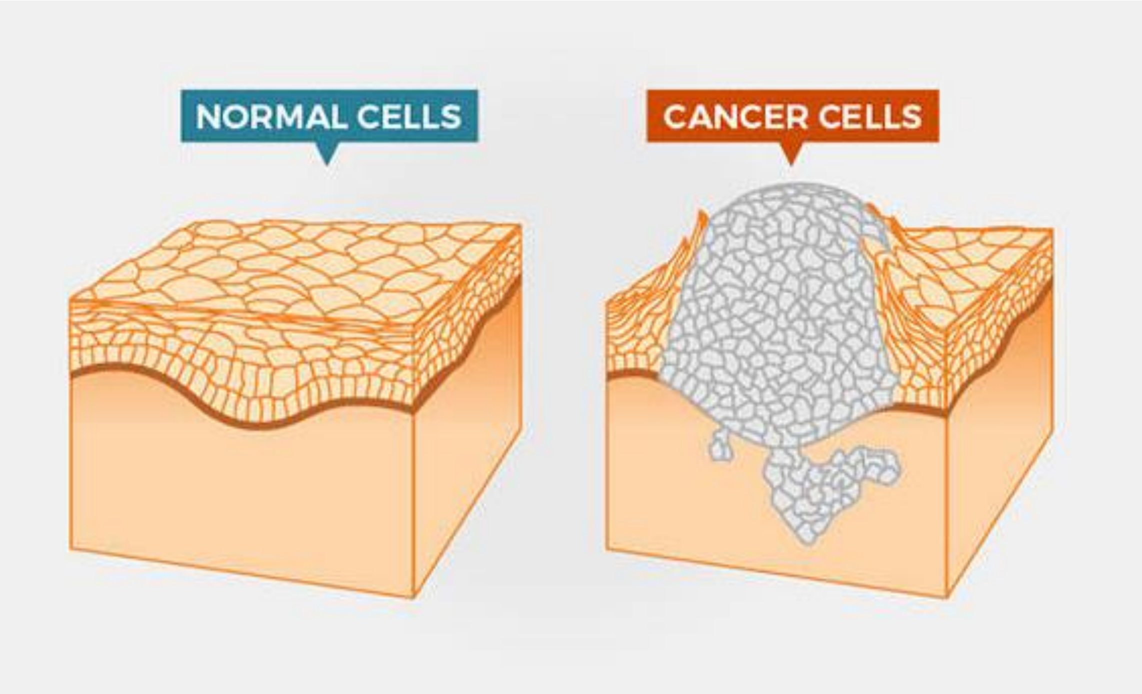
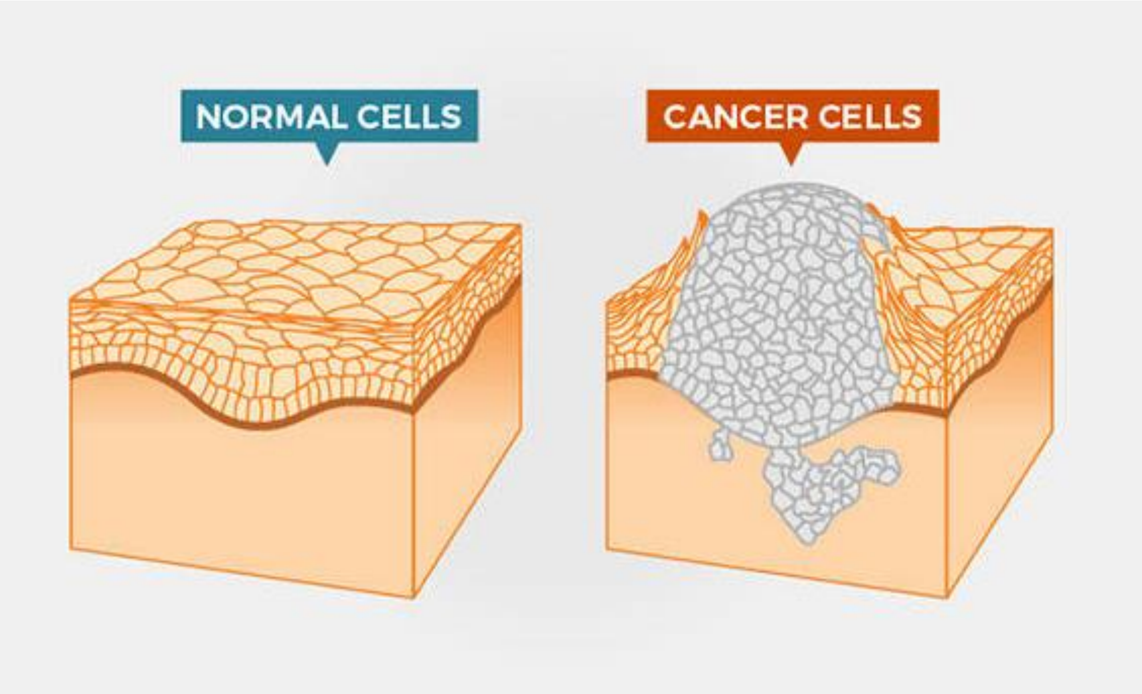


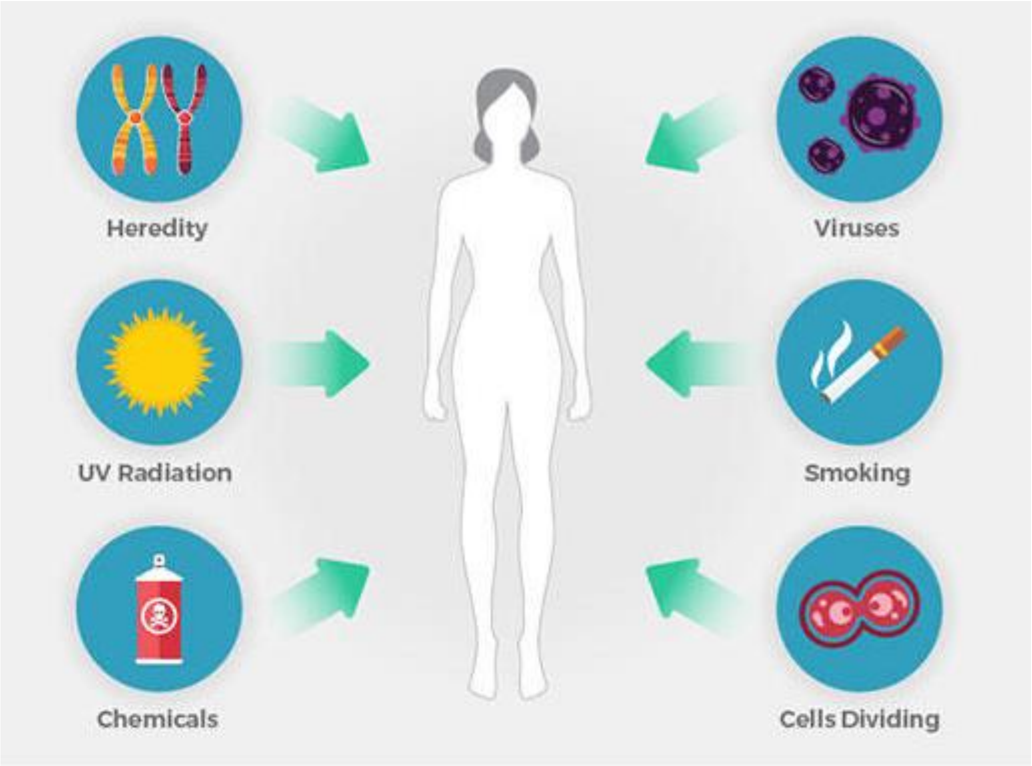
What is Cancer?

- Uncontrolled division of abnormal cells
- What makes these cells abnormal?
- Changes to DNA (usually)
- What causes these changes to our DNA?
- Lots of things!



What is Cancer?

- What causes these changes to our DNA?
  - Toxins (smoking, alcohol)
  - Radiation (sun, prior cancer treatment)
  - Viruses (STI and non-STI)
  - Genetics
  - Chronic inflammation
  - Obesity



Cancer is Common

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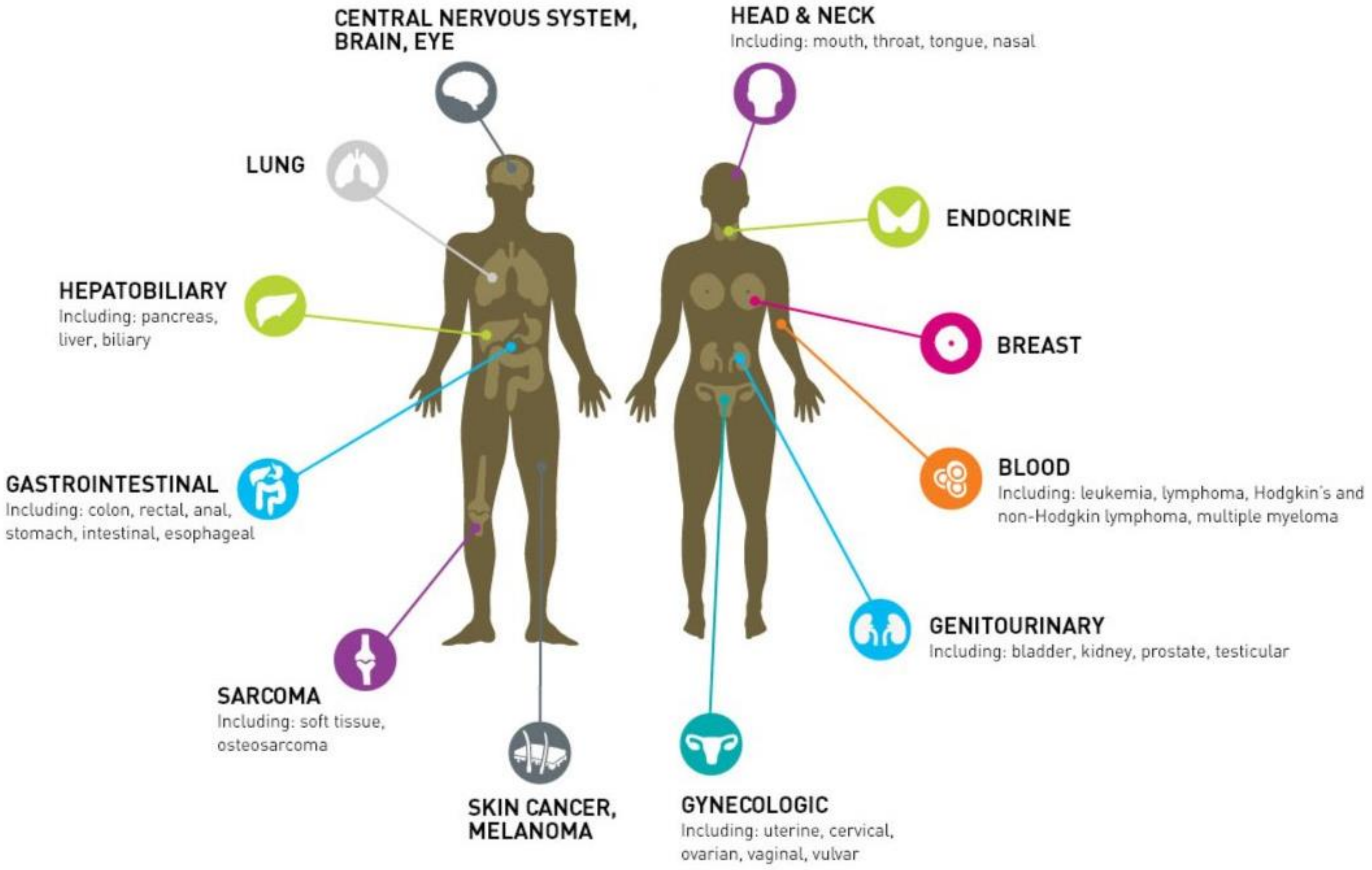
	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	All Ages
1	Congenital Anomalies 3,963	Unintentional Injury 1,299	Unintentional Injury 827	Unintentional Injury 915	Unintentional Injury 15,792	Unintentional Injury 34,452	Unintentional Injury 36,444	Covid-19 36,881	Malignant Neoplasms 108,023	Heart Disease 553,214	Heart Disease 695,547
2	Short Gestation 2,946	Congenital Anomalies 412	Malignant Neoplasms 347	Suicide 598	Homicide 6,635	Suicide 8,862	Covid-19 16,006	Heart Disease 34,535	Heart Disease 89,342	Malignant Neoplasms 446,354	Malignant Neoplasms 605,213
3	Sids 1,459	Homicide 309	Homicide 188	Malignant Neoplasms 449	Suicide 6,528	Homicide 7,571	Heart Disease 12,754	Malignant Neoplasms 33,567	Covid-19 73,725	Covid-19 282,457	Covid-19 416,893
4	Unintentional Injury 1,306	Malignant Neoplasms 282	Congenital Anomalies 171	Homicide 298	Covid-19 1,401	Covid-19 6,133	Malignant Neoplasms 11,194	Unintentional Injury 31,407	Unintentional Injury 33,471	Cerebrovascular 139,257	Unintentional Injury 224,935
5	Maternal Pregnancy Comp. 1,113	Heart Disease 116	Heart Disease 66	Congenital Anomalies 179	Malignant Neoplasms 1,323	Heart Disease 4,155	Suicide 7,862	Liver Disease 10,501	Diabetes Mellitus 18,603	Chronic Low. Respiratory Disease 120,152	Cerebrovascular 162,890

(2021 data) https://www.cdc.gov/injury/wisqars/LeadingCauses.html

Cancer is Complicated!



Cancers of the Head and Neck

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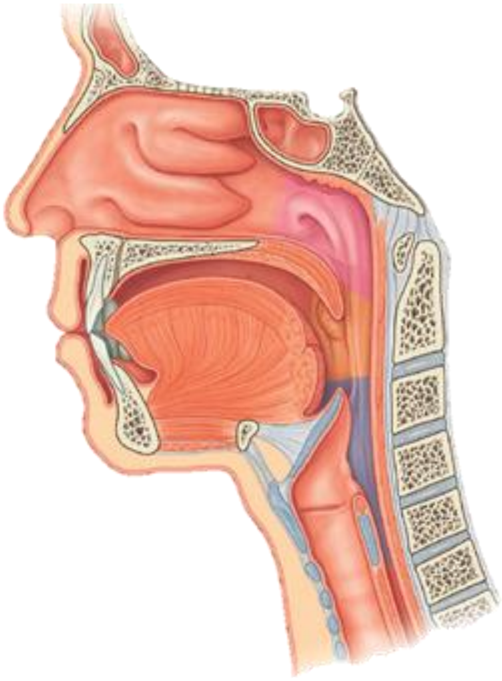
TWO BROAD CATEGORIES

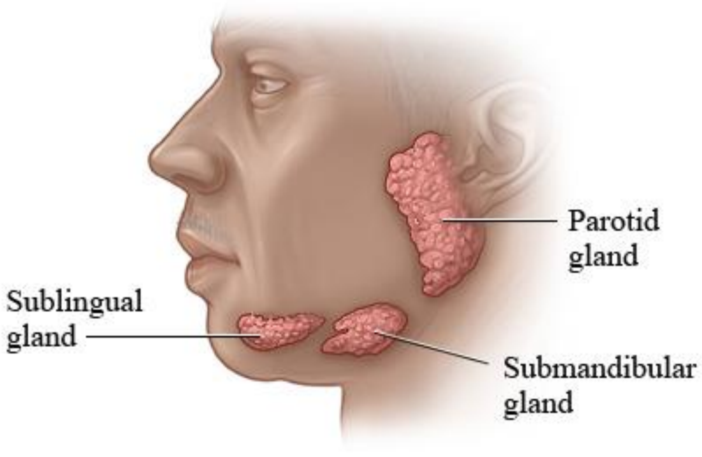
Mouth and throat lining epithelial cells ("squamous")



Gland epithelial cells that normally make hormones (thyroid) or saliva

Thyroid

Salivary



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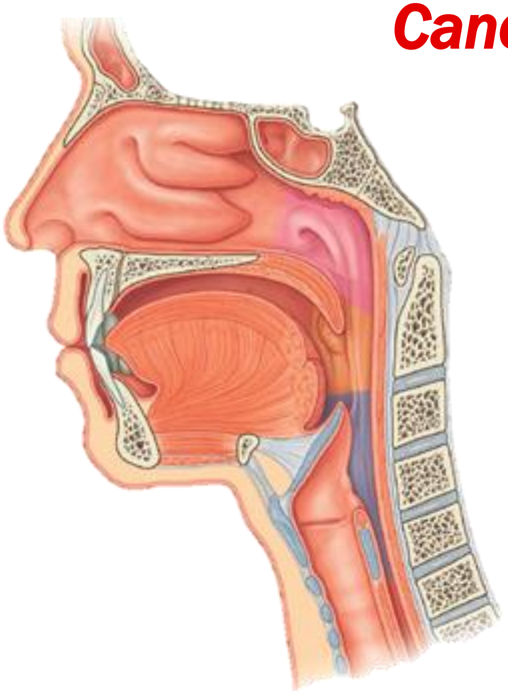
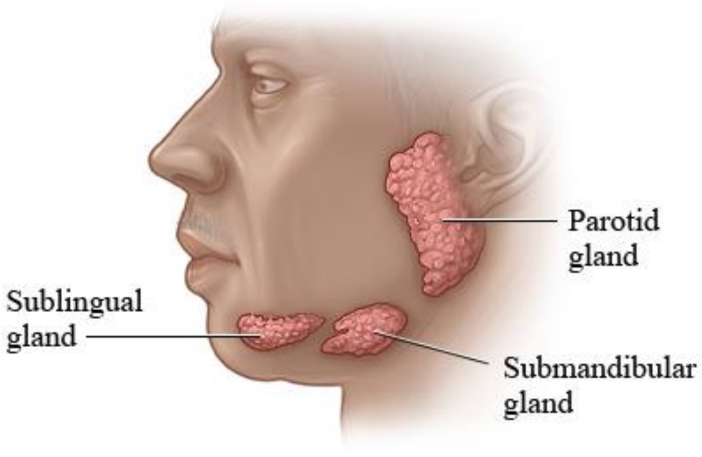


Cancer of epithelium = "carcinoma"

Gland epithelial cells that normally make hormones (thyroid) or saliva

Thyroid

Salivary



Head and Neck Cancer Incidence

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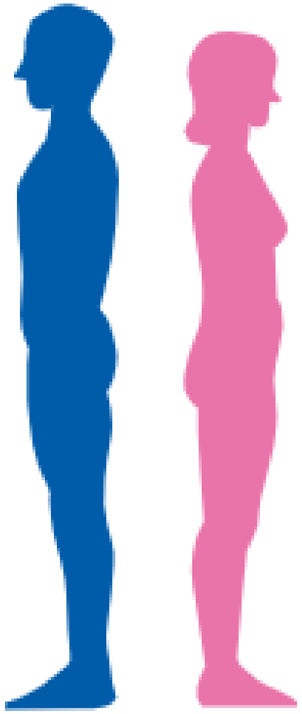
Estimated New Cases

