

Adolescent and Young Adult Cancers



**Department of Pathology & Laboratory Medicine
University of North Carolina at Chapel Hill
Introduction to Pathology of Disease
November 13, 2025**

Lecture Overview & Learning Goals



1. Adolescent and Young Adult (AYA) Cancer Statistics
 - a. Increasing incidences in younger age groups
2. Specific Cancers of Interest
 - a. Nonseminomatous Germ Cell Tumors
 - b. Triple-Negative Breast Cancer
 - c. Colorectal Cancer
3. Environmental factors and correlations
 - a. Areas of modern research – what are the unknowns, and what can YOU do?

Cancer rates increasing in younger populations



Rising rate of young people getting cancer

Cumulative percent change in cancer incidence rates per 100,000 from 1975 by age group

■ 15-39 ■ 40-64 ■ 65-74 ■ 75+

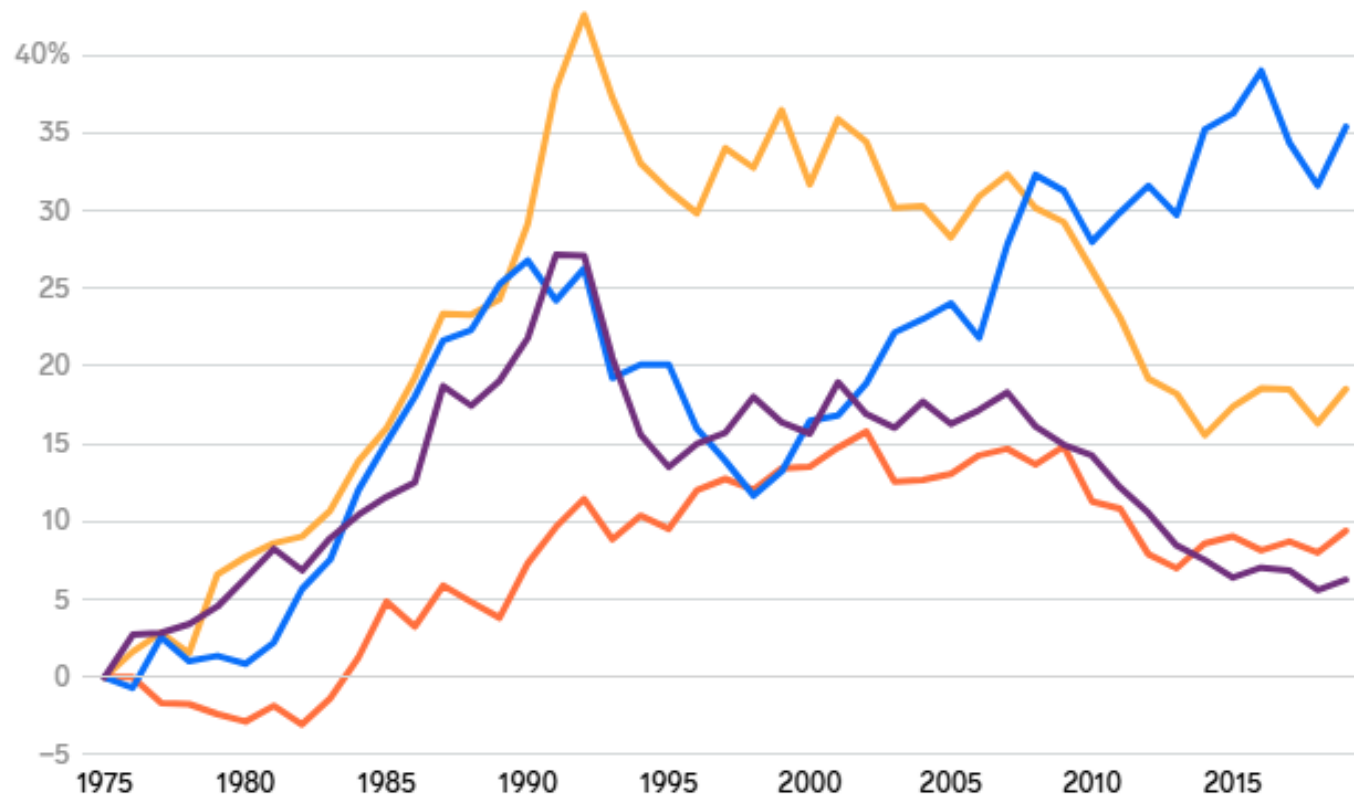
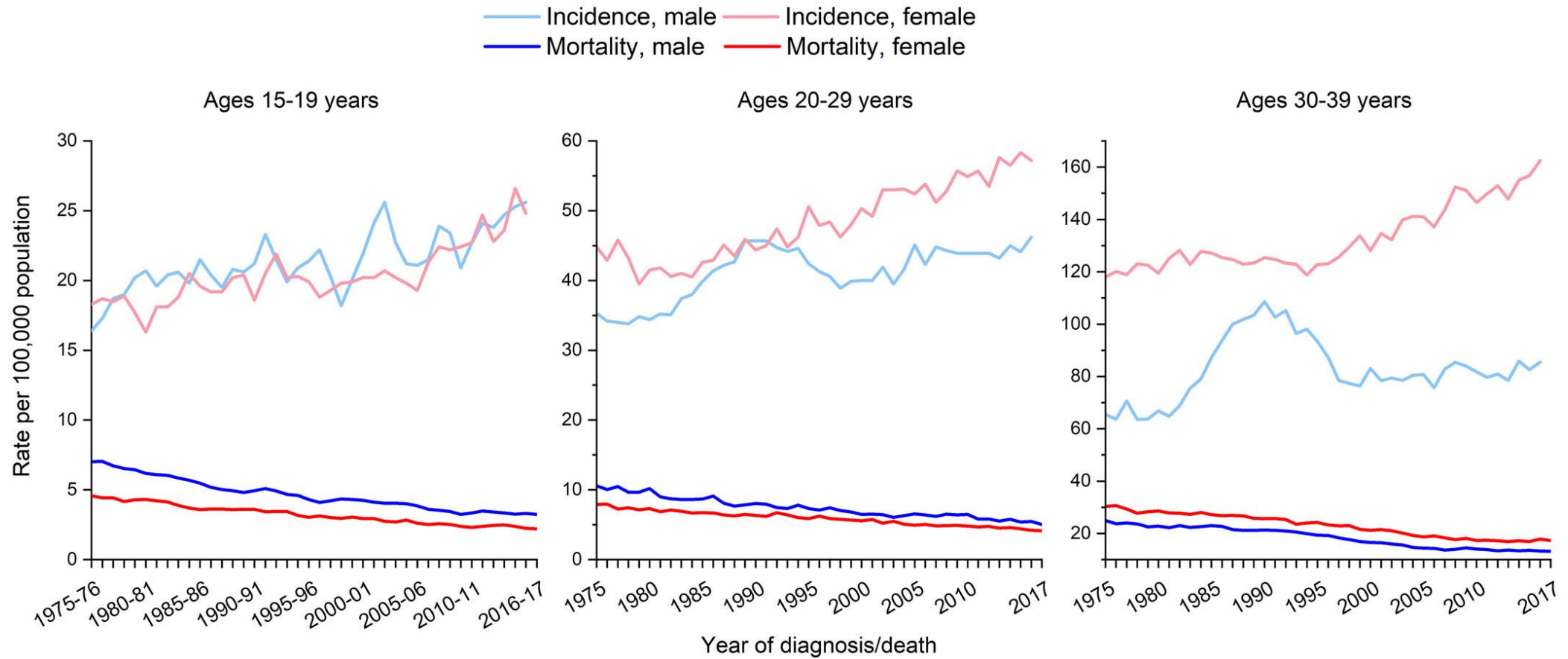