	Males			Females			
	Prostate	248,530	26%	Breast		281,550	30%
	Lung & bronchus	119,100	12%	Lung & bronchus		116,660	13%
	Colon & rectum	79,520	8%	Colon & rectum		69,980	8%
	Urinary bladder	64,280	7%	Uterine corpus		66,570	7%
	Melanoma of the skin	62,260	6%	Melanoma of the skin		43,850	5%
	Kidney & renal pelvis	48,780	5%	Non-Hodgkin lymphoma		35,930	4%
	Non-Hodgkin lymphoma	45,630	5%	Thyroid	#7	32,130	3%
#8	Oral cavity & pharynx	38,800	4%	Pancreas		28,480	3%
	Leukemia	35,530	4%	Kidney & renal pelvis		27,300	3%
	Pancreas	31,950	3%	Leukemia		25,560	3%
	All Sites	**970,250**	**100%**	**All Sites**		**927,910**	**100%**



https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21654

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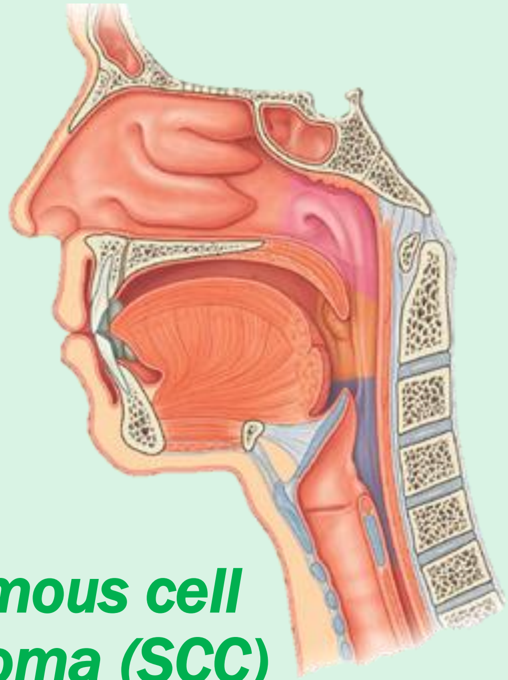

Squamous cell carcinoma (SCC)

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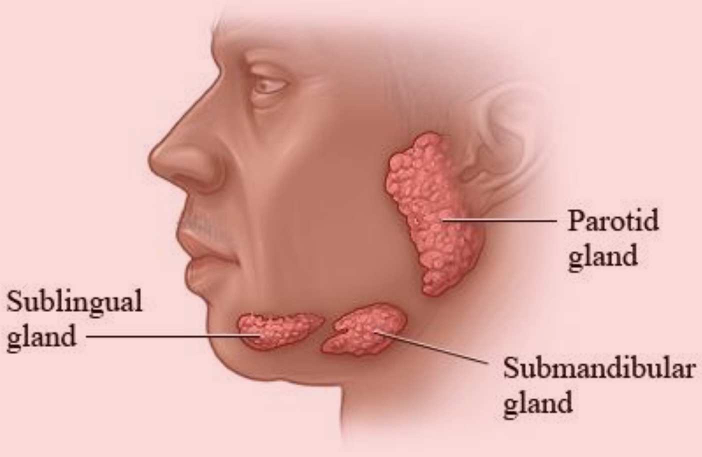
Thyroid

Salivary



We won't have time to get into these today…

Anatomy and Histology Review

Anatomy: Oral Cavity (Mouth, tongue)

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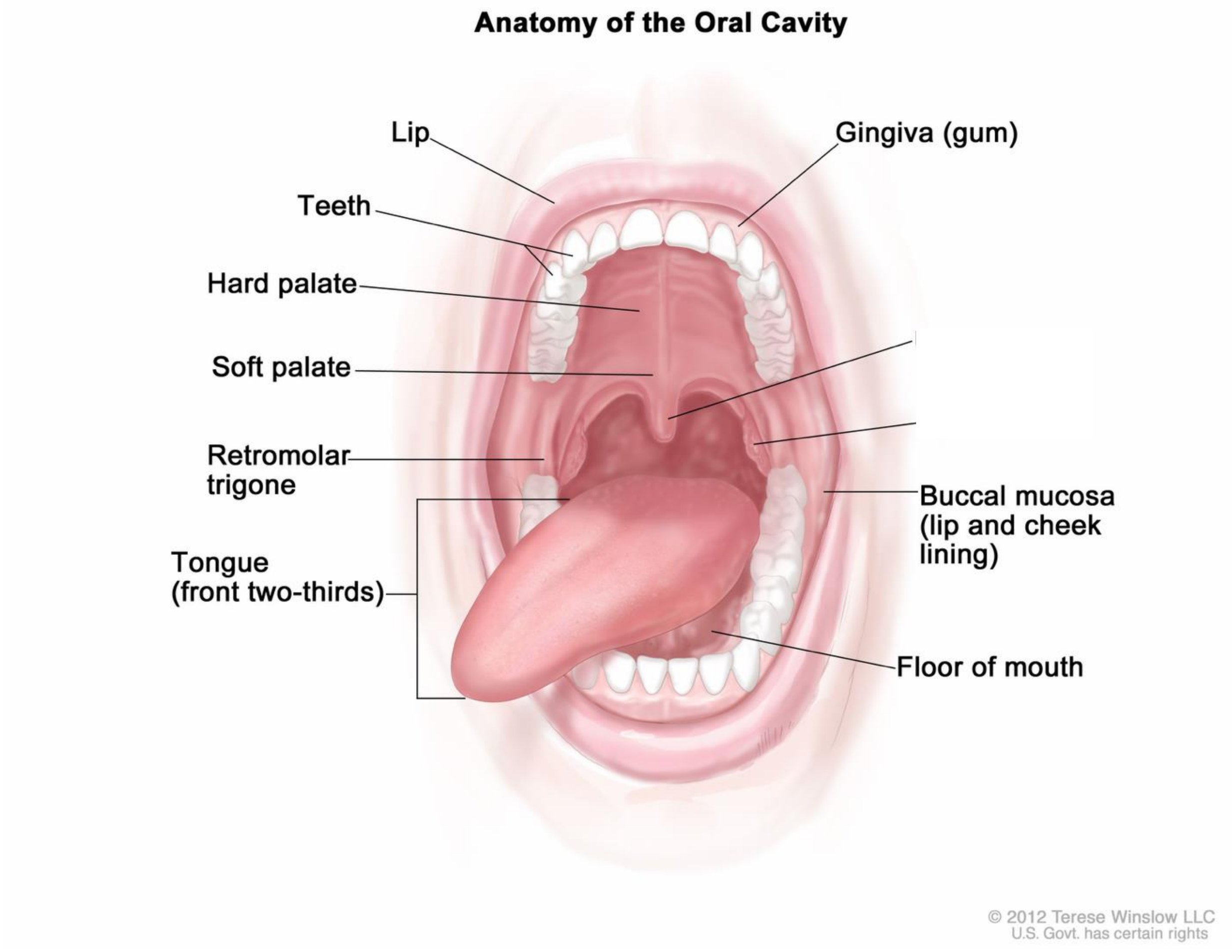
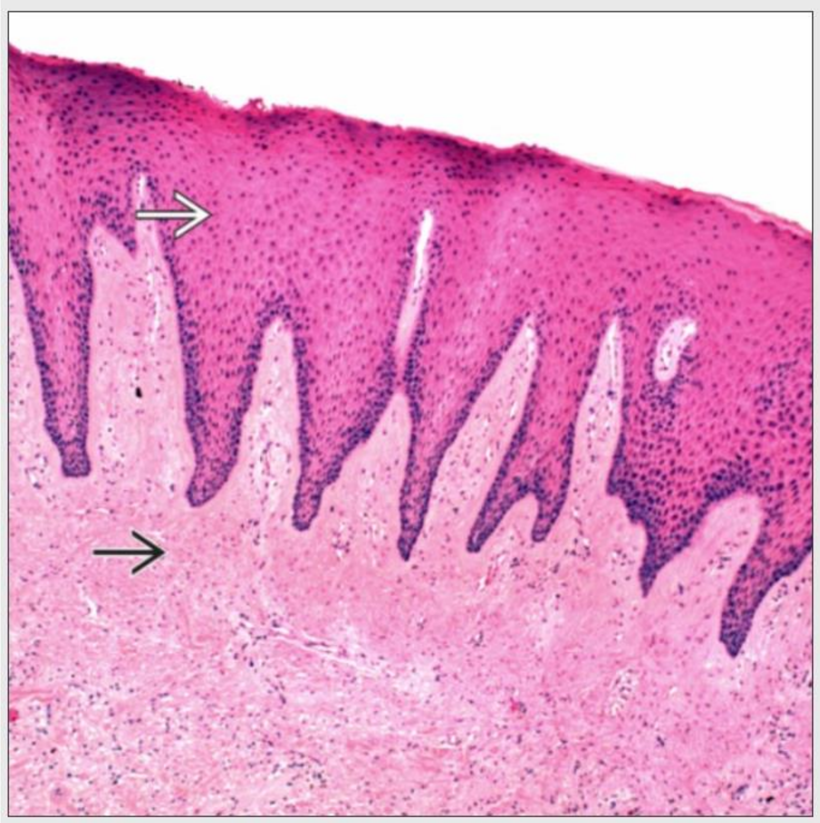
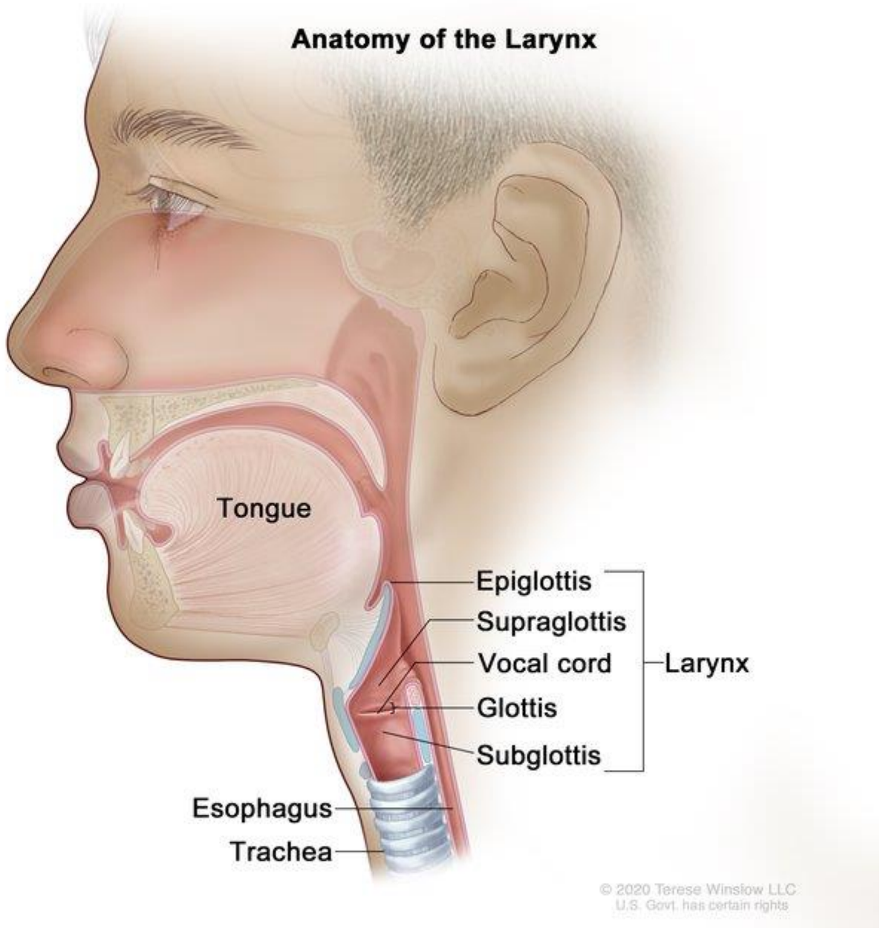


Squamous lining epithelium that is pink/orange by H&E



Anatomy: Larynx (Voice box)



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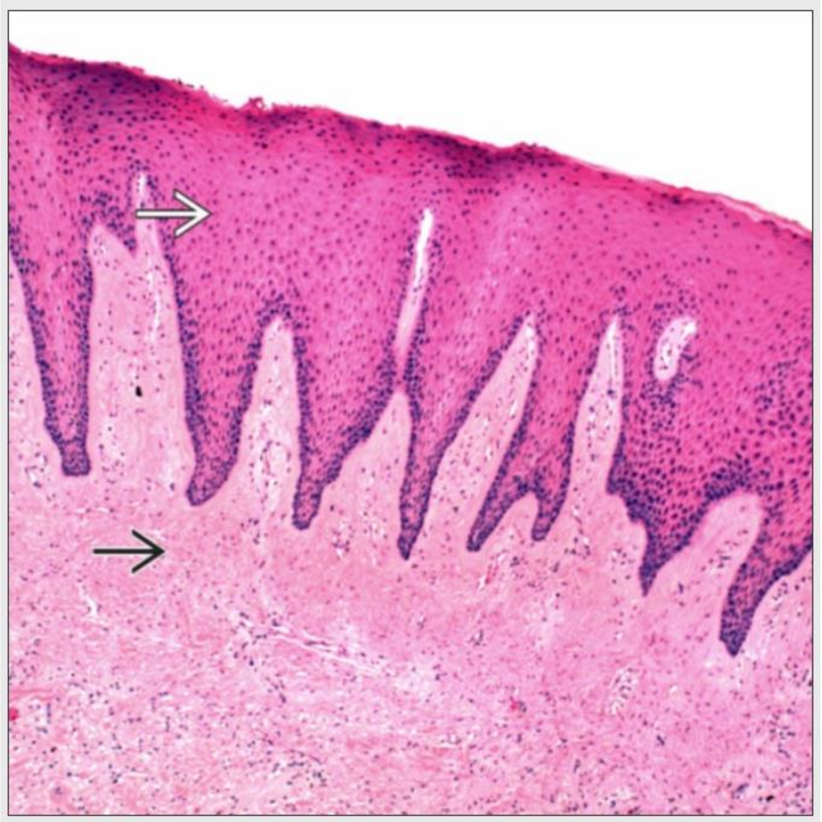
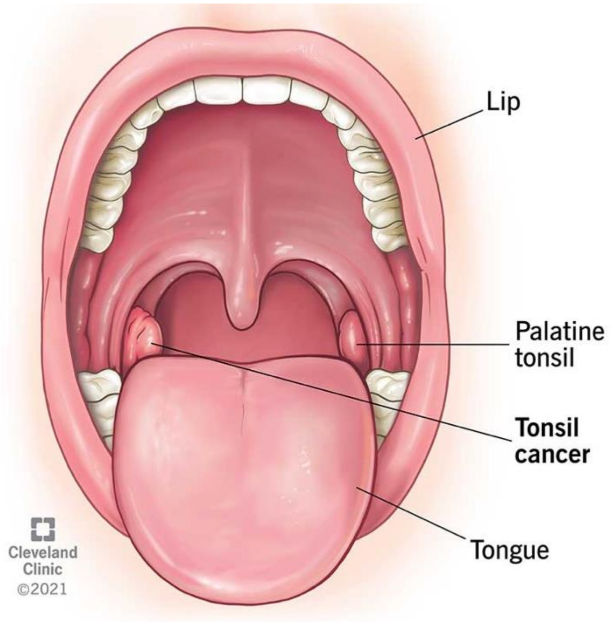
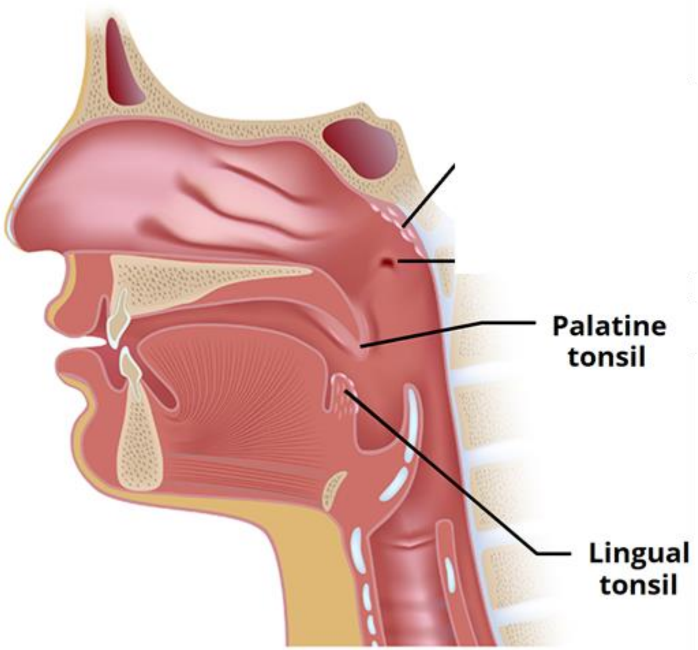
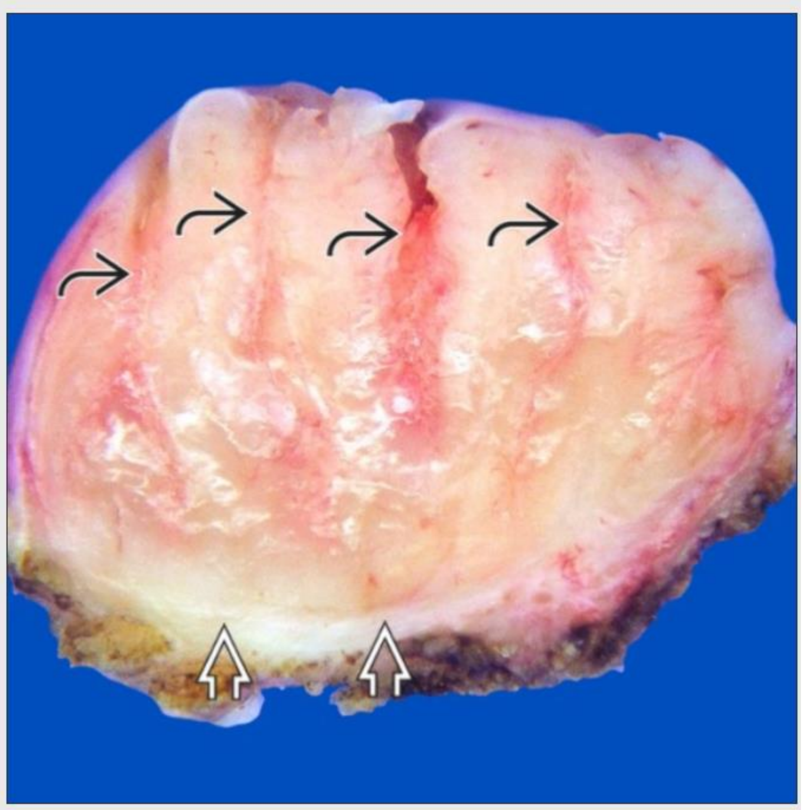