Chart: Madison Hoff/Business Insider • Source: [National Cancer Institute](#)

**BUSINESS
INSIDER**

AYA Incidence and Mortality by Gender



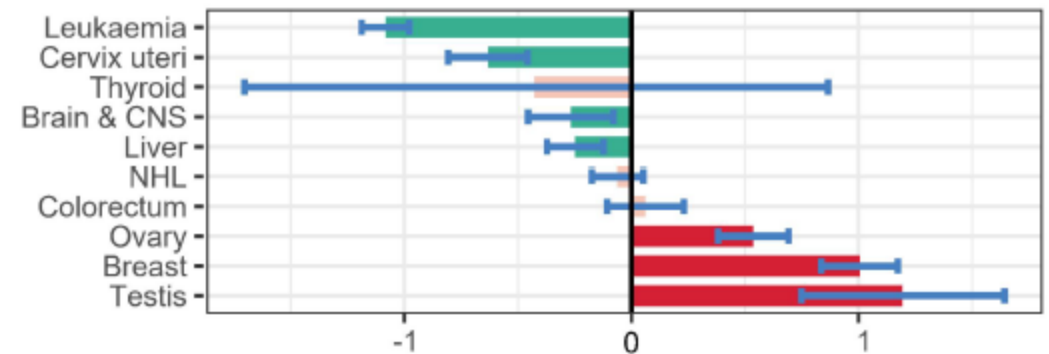
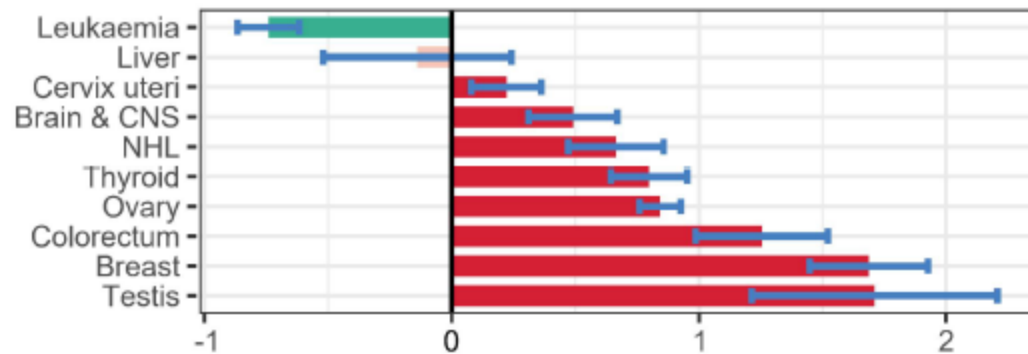
Incidence and mortality of AYA cancers