Anatomy: Oropharynx (Tonsils)



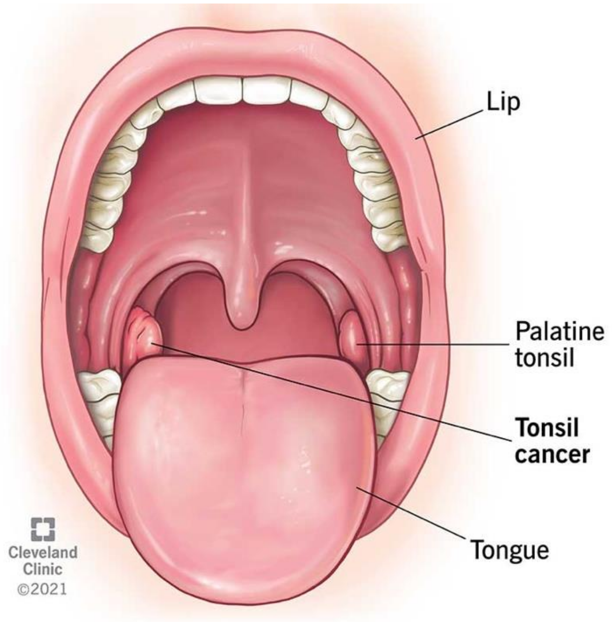


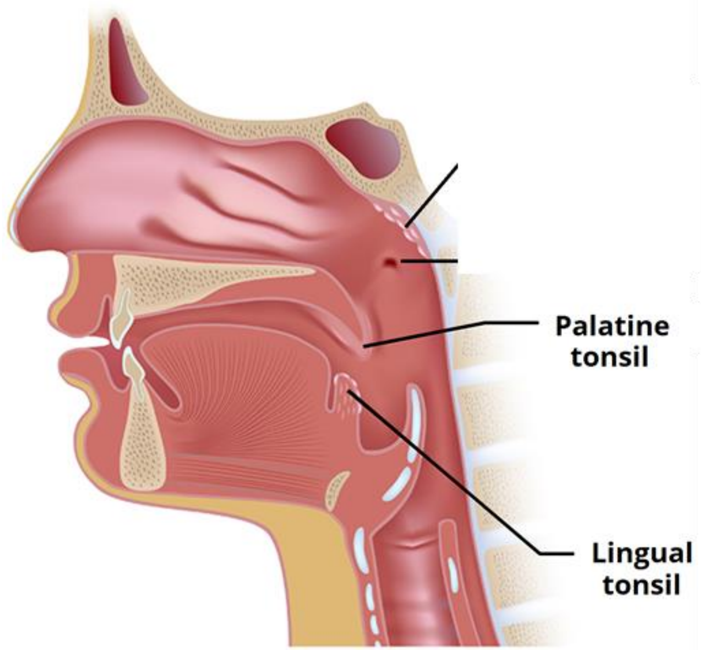
Tonsillar "crypts"



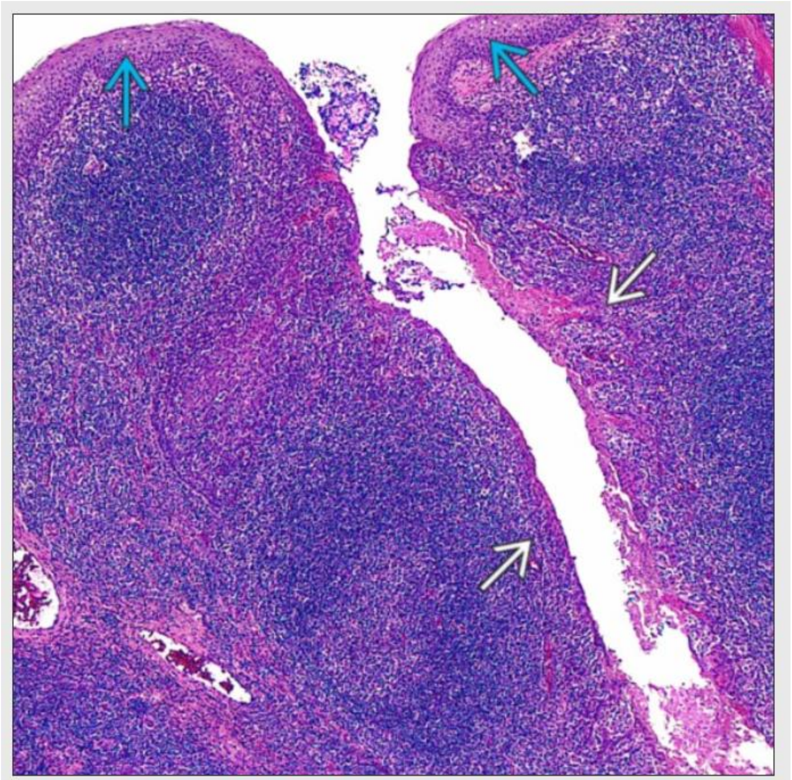
Tonsil Cross Section

Anatomy: Oropharynx (Tonsils)





Squamous crypt epithelium that is dark blue/purple by H&E + lots of lymphocytes



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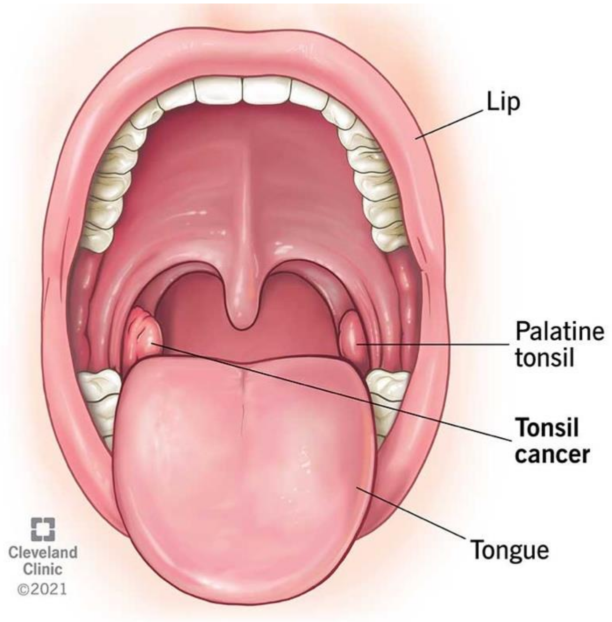

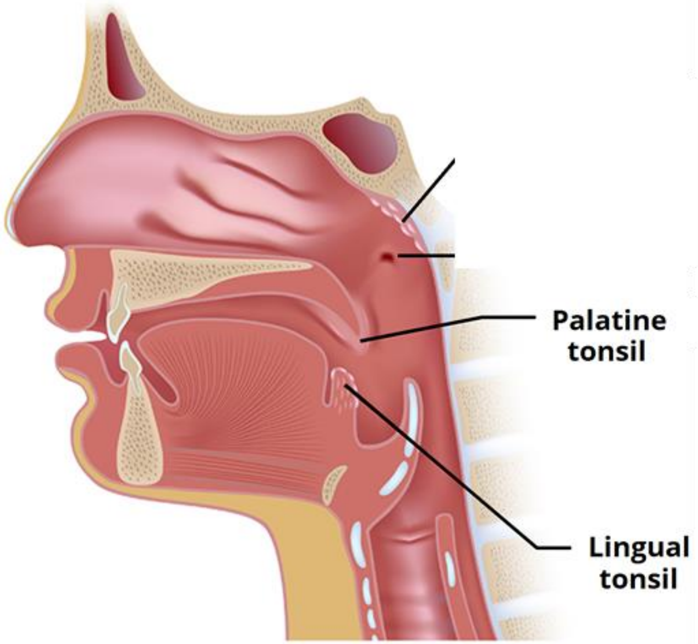

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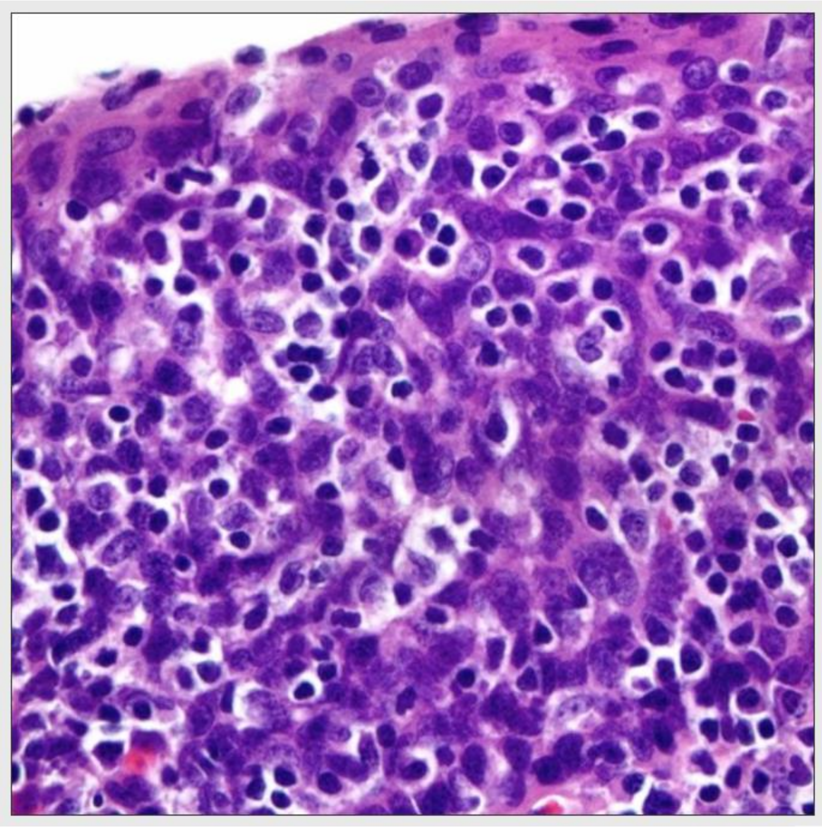
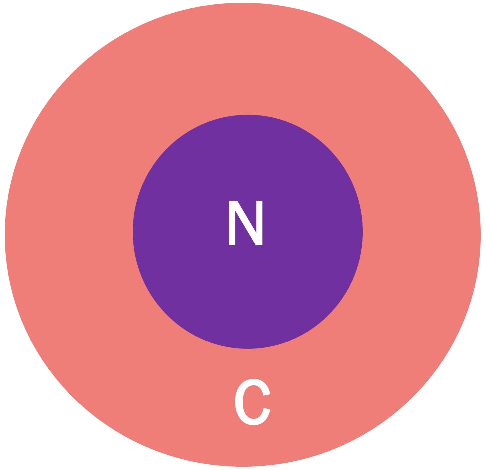


Microanatomy: Oral cavity and larynx



Example cell

N = nucleus = DNA = strong hematoxylin staining

C = cytoplasm = proteins = strong eosin staining

Normal oral cavity and larynx

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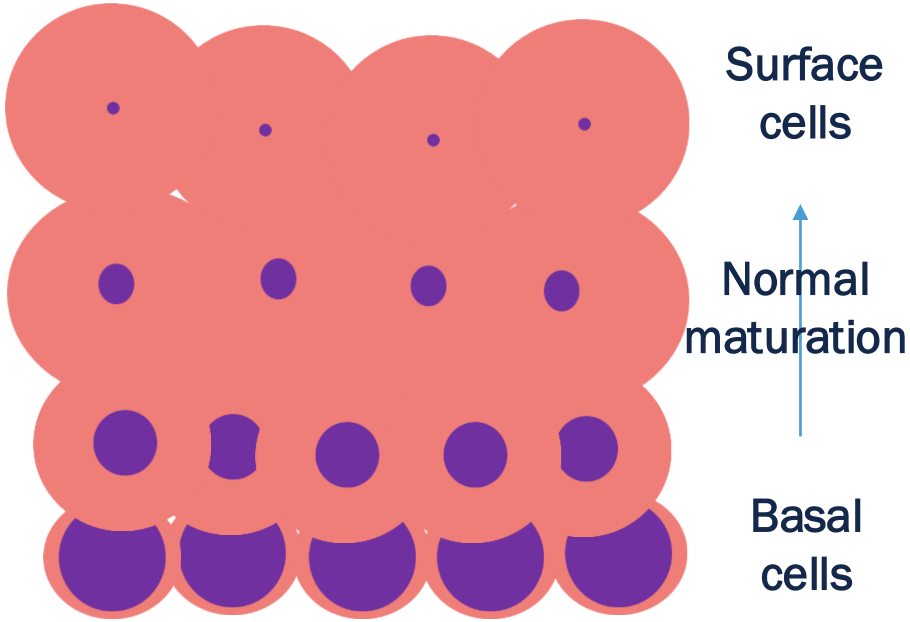

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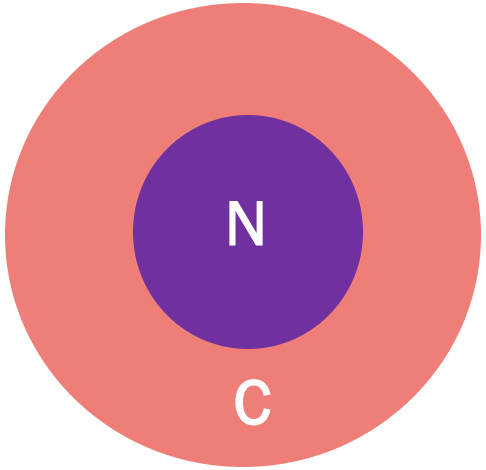

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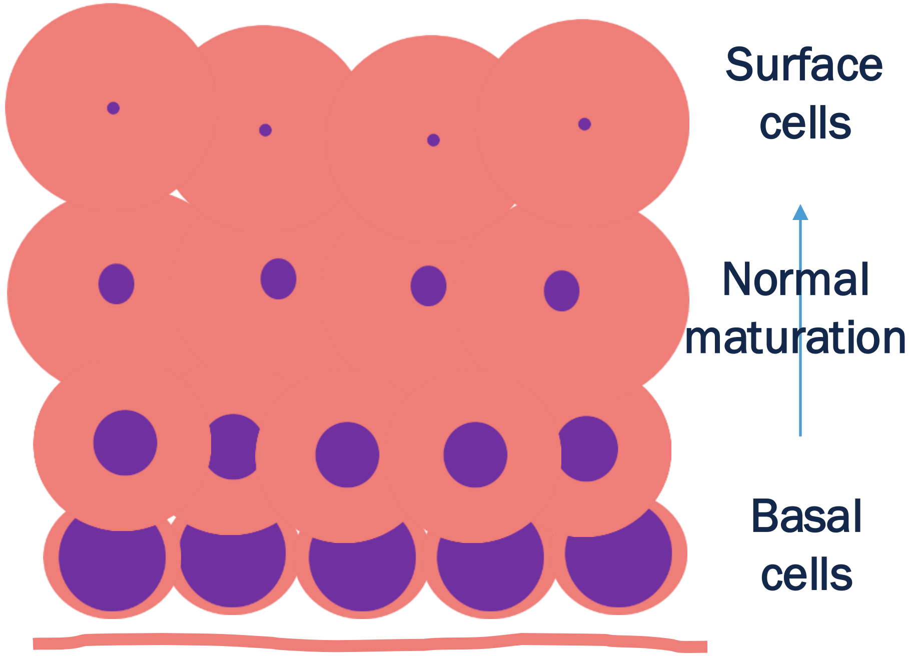
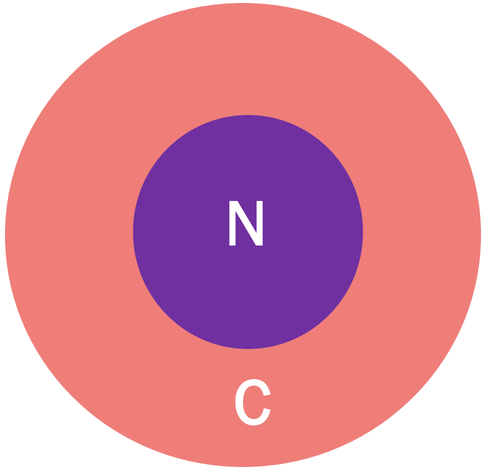


Microanatomy: Oropharynx (tonsils)



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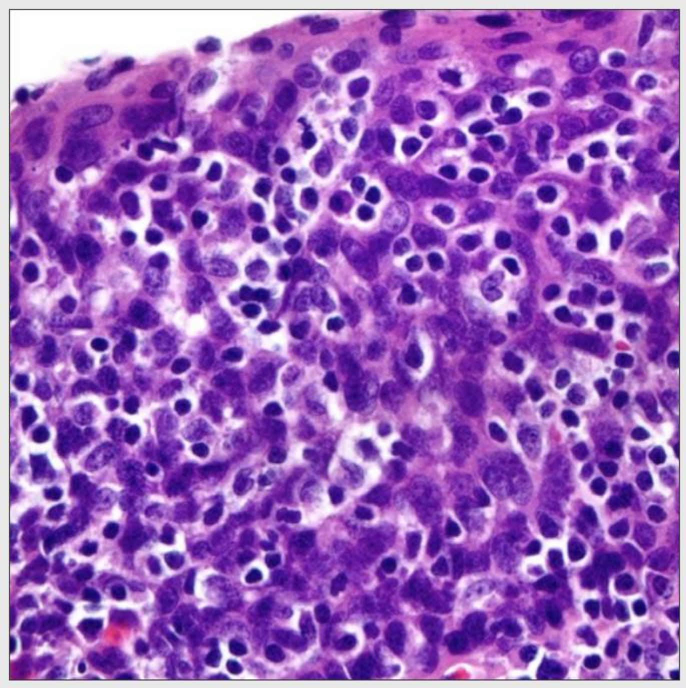