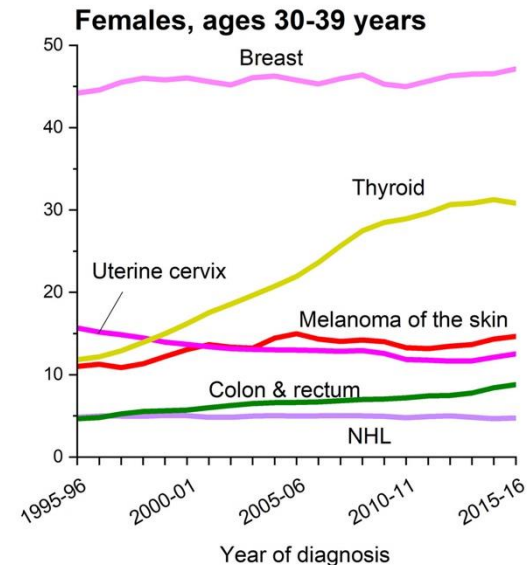
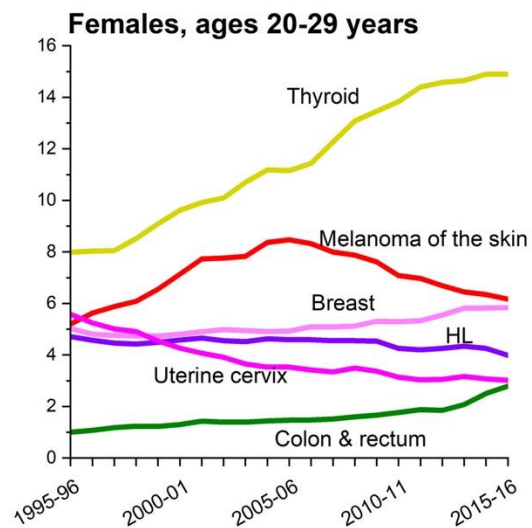
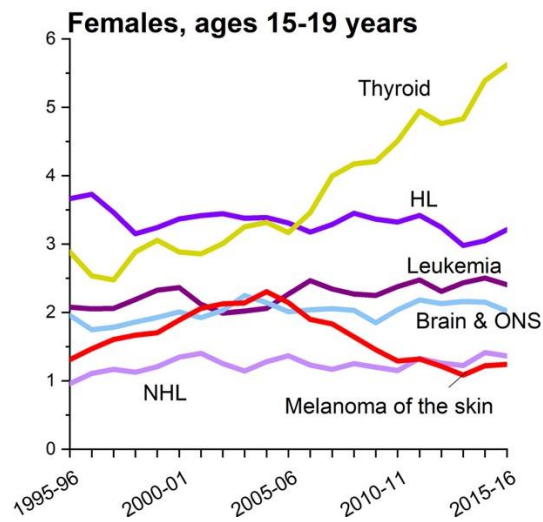
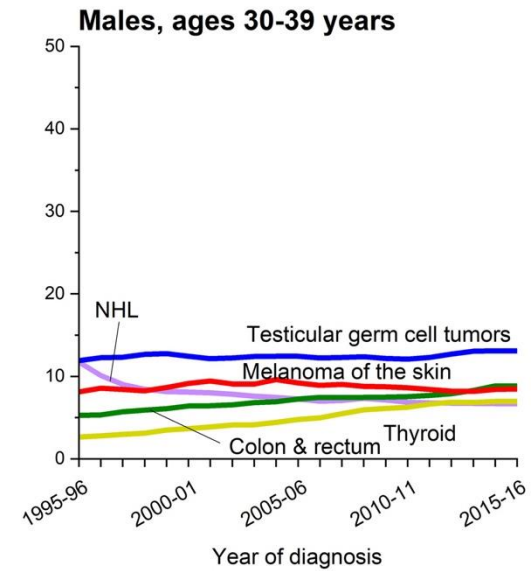
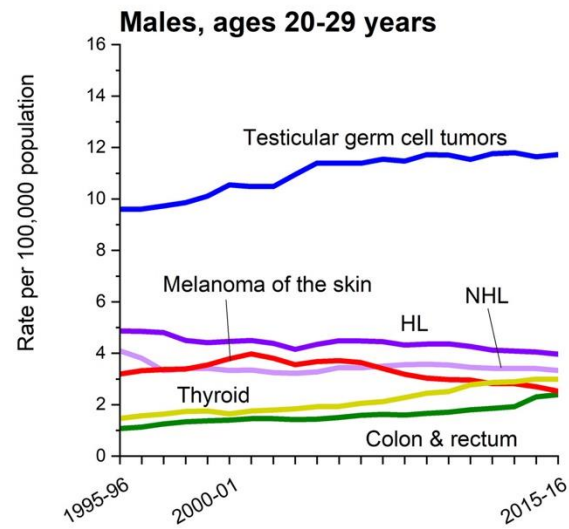
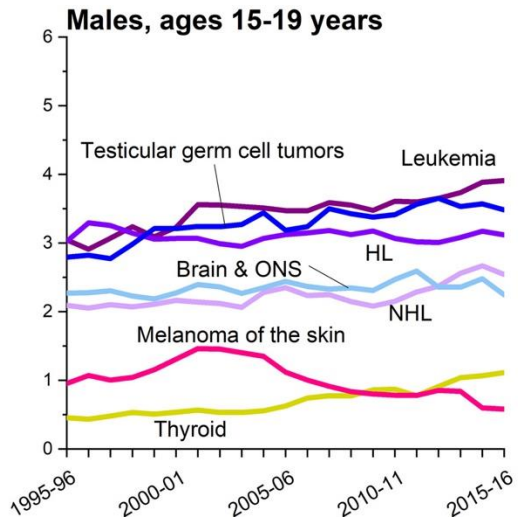
AAPC in age-standardised incidence rate (2012-2021)

AAPC in age-standardised mortality rate (2012-2021)

CI — Overall trend ■ Decrease ■ Increase ■ Stable



Increasing incidence by cancer and age

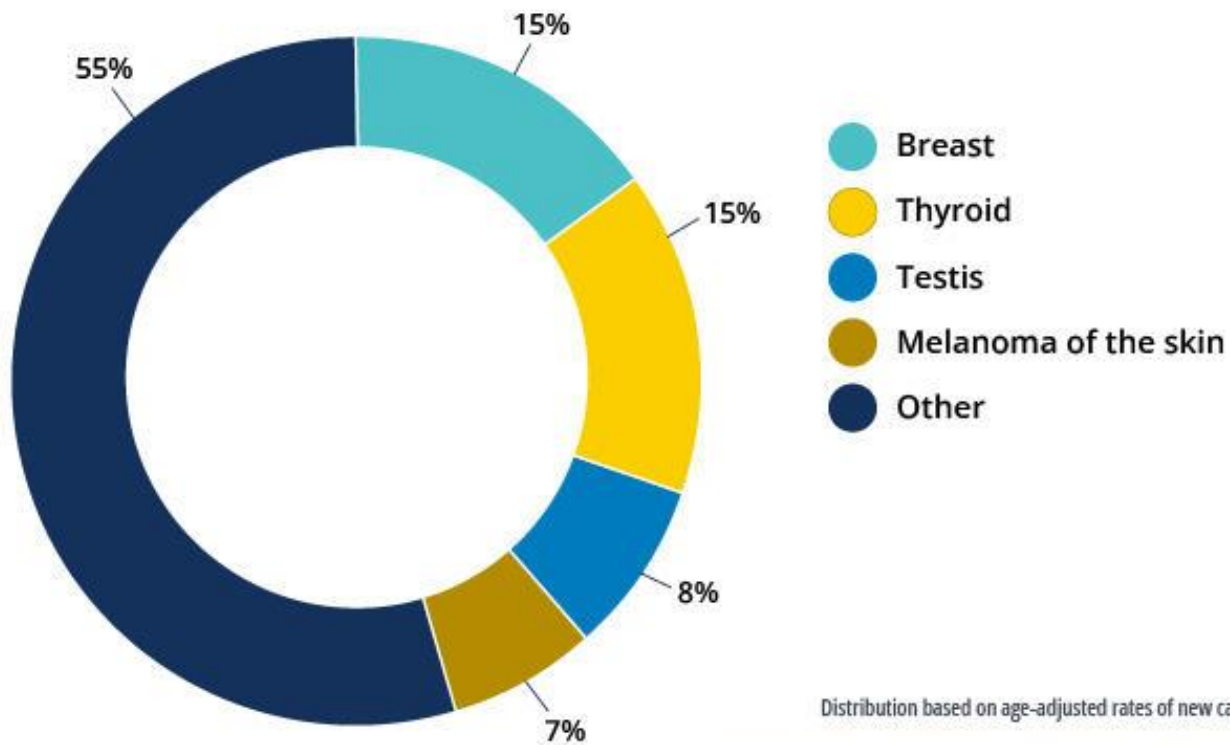


NHL = Non-Hodgkin Lymphoma
HL = Hodgkin Lymphoma

Most Common AYAs



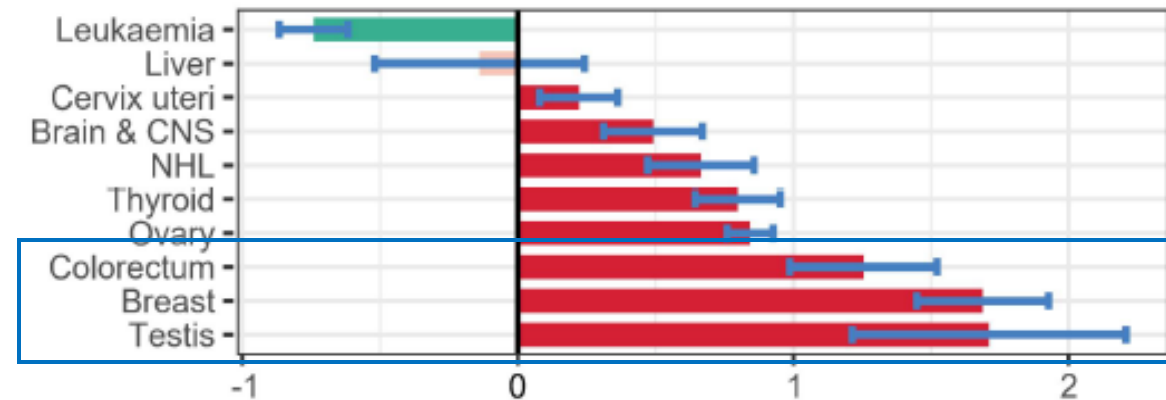
Common types of new cancers among AYAs



Distribution based on age-adjusted rates of new cases.

NCI's Surveillance, Epidemiology, and End Results (SEER) Program
SEER 22, 2017-2021

Temporal trend in burden of adolescent and young adult cancers from 2000 to 2021 by the 10 most frequent cancer types