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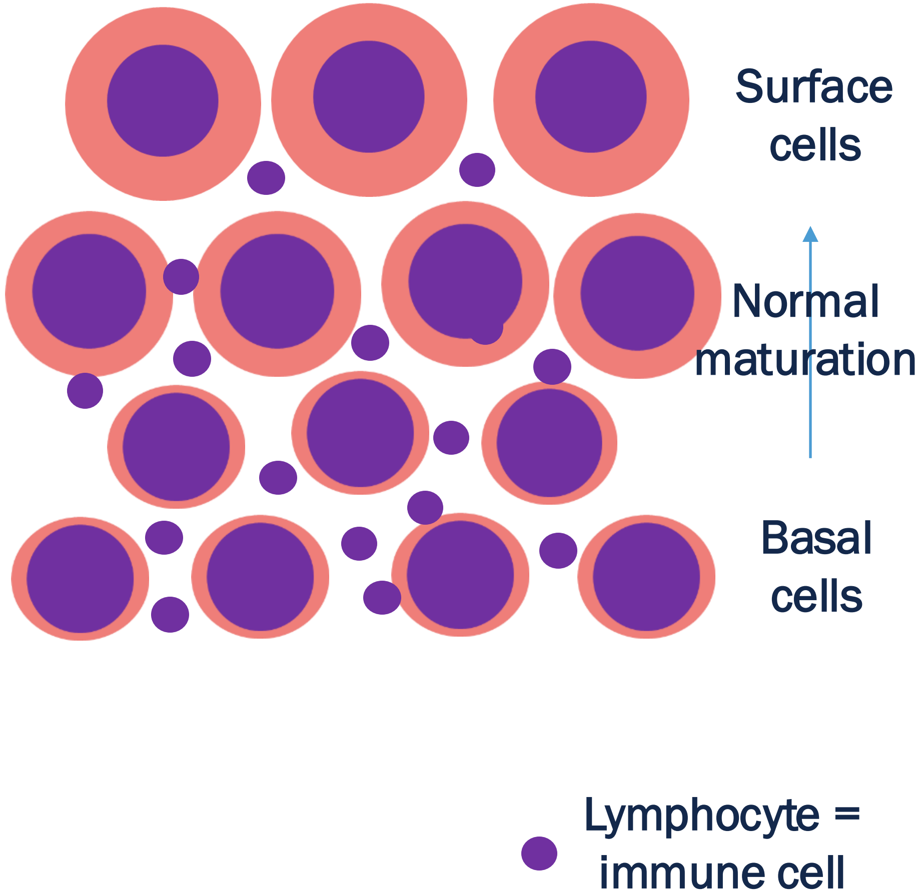

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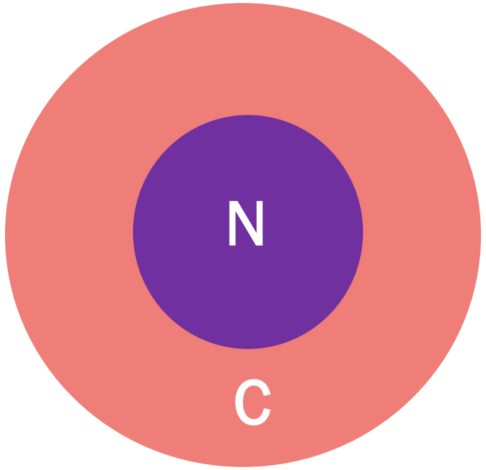

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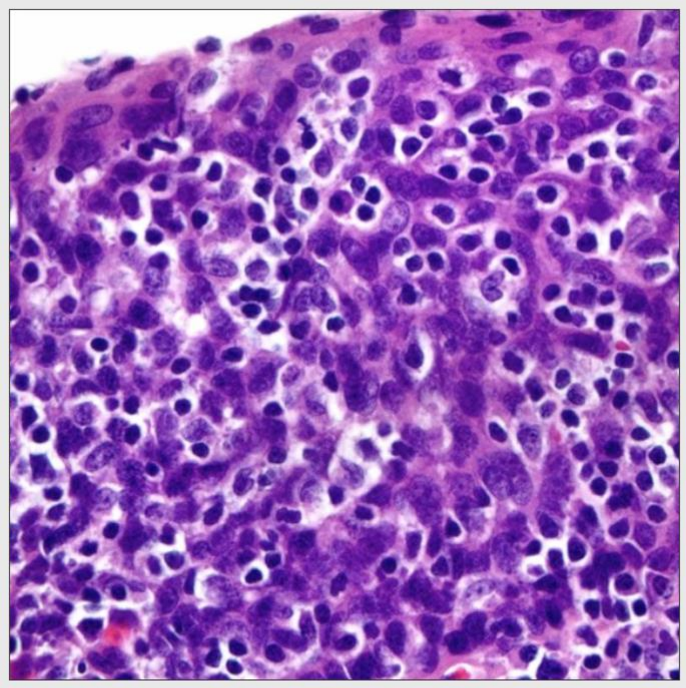

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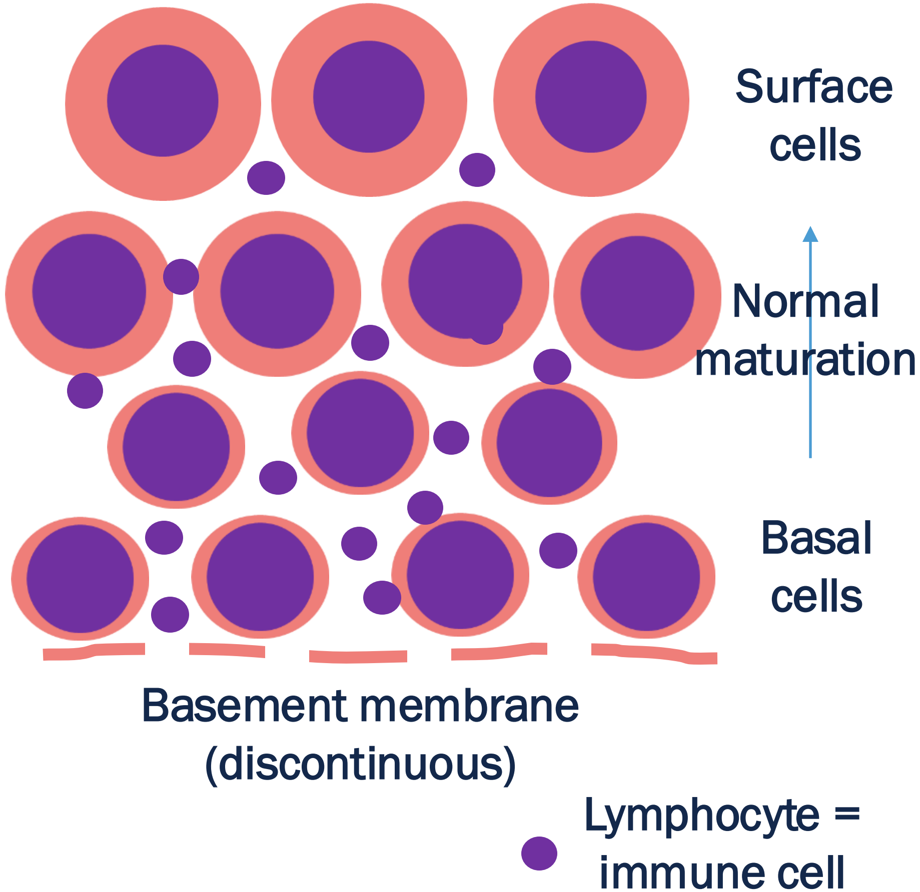
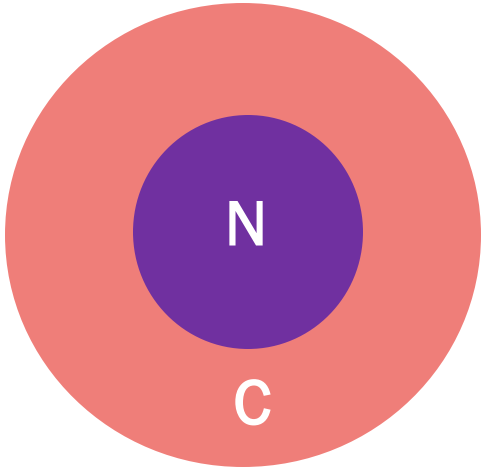


Microanatomy Comparison



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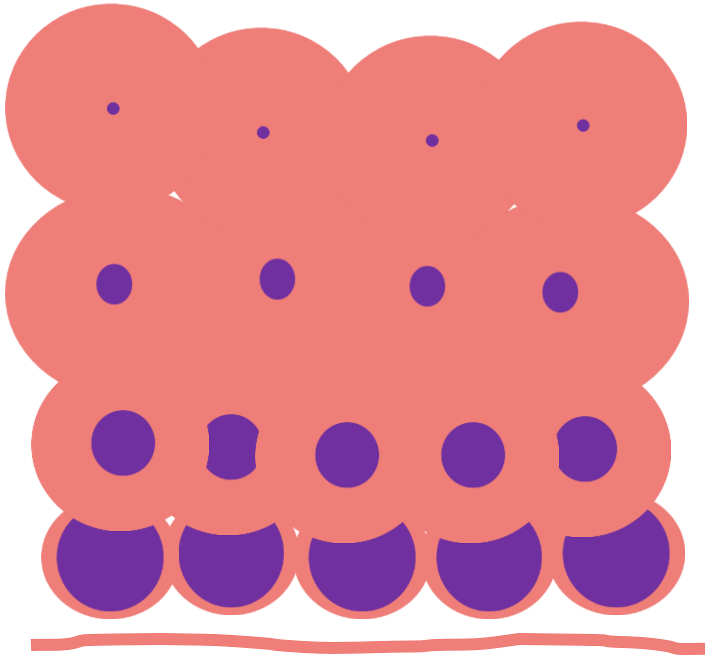
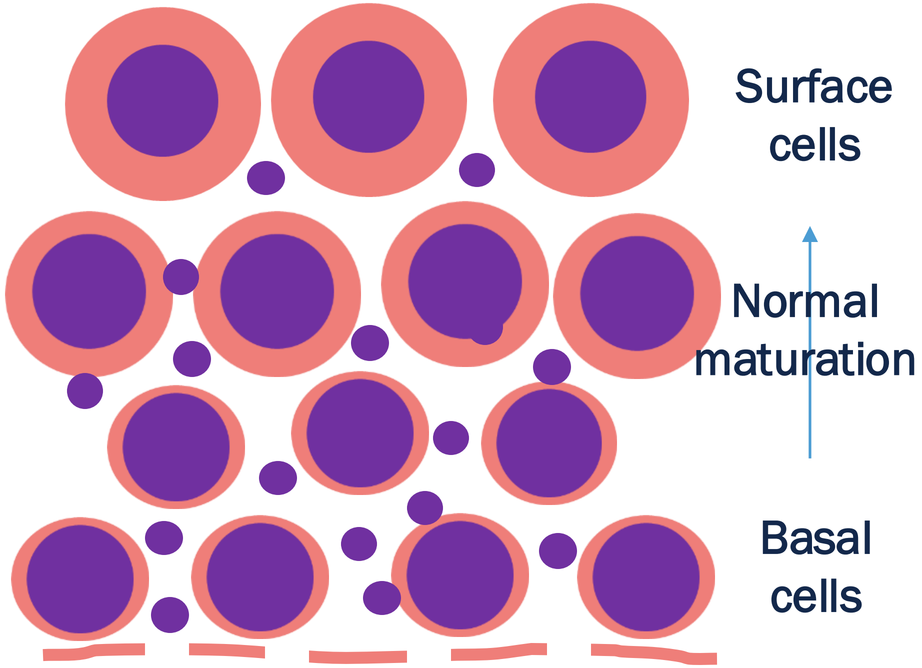


Basement membrane (continuous)

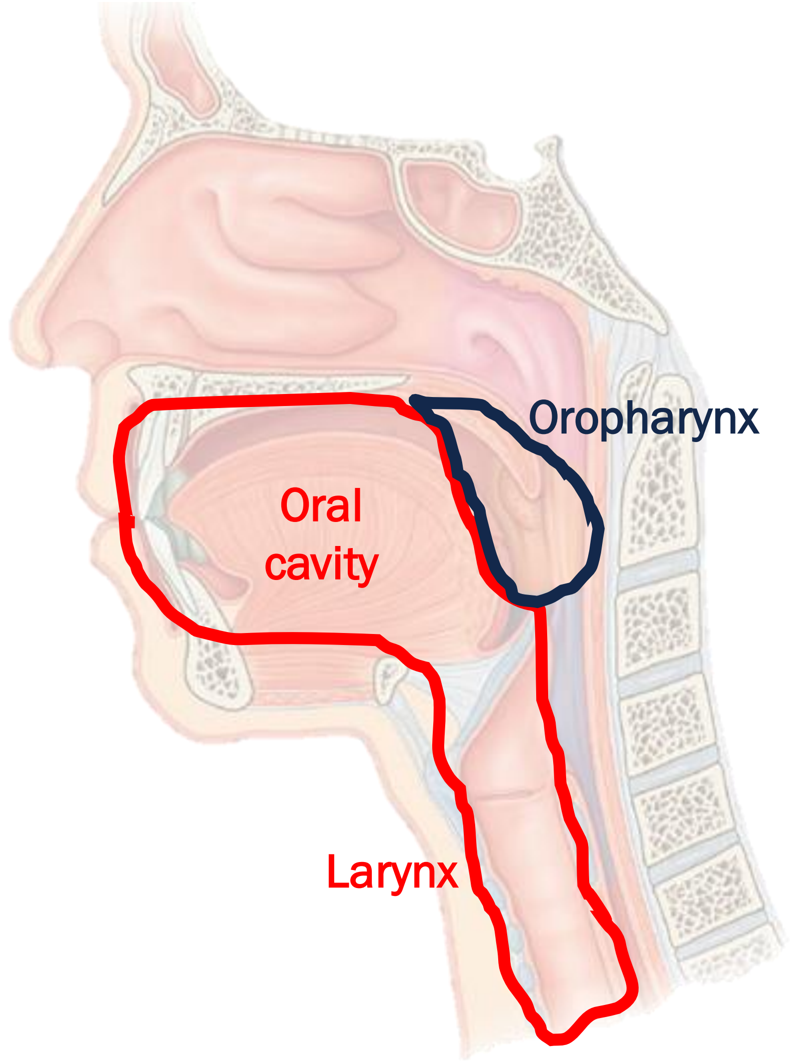
Normal tonsil



Basement membrane (discontinuous)

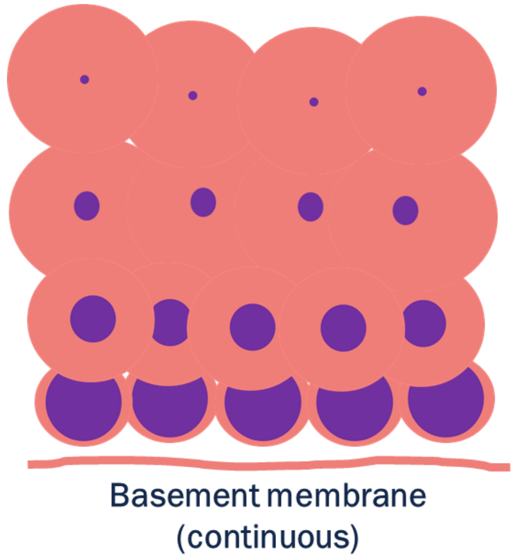
Lymphocyte = immune cell

Anatomy Recap: Form ≈ Function



<u>Most important function</u>

<u>Oral cavity and larynx</u>
Mechanical barrier for protection



Anatomy Recap: Form ≈ Function

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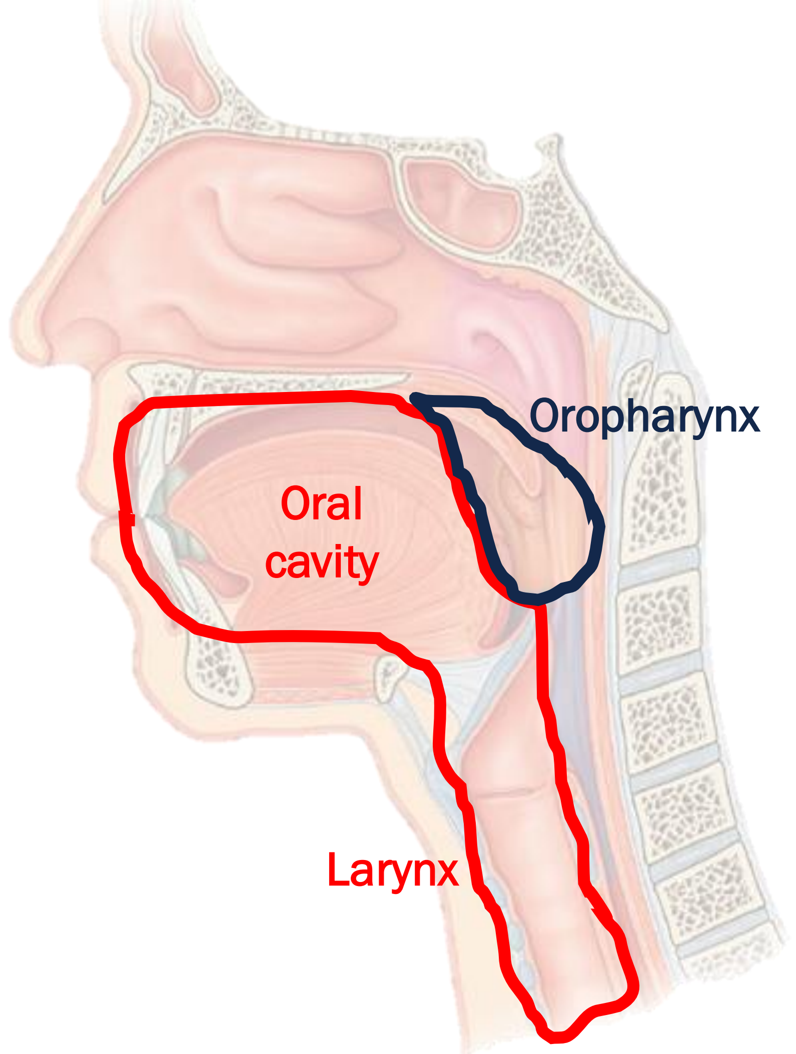

Most important function

Oral cavity and larynx
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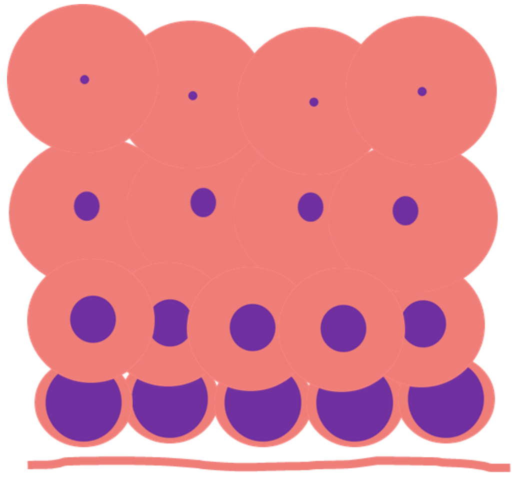
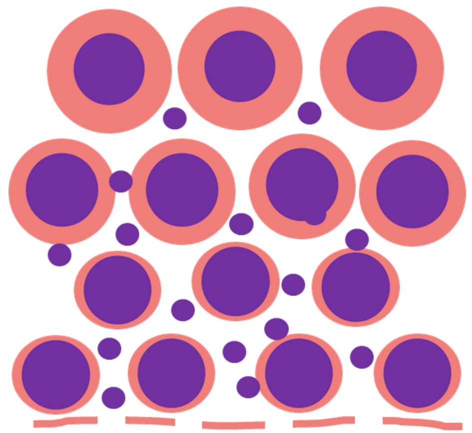
Oropharynx (tonsils)
Immune system's first line of defense against ingested or inhaled foreign pathogens