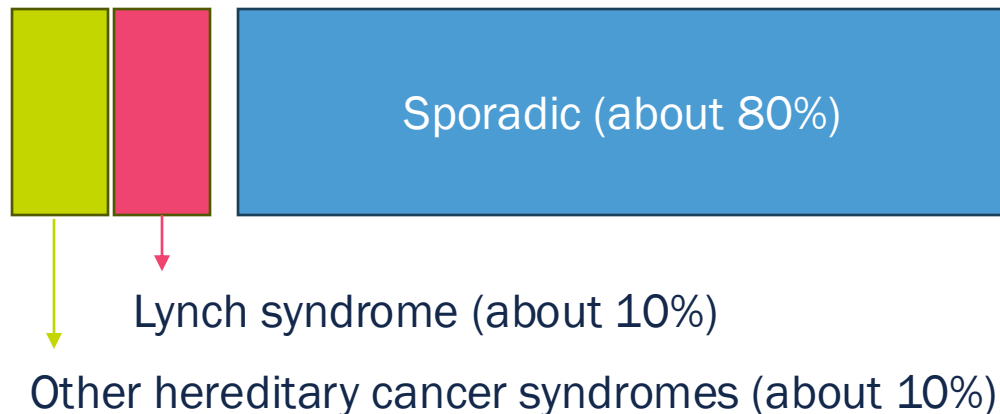
Colorectal Cancer

Colorectal Cancer

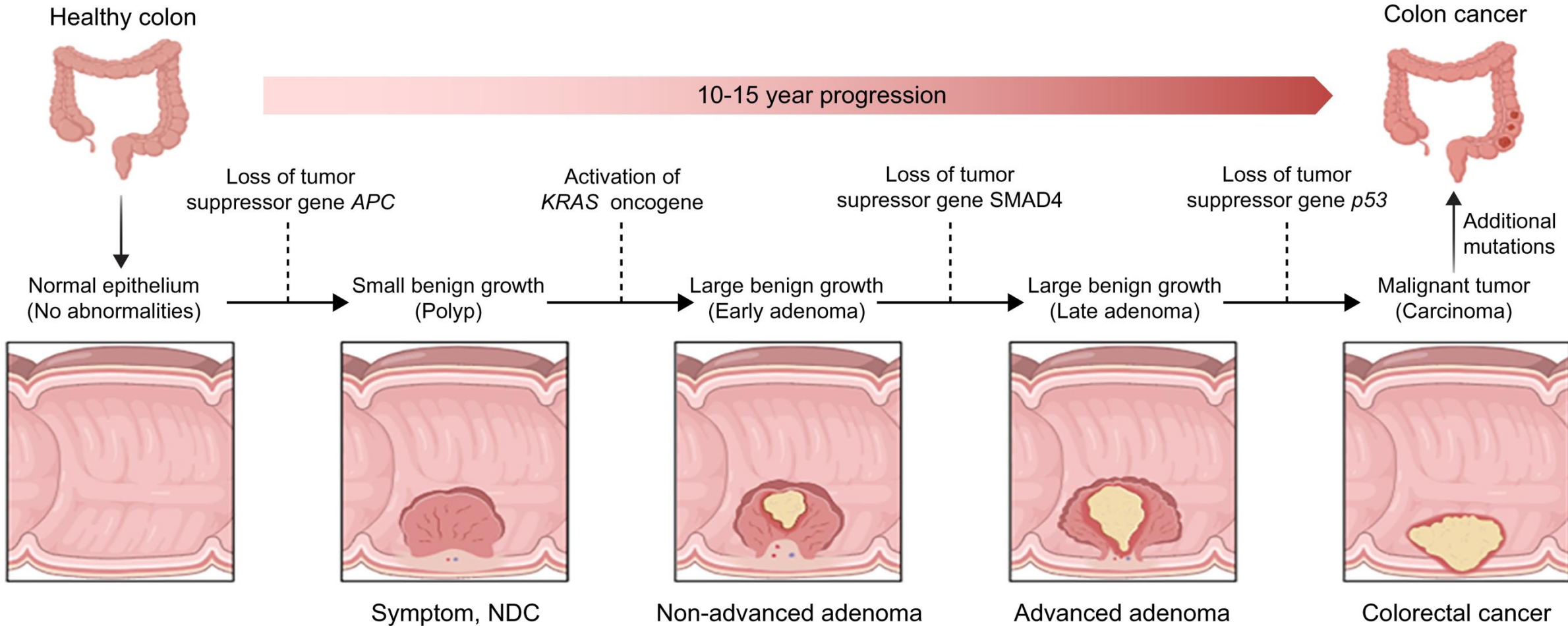


- “Colorectal cancer was the fourth-leading cause of cancer death in both men and women younger than 50 years in the late-1990s but is now first in men and second in women.”
<https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21820>
- **Birth cohort** effect, rather than a period effect impacting people of all ages during a specific time
- Early onset colorectal cancer (EO-CRC): diagnosed < age 50 (until recently, age of routine screening)

Early-onset colorectal cancer (EO-CRC):