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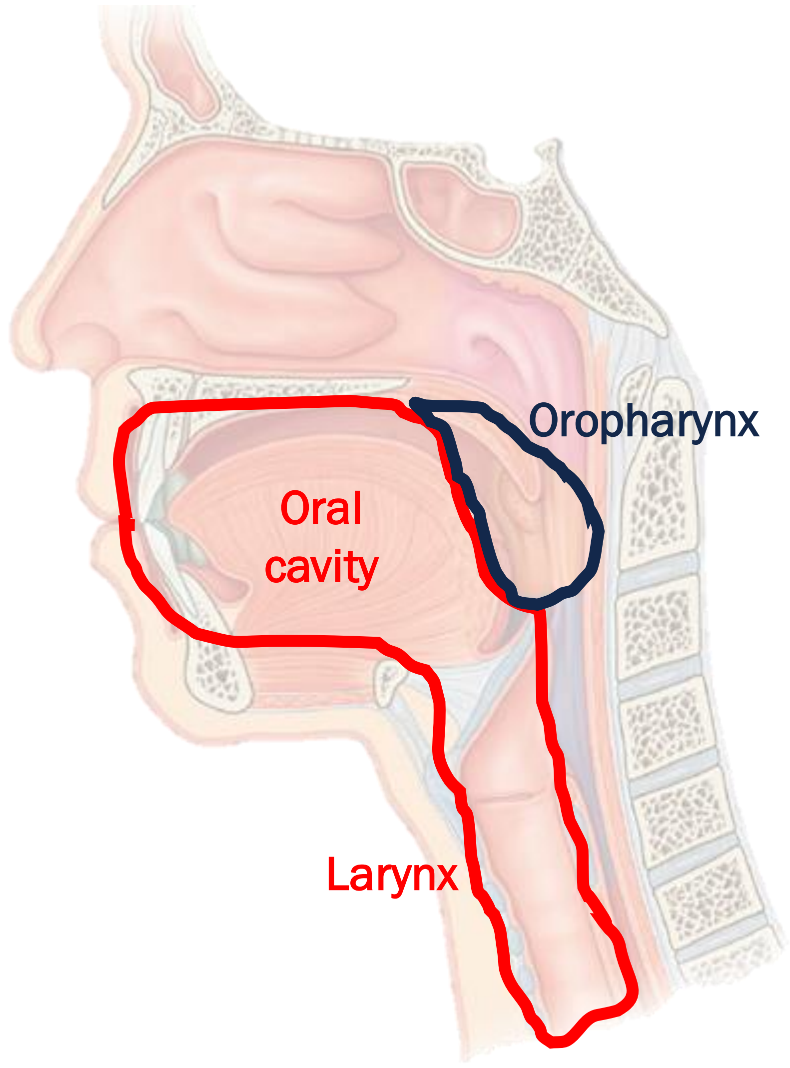


Most important function

Oral cavity and larynx
Mechanical barrier for protection

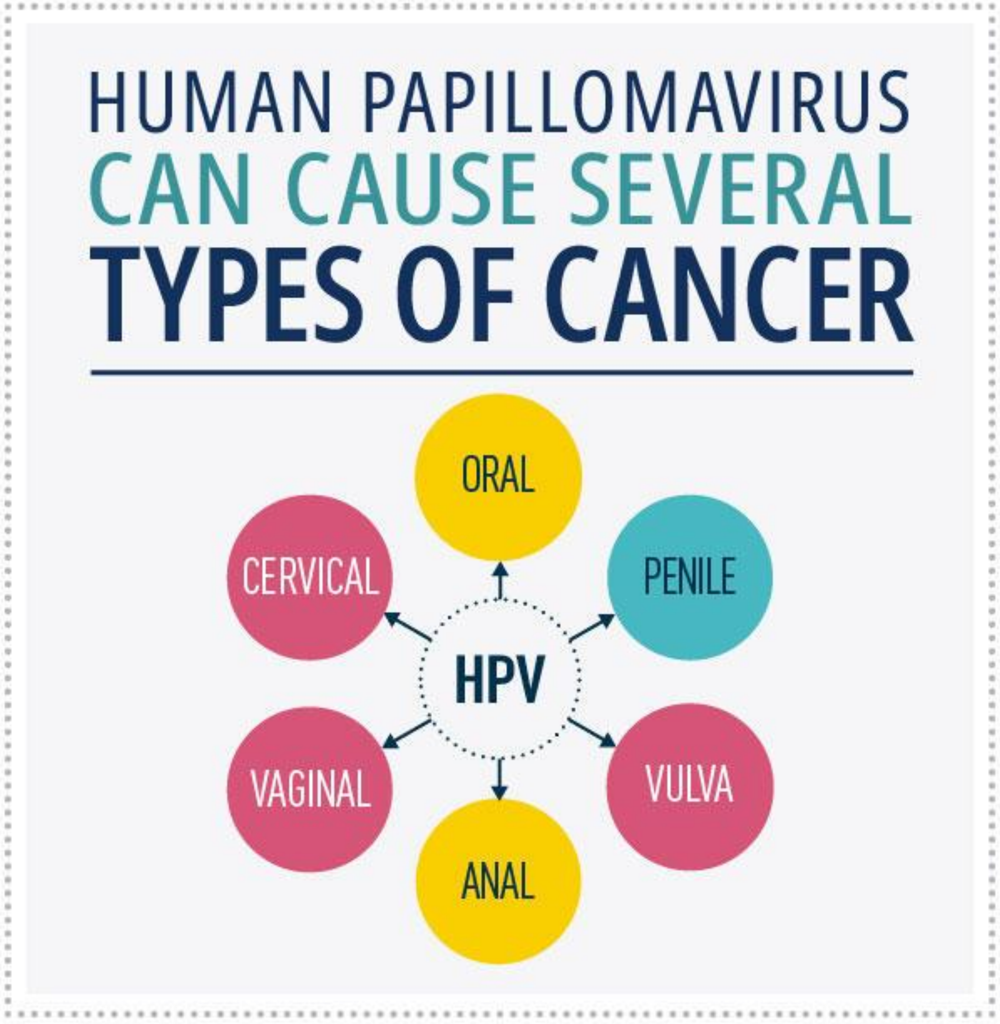
Oropharynx (tonsils)
Immune system's first line of defense against ingested or inhaled foreign pathogens

Most common cause of squamous cell carcinoma (SCC) in these sites

Tobacco >> alcohol

Human Papillomavirus (HPV)

HPV-associated Cancers



cancer.gov/hpv

Other Infectious Agents Associated with Cancer

Infectious Agent	Cancers
Viruses	
Epstein-Barr Virus (EBV)	Lymphomas, Nasopharyngeal carcinoma
Hepatitis B and C Viruses (HPV, HCV)	Liver (hepatocellular) carcinoma
Human T-Cell Leukemia/Lymphoma Virus Type 1 (HTLV-1)	Adult T-cell leukemia/lymphoma (rare blood cancer)
Human Herpesvirus 8 (HHV8)	Kaposi sarcoma, lymphomas
Merkel Cell Polyomavirus (MCPyV)	Merkel cell carcinoma (rare skin cancer)
Human Immunodeficiency Virus (HIV)	Not a direct cause, but weakens immune system
Bacteria	
Helicobacter pylori (H. pylori)	Stomach carcinoma and lymphoma
Parasites	
Opisthorchis viverrini	Cholangiocarcinoma (cancer of bile ducts)
Schistosoma hematobium	Bladder cancer

Two Types of Head and Neck Squamous Cell Carcinoma (SCC)

SCC: Smoking-related vs. HPV-related

Characteristics	Smoking-related aka HPV-negative	HPV-related aka HPV-positive
Site	Oral cavity, larynx, ~95%	Oropharynx (tonsils), 70-80%
Age	>60	40-50
Presentation/symptoms	Varies (usually large primary)	Large neck mass, small primary tumor
Risk factors	Smoking +/- drinking	Number of oral sex partners +/- smoking
Trends in occurrence	Decreasing	Increasing

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- Different cancers have different risk factors. **<u>Remember, cancer is complicated!</u>**

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- A risk factor is anything that increases a person’s chance of getting a disease such as cancer.
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- Some risk factors, like smoking, can be changed. Others, like a person’s age or family history, can’t be changed.

Risk Factors

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- A risk factor is anything that increases a person’s chance of getting a disease such as cancer.
- Different cancers have different risk factors. Remember, cancer is complicated!
- Some risk factors, like smoking, can be changed. Others, like a person’s age or family history, can’t be changed.
- But risk factors don't tell us everything. Having a risk factor, or even many, does not mean that a person will get the disease. And many people who get the disease have few or no known risk factors.

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Biology of Head and Neck Squamous Cell Carcinoma (HNSCC)

HPV-negative SCC: Sequence of Events

Normal mucosa

HPV-negative SCC: Sequence of Events

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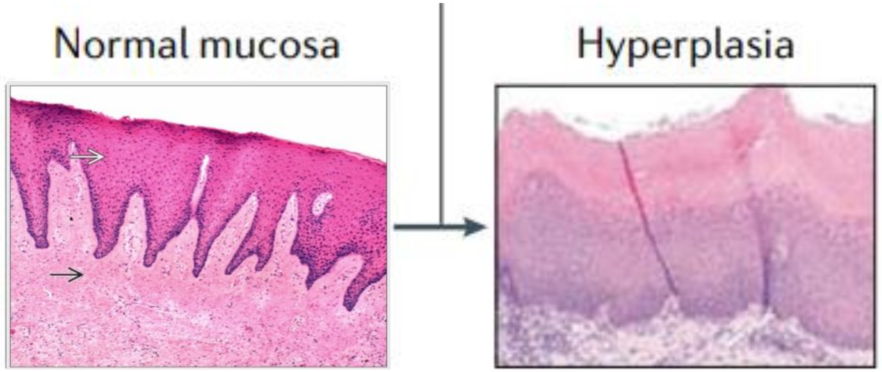
Toxin

TSG #1



Pre-cancer

Often clinically apparent!

Often makes abnormal pink/orange surface keratin

= mutation

TSG = tumor suppressor gene (e.g. *TP53*)

HPV-negative SCC: Sequence of Events

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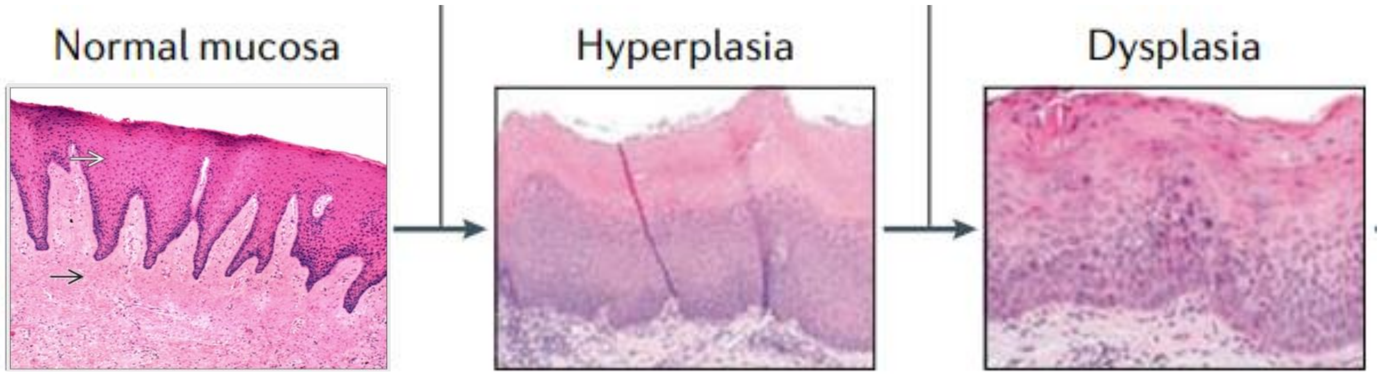
Toxin

TSG #1

Toxin

TSG #2



***Pre*-cancer**

Often makes abnormal pink/orange surface keratin

Often clinically apparent!

Abnormal epithelial cells are still confined to the surface with an intact basement membrane

= mutation

TSG = tumor suppressor gene (e.g. *TP53*)

HPV-negative SCC: Sequence of Events

Toxin

TSG #1

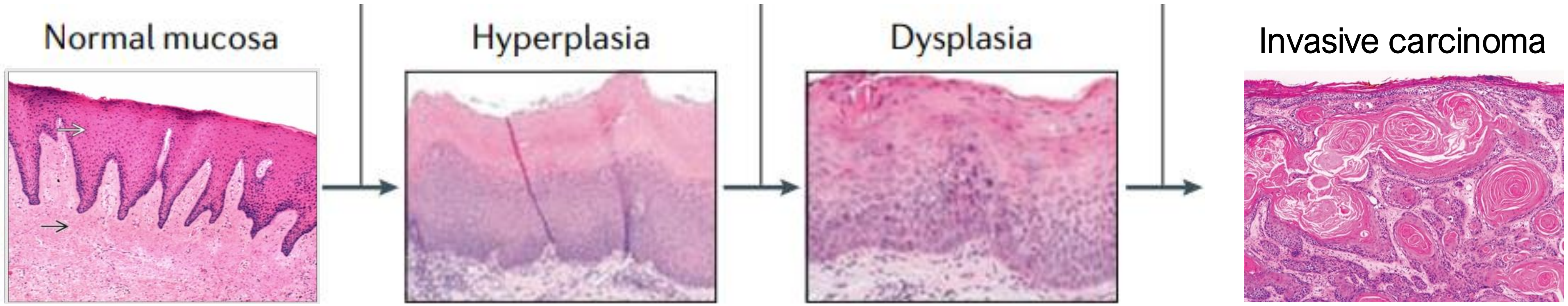
Toxin

TSG #2

Toxin

TSG #3

"Invasive" = invades through basement membrane → access to blood vessels and lymphatics



Pre-cancer

Often makes abnormal pink/orange surface keratin

Cancer

= mutation

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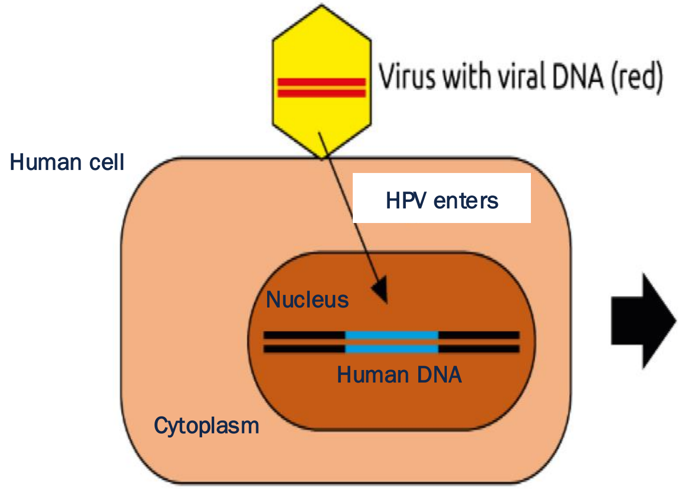
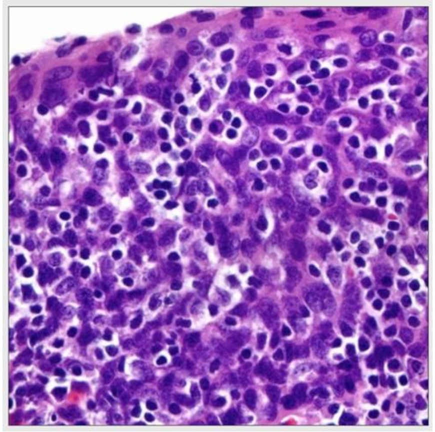
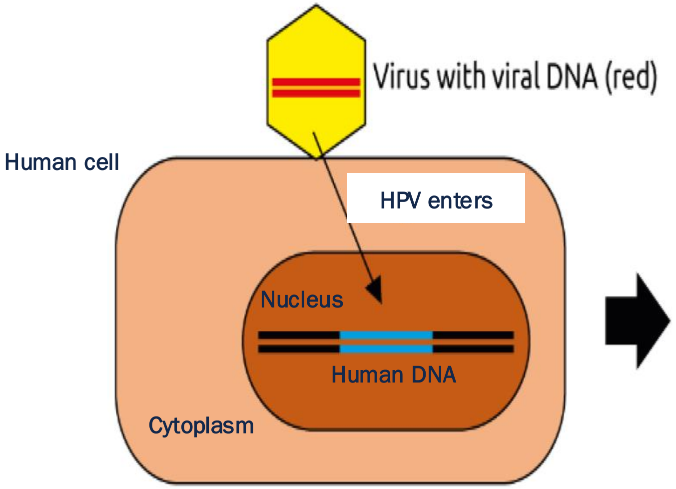
HPV-positive SCC: Sequence of Events

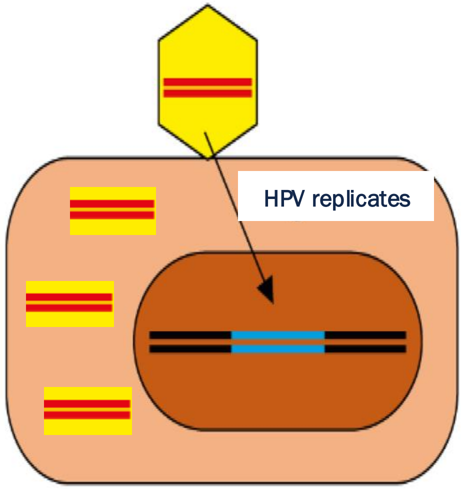


Tonsil basal cell, newly infected by HPV



HPV-positive SCC: Sequence of Events





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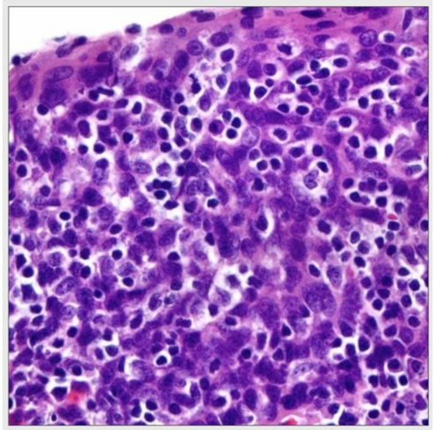
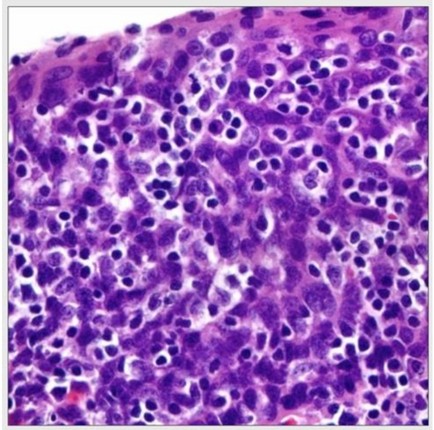
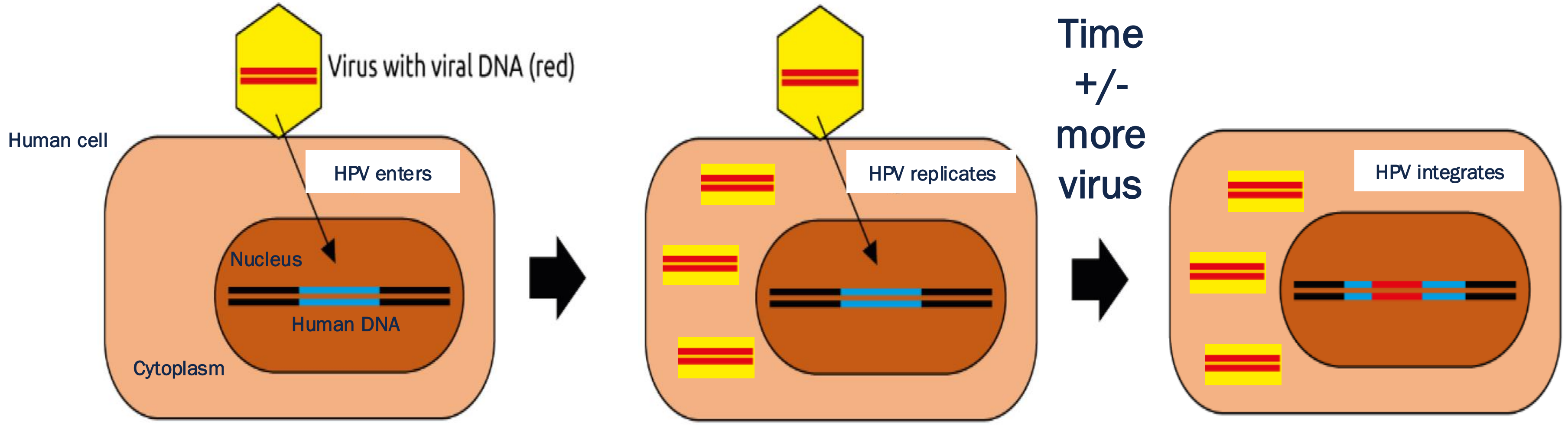
HPV replication in cell





Not clinically apparent!

HPV-positive SCC: Sequence of Events



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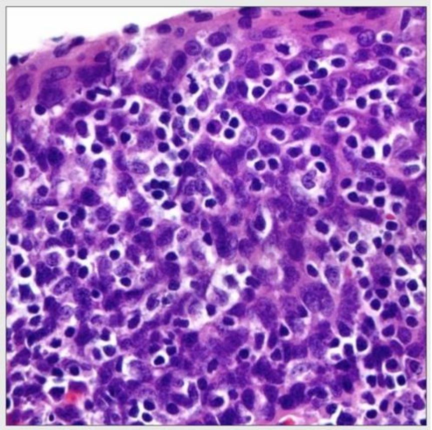
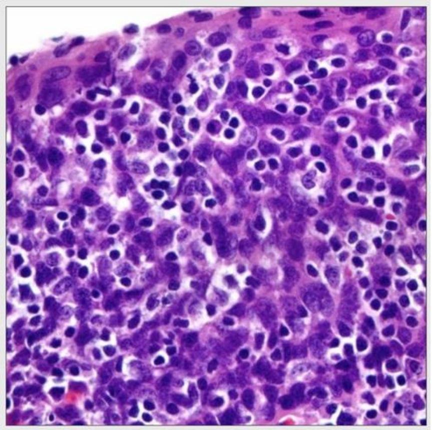
Tonsil basal cell with HPV genome integration





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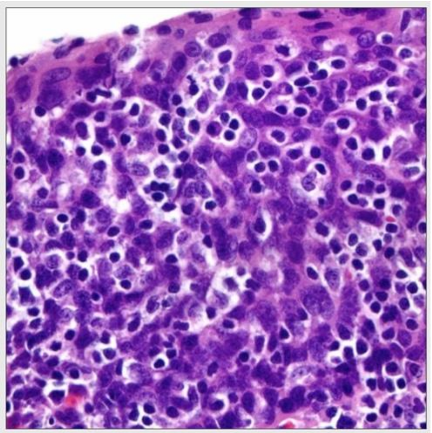

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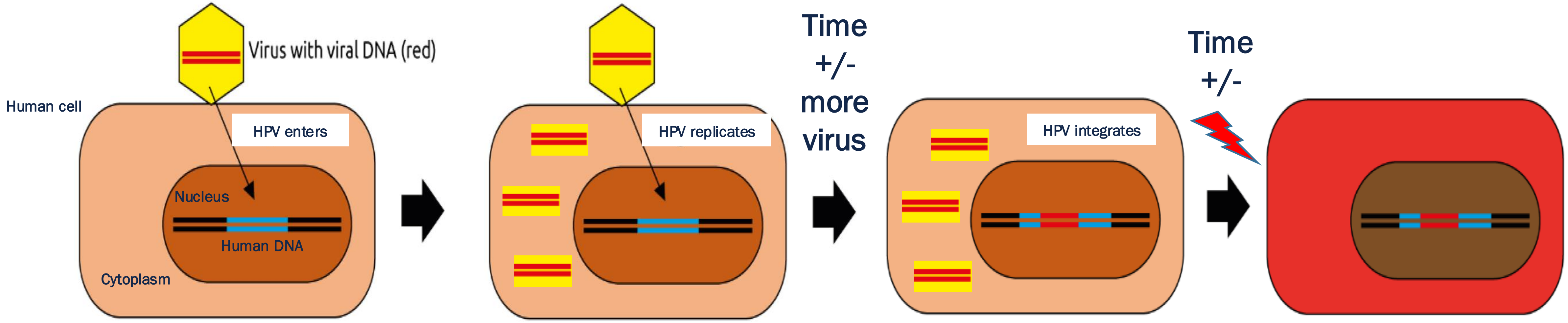

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HPV replication in cell

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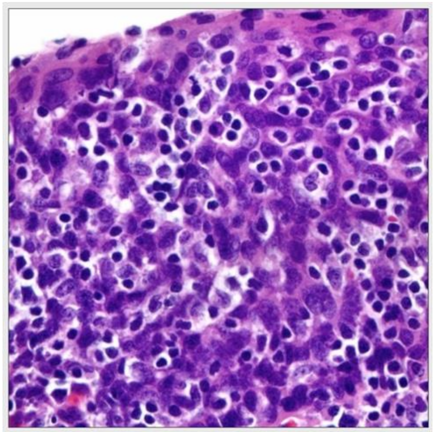
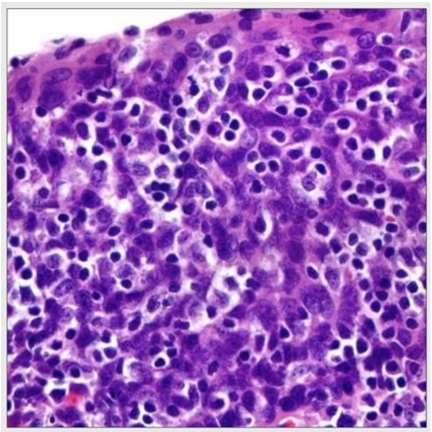
Transformed cancer cell





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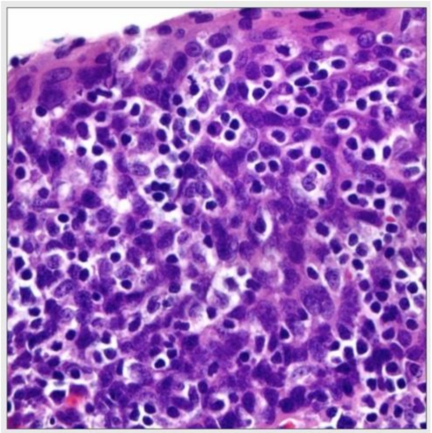

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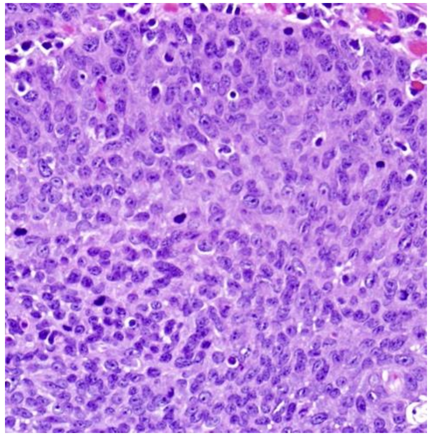
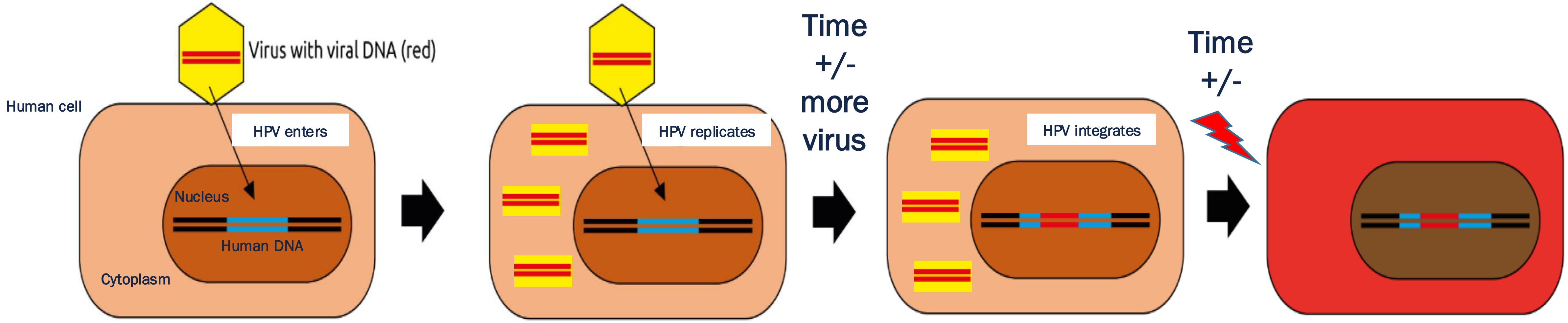


Now is clinically apparent!

HPV-positive SCC: Sequence of Events



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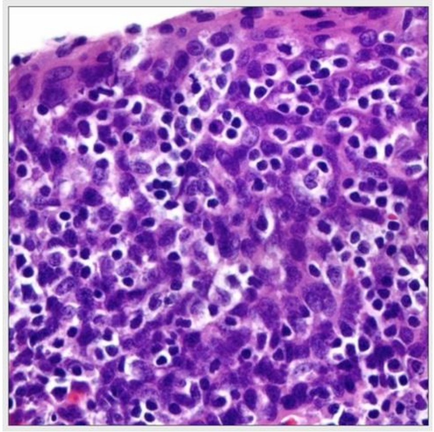

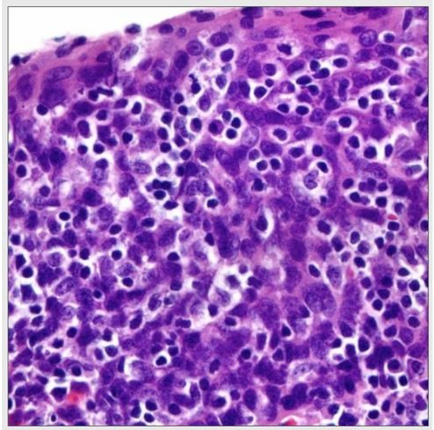

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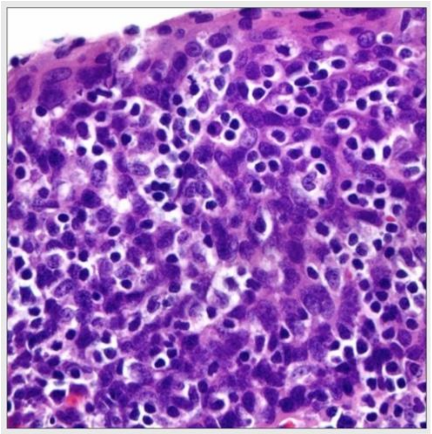

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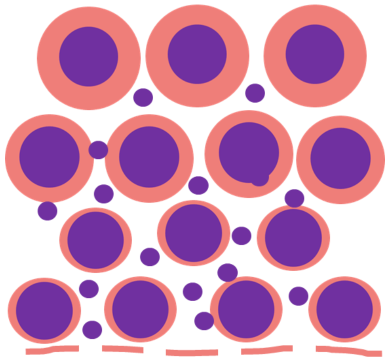

SCC: Smoking-related vs. HPV-related

Characteristics	Smoking-related aka HPV-negative	HPV-related aka HPV-positive
Site	Oral cavity, larynx, ~95%	Oropharynx (tonsils), 70-80%
Age	>60	40-50
Presentation/symptoms	**Varies (usually large primary)**	**Large neck mass, small primary tumor**
Risk factors	Smoking +/- drinking	Number of oral sex partners +/- smoking
Trends in occurrence	Decreasing	Increasing
Associated with *precancer*	Yes	No
Number of mutations	Many (tumor suppressors)	Few

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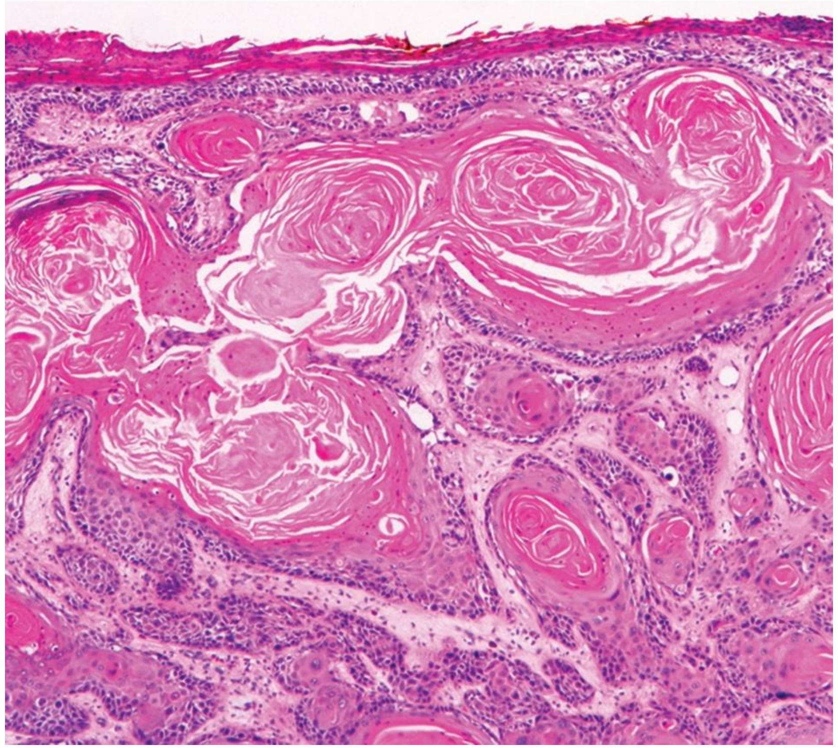
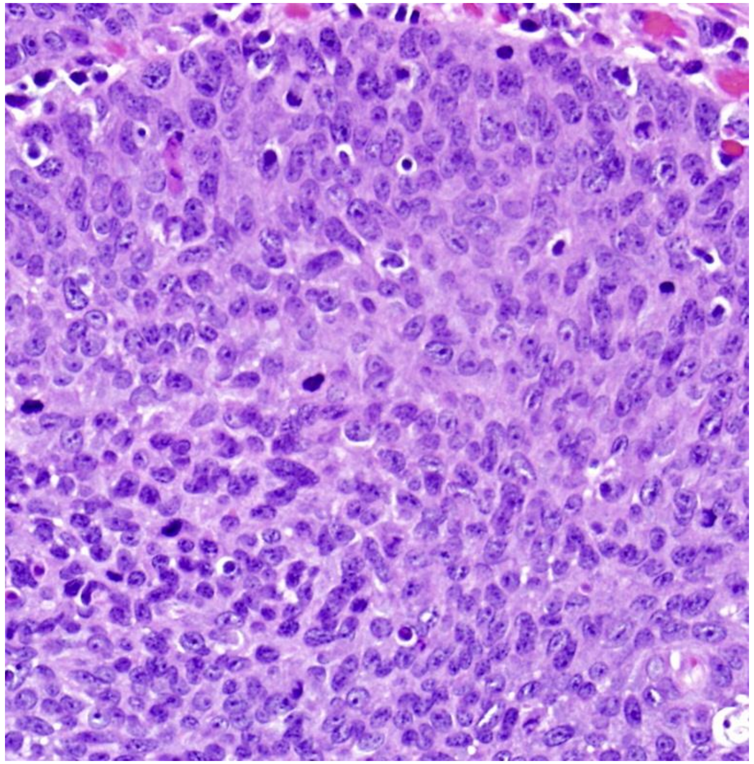
Tumor appearance	Pink/orange ("keratinizing")	Dark blue/purple ("non-keratinizing")





Is one type of SCC worse to get than the other?