Disease Pathogenesis

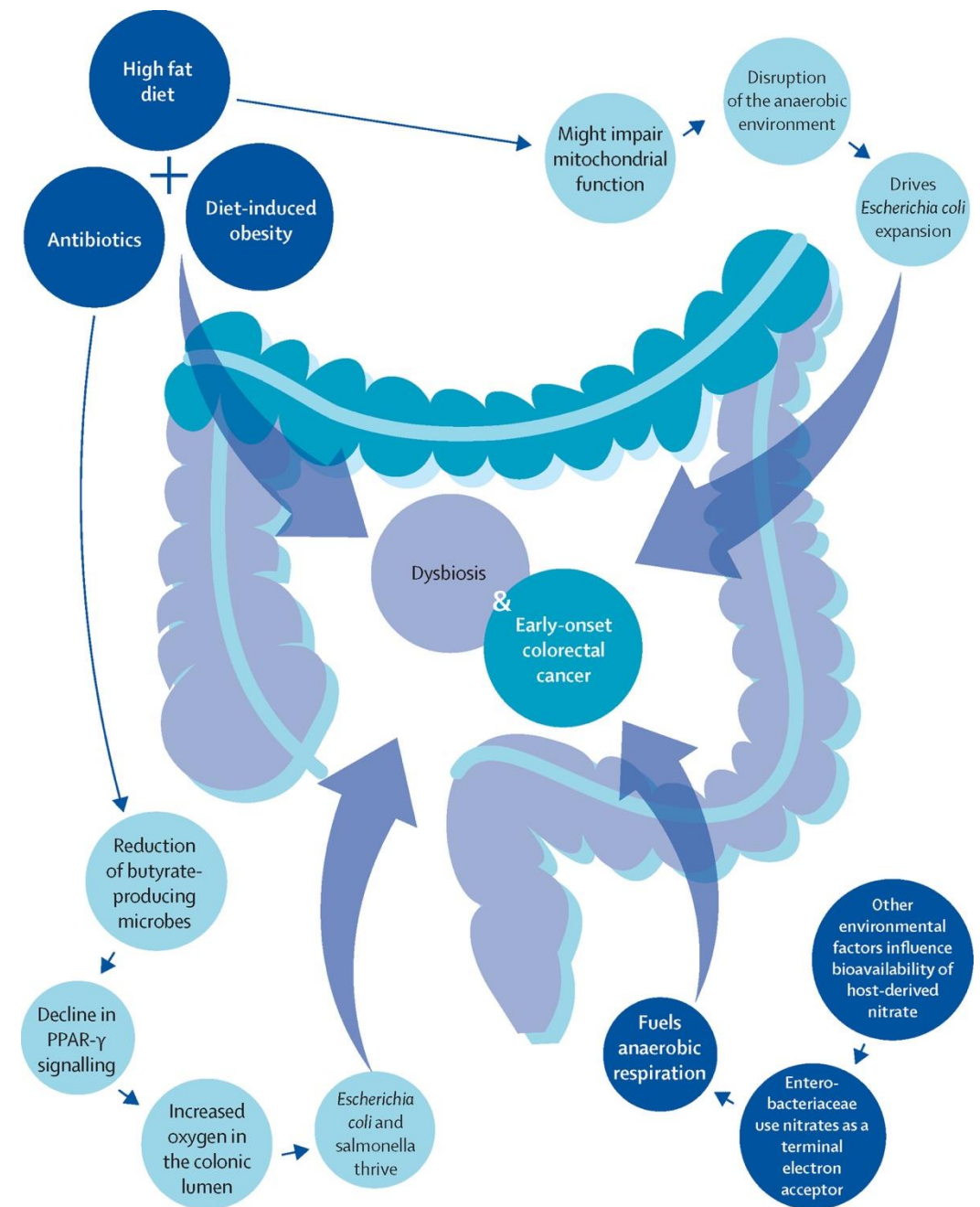


Increasing incidence

Reactome:

- global set of exposures that modulate risk
- Obesity, especially early in life
- Physical inactivity
- Diabetes mellitus
- Change in gut flora (dysbiosis)
- Diet: high fat, low fiber, red meat, processed meat
- Alcohol
- Tobacco

Many associations,
but causal link remains elusive



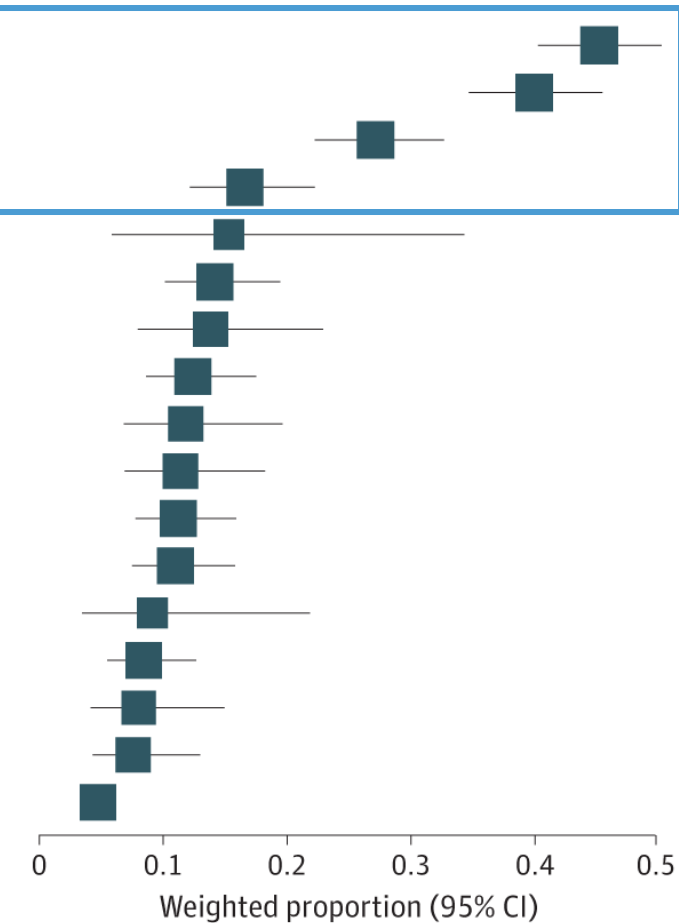
Clinical features



Early onset CRC is more likely to be:

- symptomatic
- rectal/distal colon
- advanced stage
- diagnosed late

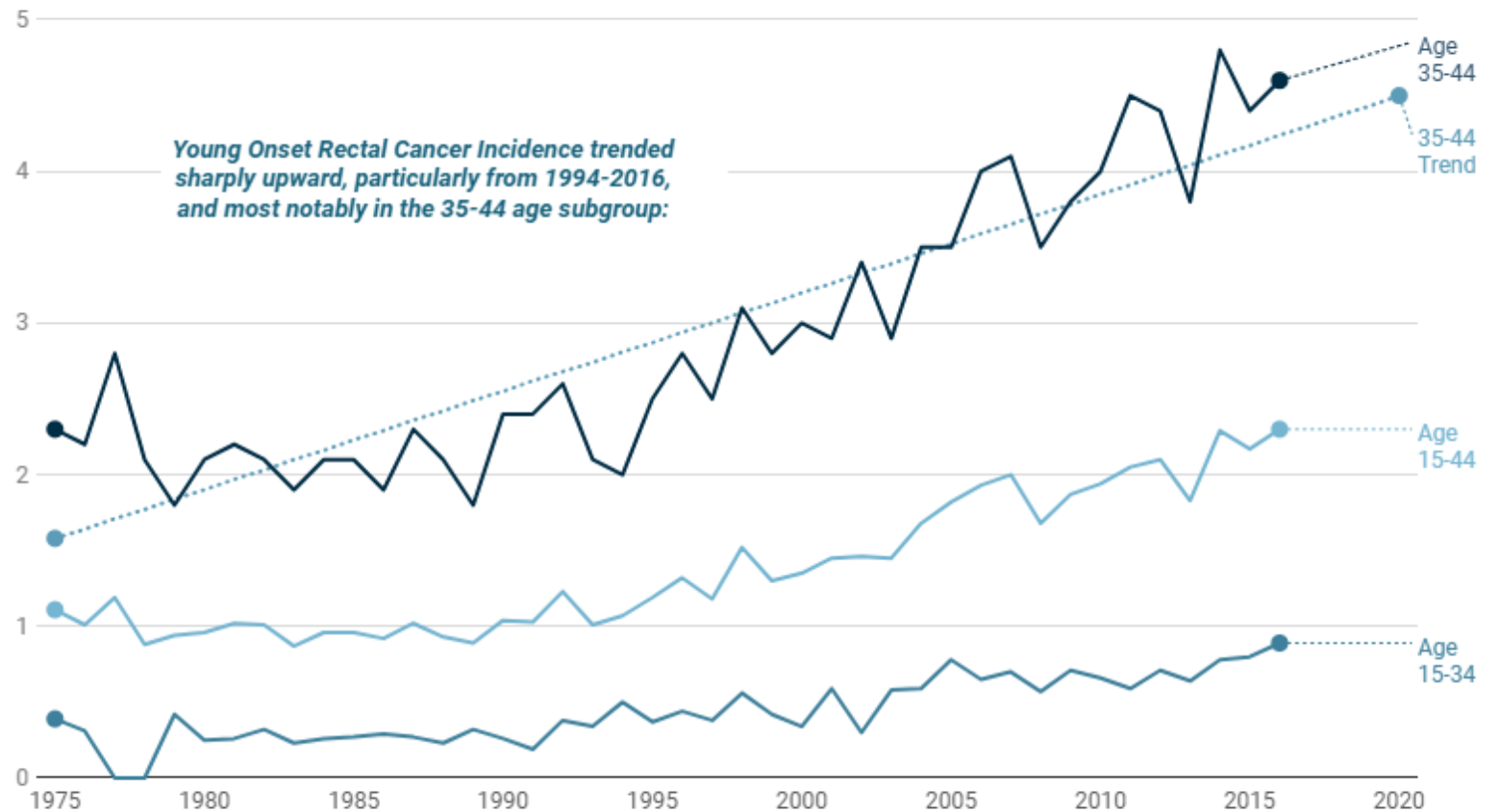
Sign/symptom	Studies, No.	Patients, No./ total No.	Weighted proportion (95% CI)
Hematochezia	76	11 319/35 431	0.45 (0.40-0.50)
Abdominal pain	73	12 527/32 447	0.40 (0.35-0.45)
Altered bowel habits	63	5737/24 660	0.27 (0.22-0.33)
Weight loss	53	2679/25 075	0.17 (0.12-0.22)
Loss of appetite	9	234/3213	0.15 (0.06-0.34)
Constipation	23	1709/15 425	0.14 (0.10-0.19)
Abdominal distension	12	205/1507	0.14 (0.08-0.23)
Diarrhea	21	1941/15 361	0.12 (0.09-0.18)
Acute presentation	7	59/590	0.12 (0.07-0.20)
Tenesmus	11	108/874	0.11 (0.07-0.18)
Anemia	34	3241/25 350	0.11 (0.08-0.16)
Obstruction	27	652/9135	0.11 (0.08-0.16)
Perforation	10	124/945	0.09 (0.04-0.22)
Fatigue	15	939/13 083	0.08 (0.06-0.13)
Nausea or vomiting	12	771/7637	0.08 (0.04-0.15)
Abdominal mass	13	110/1807	0.08 (0.04-0.13)
Rectal pain	12	495/11 886	0.05 (0.03-0.07)



Increasing incidence



Rising Rectal Cancer Incidence - Young Adult Subgroups



Selections from Database: SEER 9 Incidence - 1975-2016. Rates are per 100,000 and are age-adjusted to the World Health Organization (WHO 2000-2025) Standard Population Estimates.

Chart: Jarod DCamp • Source: SEER 9, Surveillance Research Program (SRP) in NCI's Division of Cancer Control and Population Sciences (DCCPS) • Embed

Rectal > left colon > right colon

Exposure that primarily affects the distal colon/rectum,

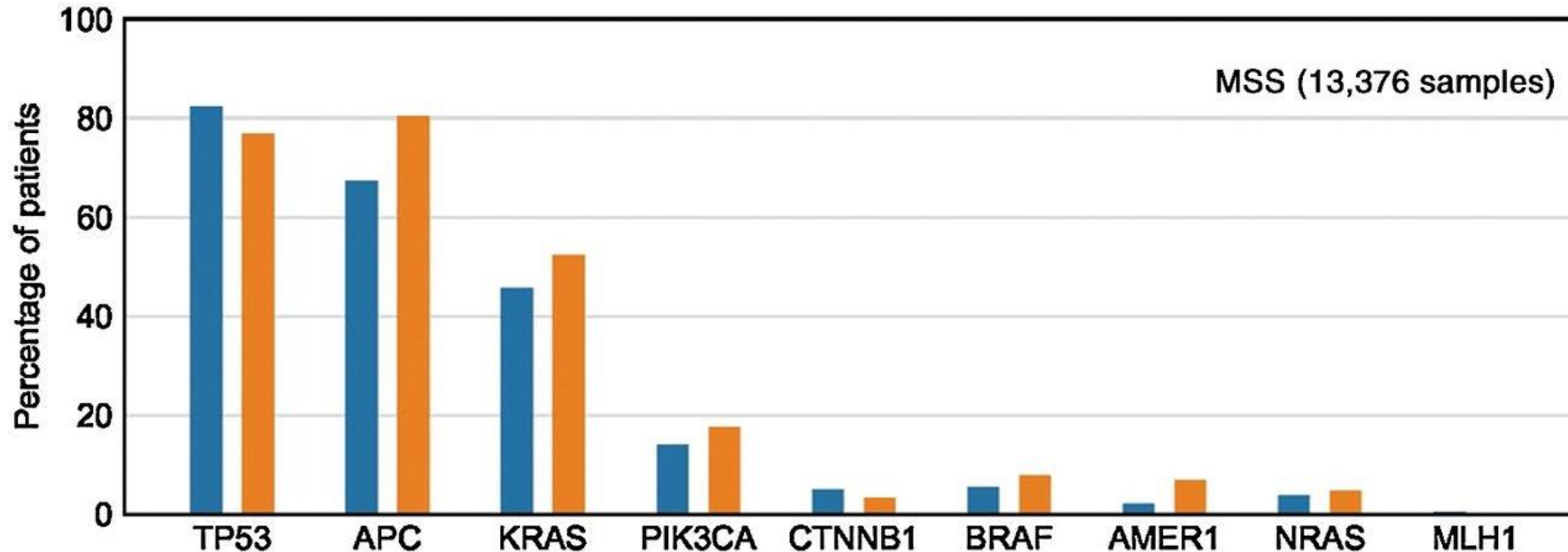
or related to underlying biology (right and left colon have separate embryonic origins)?