SCC: Smoking-related vs. HPV-related

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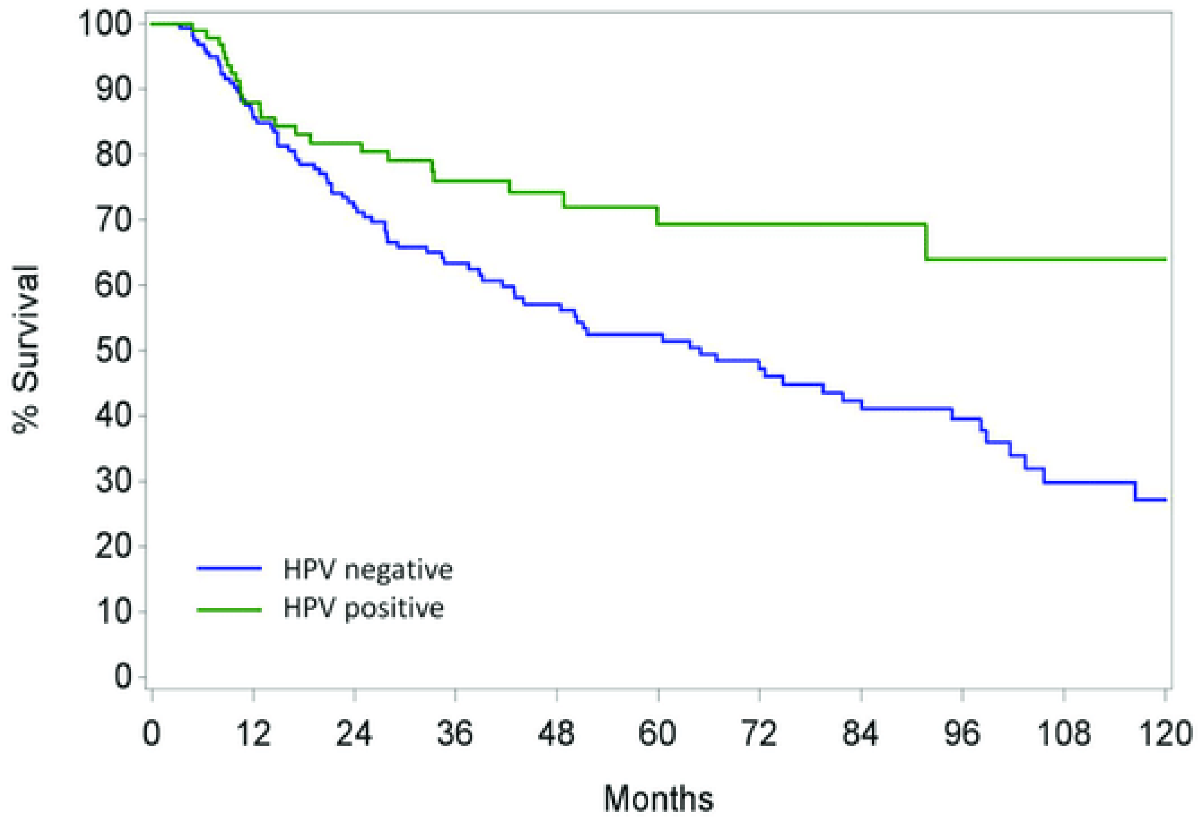
Associated with *precancer*	Yes	No
Number of mutations	Many (tumor suppressors)	Few
Tumor appearance	Pink/orange ("keratinizing")	Dark blue/purple ("non-keratinizing")
Survival	**Slightly worse**	**Slightly better**

Outcomes: HPV-positive vs. HPV-negative

<u>"Survival curves"</u>

How scientists measure differences in survival between two groups

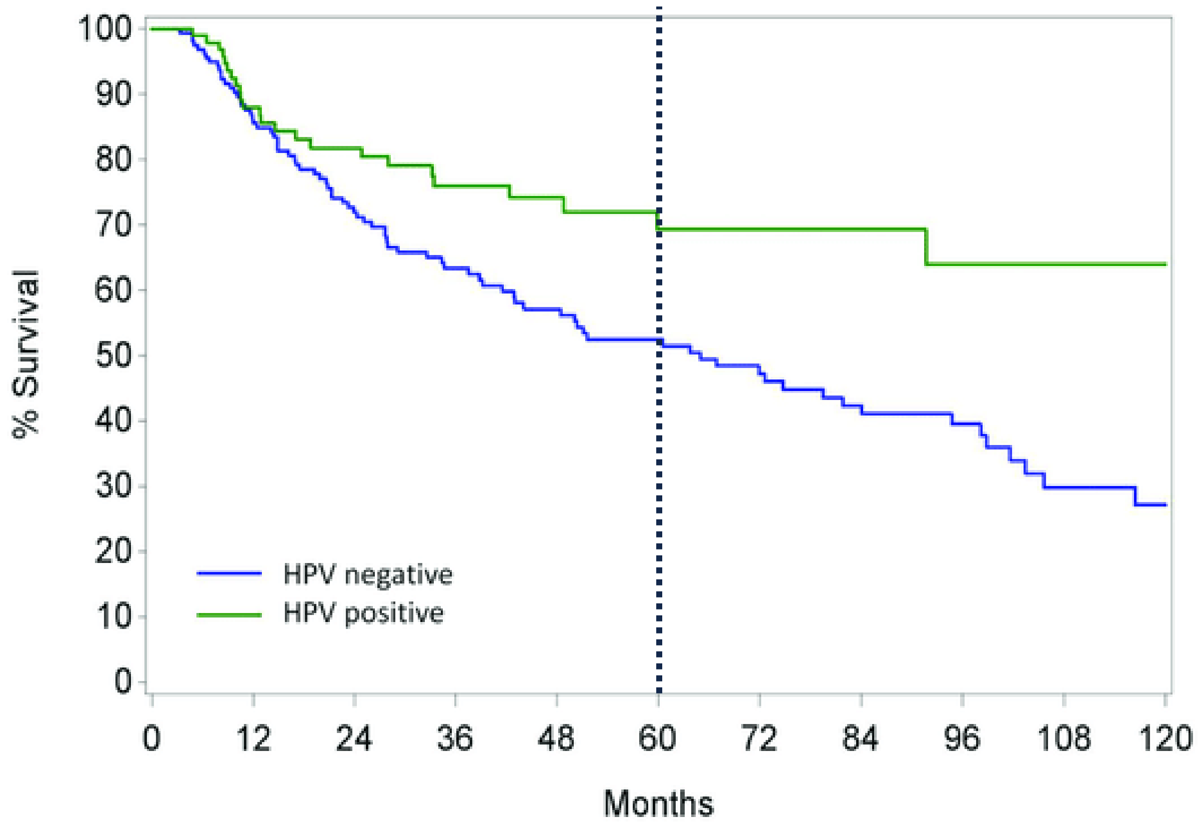


Outcomes: HPV-positive vs. HPV-negative

<u>"Survival curves"</u>

How scientists measure differences in survival between two groups

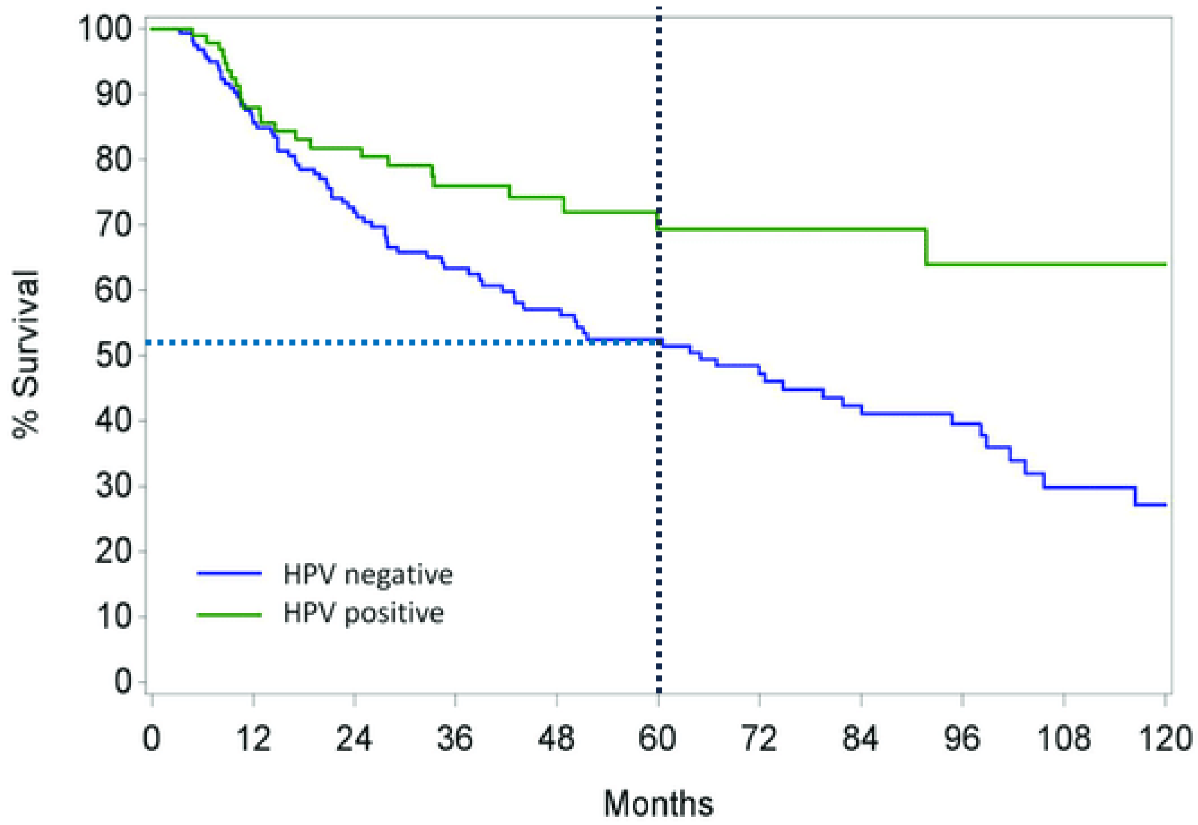
For example, we can see that at 5 years (60 months) since diagnosis



Outcomes: HPV-positive vs. HPV-negative

<u>"Survival curves"</u>
How scientists measure differences in survival between two groups

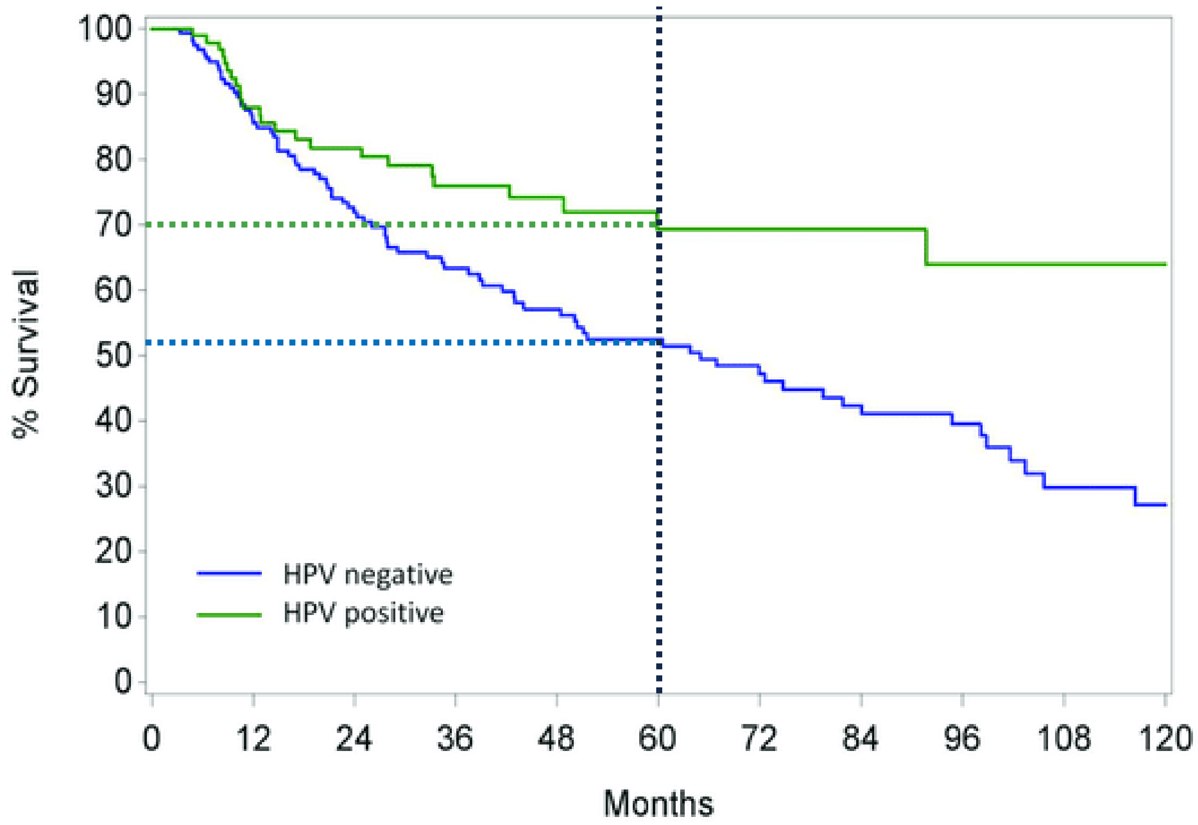
For example, we can see that at 5 years (60 months) since diagnosis, ~50% of HPV-negative patients were still alive



Outcomes: HPV-positive vs. HPV-negative

<u>“Survival curves”</u>
How scientists measure differences in survival between two groups

For example, we can see that at 5 years (60 months) since diagnosis, ~50% of HPV-negative patients were still alive, while ~70% of HPV-positive patients were still alive



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So, patients with HPV-positive tumors often have better outcomes than HPV-negative (smoking-related) SCC. Thus, we need to tell the treating physicians if a tumor is HPV positive or HPV negative.

BUT remember: MOST but not all SCCs in the tonsils are HPV-positive and MOST but not all SCCs of the oral cavity/larynx are HPV-negative.

And not all HPV-positive tumors are blue/purple. Sometimes they can be pink/orange .

HOW DO WE CONFIRM HPV STATUS IN NEW SCC CASES?

How Pathologists Tests for HPV

- Two main ways

How Pathologists Tests for HPV

- Two main ways
  1. Mark and visualize DNA or RNA from the **actual HPV virus**

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  2. Mark and visualize a **human protein** that happens to be increased when HPV DNA is present in the human tumor cells

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  1. Mark and visualize DNA or RNA from the **actual HPV virus**
  2. Mark and visualize a **human protein** that happens to be increased when HPV DNA is present in the human tumor cells

This way is (a little) easier and cheaper

How Pathologists Tests for HPV

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- Two main ways
  1. Mark and visualize DNA or RNA from the **actual HPV virus**
  2. Mark and visualize a **human protein** that happens to be increased when HPV DNA is present in the human tumor cells
     - The human protein, **p16, a tumor-suppressor gene,** is increased ("overexpressed" or "upregulated") in human cells when infected by HPV

p16

How Pathologists Tests for HPV

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p16

Immunohistochemistry

Principles of Immunohistochemistry

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Immuno *Histo* *Chemistry*

Principles of Immunohistochemistry

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Immunο

Histo

Chemistry

=

Laboratory method

Principles of Immunohistochemistry

Immuno	*Histo*	*Chemistry*
	=	=
	Tissue (microscopic)	*Laboratory method*

Principles of Immunohistochemistry

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Immuno	*Histo*	*Chemistry*
=	=	=
Antibodies	*Tissue (microscopic)*	*Laboratory method*

Principles of Immunohistochemistry

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Immuno	*Histo*	*Chemistry*
=	=	=
Antibodies	*Tissue (microscopic)*	*Laboratory method*

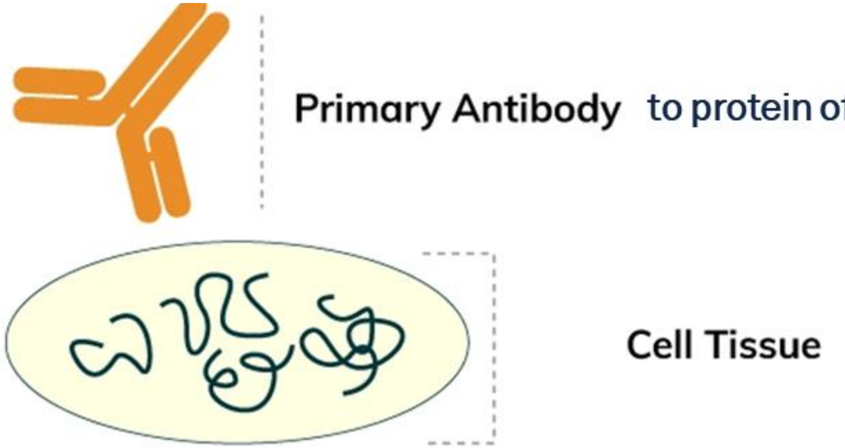
A laboratory method that uses antibodies to check for certain markers (usually proteins, human or non-human) in a sample of tissue.

Principles of Immunohistochemistry

Cell Tissue

Our tumor!

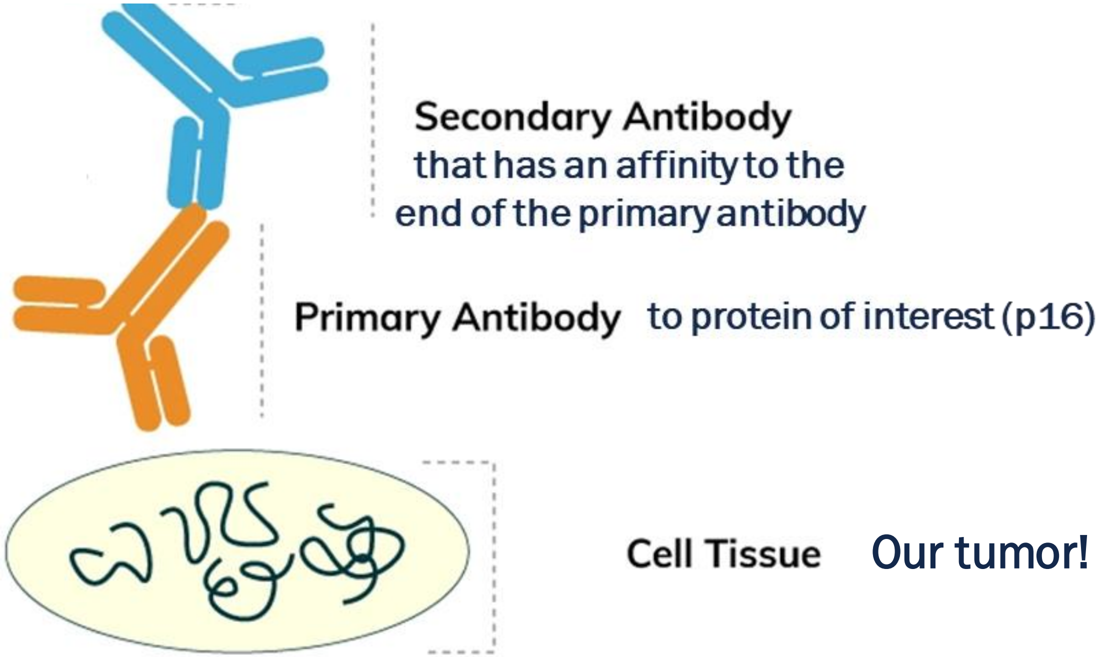
Principles of Immunohistochemistry



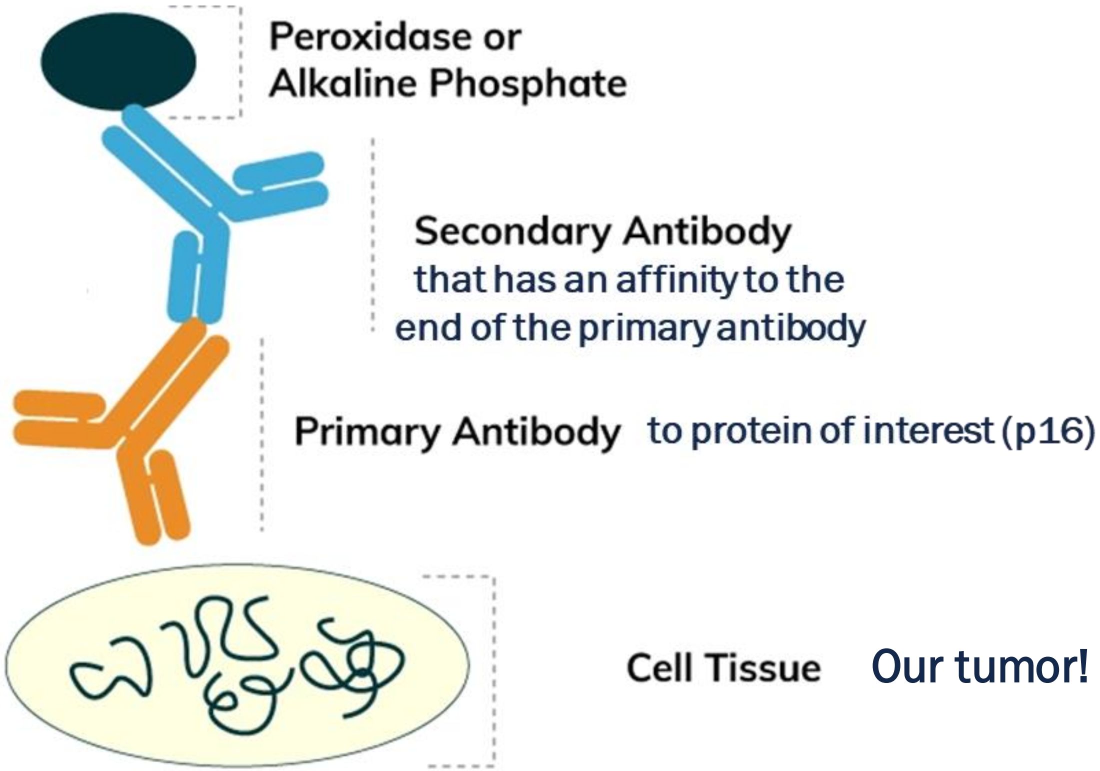
to protein of interest (p16)

Our tumor!

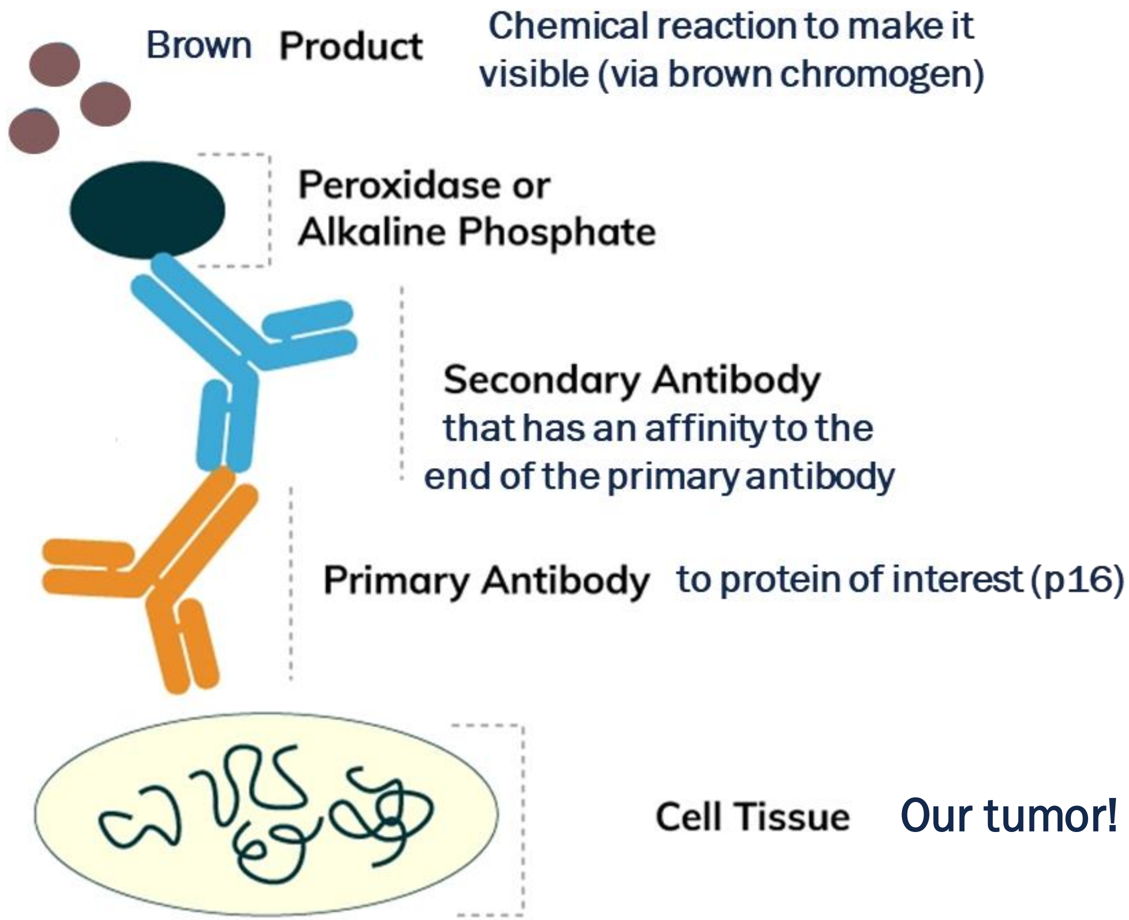
Principles of Immunohistochemistry



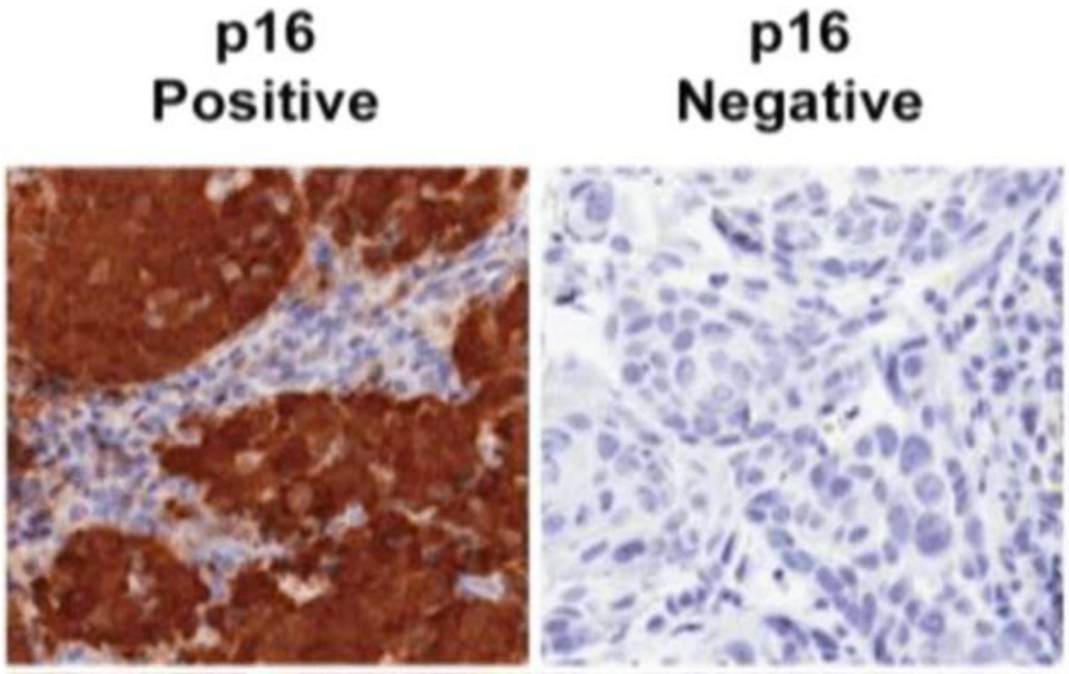
Principles of Immunohistochemistry



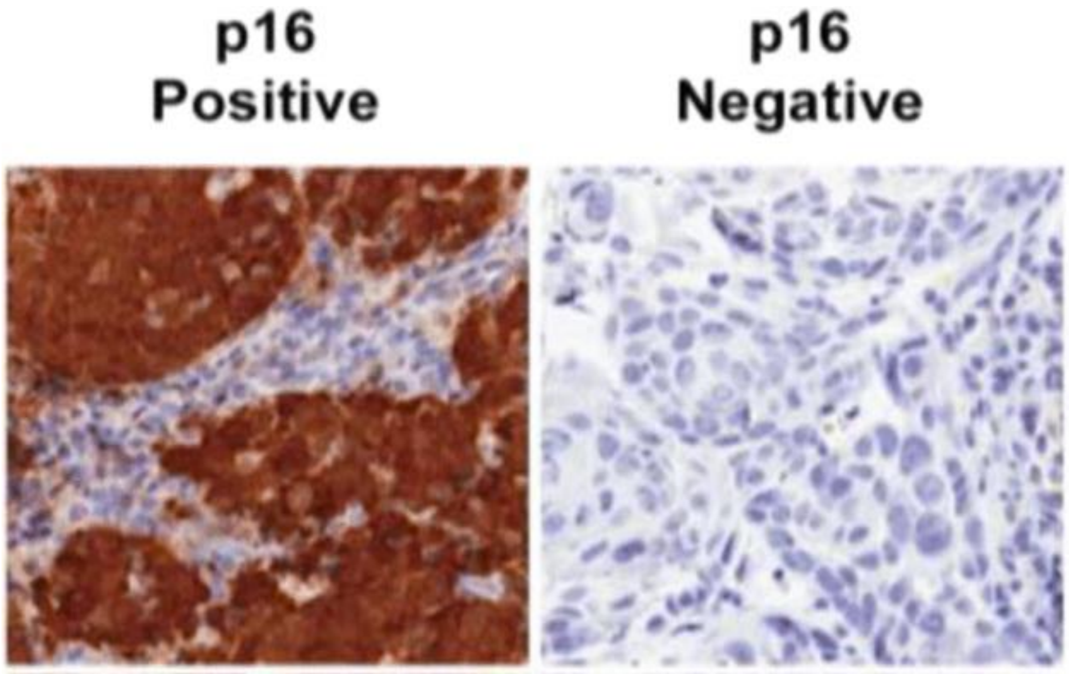
Principles of Immunohistochemistry



p16 Immunohistochemistry in SCC

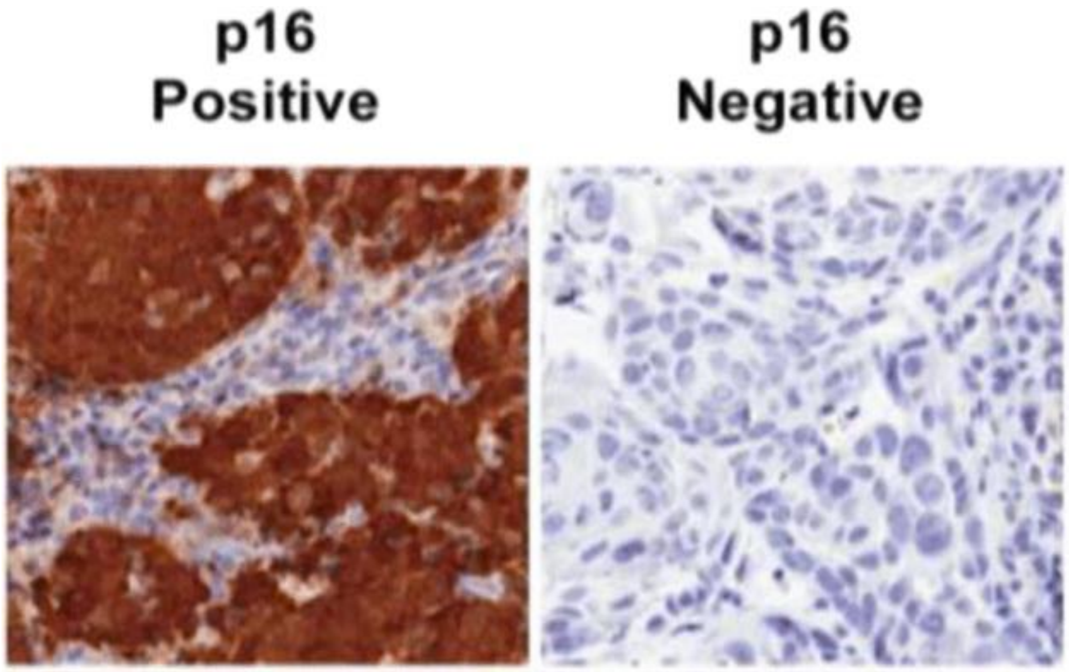


p16 Immunohistochemistry in SCC



Cells that do not stain brown are light blue because we also stain with hematoxylin but leave out the eosin so we can see the brown easier

p16 Immunohistochemistry in SCC



HPV is present

HPV is absent

Cells that do not stain brown are light blue because we also stain with hematoxylin but leave out the eosin so we can see the brown easier

p16 Immunohistochemistry in SCC

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- All new SCCs in the oropharynx (tonsils) should be tested for p16 *regardless of how the tumor looks.*
- Tumors in other sites are usually not tested.
  - Recommendations change as we learn more about cancer!

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How is squamous cell carcinoma treated once diagnosed?

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How is squamous cell carcinoma treated once diagnosed?

NO ONE SIZE FITS ALL!

How is squamous cell carcinoma treated?

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- The treatment approach to every individual patient is guided by anatomical site, stage, disease characteristics, functional considerations and patient wishes.

Distant (e.g. to bone, liver) Metastasis at Diagnosis

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Cancer Site	Distant Metastatic Disease at Presentation (%)
Prostate	5
Breast	6-10
Cervical	13
Colorectal	25
Lung	25-40
Pancreatic	30-50

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Cancer Site	Distant Metastatic Disease at Presentation (%)
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Colorectal	25
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Pancreatic	30-50
Head/neck SCC	<1-5

Real opportunity to not just *treat*, but *CURE* these patients!

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Are HPV-positive and HPV-negative SCCs treated differently?

Are HPV-positive and HPV-negative SCCs treated differently?

SOMETIMES, BUT RECOMMENDATIONS CHANGE AS WE LEARN MORE ABOUT CANCER!

How is squamous cell carcinoma treated?

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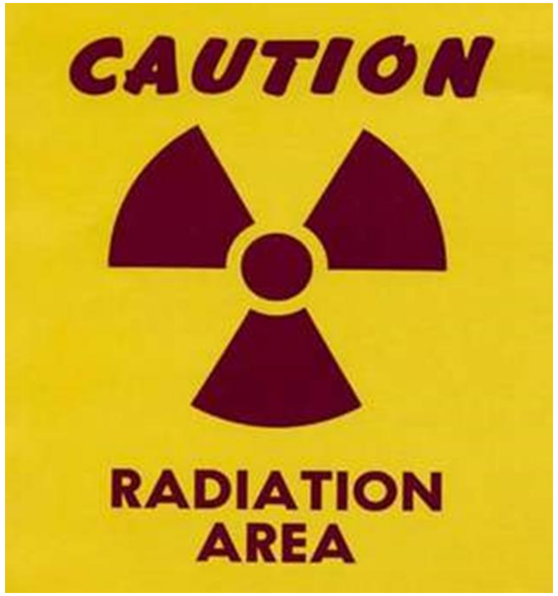
- In patients with a small cancer with no spread to lymph nodes or involvement of only a single node, cure rates of over 80% can be achieved with surgery (+/- radiation after) or radiation alone



How is squamous cell carcinoma treated?

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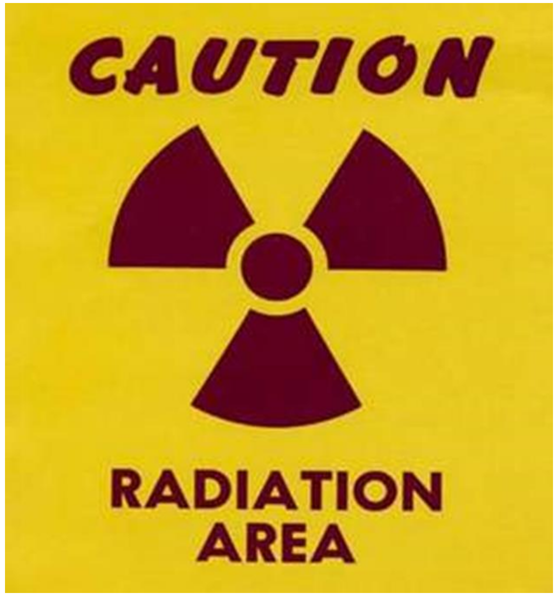
- For higher stage disease (e.g. big primary tumor or more extensive spread to lymph nodes appreciated at time of diagnosis), radiation + chemotherapy is more often recommended.



How is squamous cell carcinoma treated?

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-	TRIALS					
	Induction/ Neoadjuvant	Definitive	Adjuvant/ Maintenance	Translational/ Biomarker	Recurrent/Metastatic (Palliative)	"Other"
H&N POD	**NRG-HN006** (Hackman) Ph 2/3 of sentinel lymph node biopsy vs. elective neck dissection for early stage OSCC **LCCC 2047** (Sheth) Ph 2 of induction and maintenance pembro and olaparib (required CRT) **PBI-MST-01** (Sheth) Ph 0 CIVO Platform for IT microdoses (requires surgery)	**Nanoray312** (Shen) Phase 3 NBTXR activated by XRT ± cetuximab for platinum ineligible, elderly patients **NRG-HN-005** (Chen) Randomized Ph 2/3 of de-intensification for p16+ non-smoking OPSCC **NRG-HN-006** (Hackman) Randomized Ph 2/3 of sentinel LN biopsy vs early neck dissection (OCSCC T1-2)		**LCCC 1835** (Sheth) ctDNA in locally advanced HNSCC **LCCC 2044** (Yarbrough) Prospective study to validate ctHPVDNA and prognostic genomic biomarkers in HPV+ OPSCC	**1L+ NBXT-1100** (Shen) Ph I/II NBTXR3 activated by SABR + Pembro **1L+ GCT1046:** (Weiss) FIH Ph 1 of GEN1046 in solid tumors **1L+ TSCAN** (Weiss) Ph I of TCR-engineered T cells targeting HLA antigens **1L+ SGNTV-001** (Patel) Ph 2 of Tisotumab Vedotin in solid tumors **1L+ NX-1607-101** (Weiss) Ph 1a of Casitas B-lineage lymphoma proto-oncogene (CBL-B) inhibitor **1L+ BI 1463-0001** (Trivedi) Ph 1 bispecific Ab (CD137 + FAP) + pembro **2L+ MCLA-158-CL02** (Sheth) Ph 3 petosemtamab vs investigator choice monotherapy **2L+ 61186372HNC2002** (Trivedi) Ph 1b/2 Amivantamab Monotherapy vs Amivantamab + SOC **2L+ TAPUR** (Patel) FDA approved drugs targeting specific tumor genes	**NCI10553** (Patel) Ph 2 Darolutamide + Leuprolide in AR positive SGC **LCCC 2255** (Sheth) Ph 1b Neoadjuvant XL-092+Cemiplimab in ATC (requires surgery) **2L+ A092105** (Sheth) Ph 2 of ipi + nivo +/- Cabozantinib in NPC

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How could squamous cell carcinoma be *prevented*?

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How could squamous cell carcinoma be *prevented*?

DECREASING RISK FACTORS AND STRENGTHENING PROTECTIVE FACTORS

SCC Prevention

Characteristics	Smoking-related aka HPV-negative	HPV-related aka HPV-positive
Risk factors	Smoking +/- drinking	Number of oral sex partners +/- smoking

SCC Prevention

Characteristics	Smoking-related aka HPV-negative	HPV-related aka HPV-positive
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Smoking cessation

SCC Prevention

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Smoking cessation

HPV vaccine

Summary

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Tumor appearance	Pink/orange ("keratinizing")	Dark blue/purple ("non-keratinizing")
p16 immunohistochemistry	Negative	Positive
Treatment	No difference	No difference
Survival	Slightly worse	Slightly better
Prevention techniques	Smoking cessation	HPV vaccine

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Thanks!

Questions?