Molecular features



Germline cancer risk syndromes are overrepresented in EO-CRC, but *sporadic* cancers account for increased incidence by birth cohort

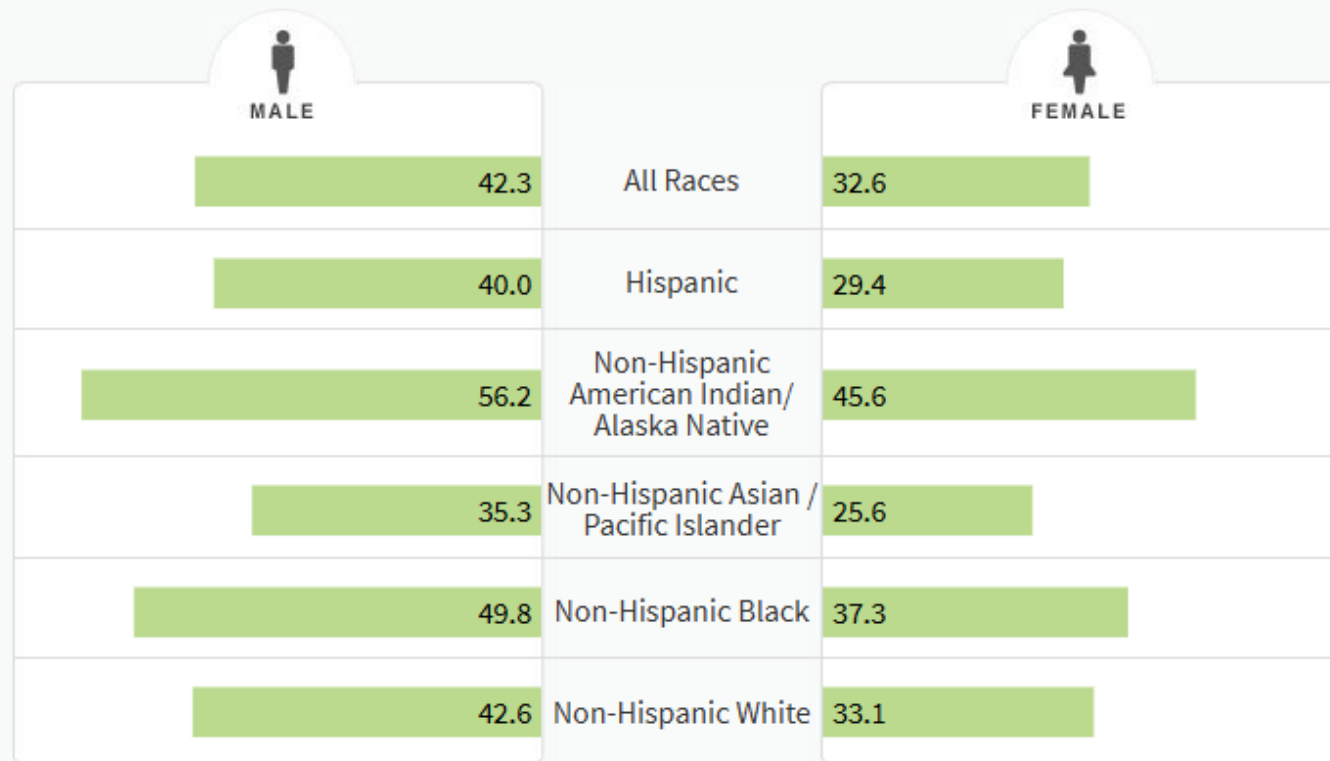
Lower abundance of KRAS mutation, but activation of downstream RAS/MAPK signaling



Colorectal Cancer Rates by Race/Ethnicity & Sex






Rate of New Cases per 100,000 Persons by Race/Ethnicity & Sex: Colorectal Cancer



SEER 21 2018-2022, Age-Adjusted

Screening



	 USA			 Asia-Pacific	 Europe
	American College of Gastroenterology	American Cancer Society	US Preventative Service Task Force and US Multi-Society Task Force	Asia Pacific Colorectal Cancer Working Group	European Council
Age to start and cease screening	<ul style="list-style-type: none"> Start screening at age 45 years Stop screening at age 75 years Individualise decision to continue screening for patients aged >75 years 	<ul style="list-style-type: none"> Start screening at age 45 years Stop screening at age 75 years Individualise decision to continue screening for patients aged 76–85 years No screening for patients aged >85 years 	<ul style="list-style-type: none"> Start screening at age 45 years Stop screening at age 75 years Individualise decision to continue screening for patients aged 76–85 years No screening for patients aged >85 years 	<ul style="list-style-type: none"> Start screening at age 50 years Stop screening at age 75 years 	<ul style="list-style-type: none"> Start screening at age 50 years Stop screening at age 75 years
Screening age modality	Structural exam	<ul style="list-style-type: none"> Colonoscopy every 10 years CT colonography every 5 years Flexible sigmoidoscopy every 5–10 years 	<ul style="list-style-type: none"> Colonoscopy every 10 years CT colonography every 5 years Flexible sigmoidoscopy every 5 years 	<ul style="list-style-type: none"> Colonoscopy every 10 years CT colonography every 5 years Flexible sigmoidoscopy every 5 years, or every 10 years with FIT every year 	<ul style="list-style-type: none"> Colonoscopy every 10–20 years Flexible sigmoidoscopy interval not suggested
	Stool-based	<ul style="list-style-type: none"> Multitargeted stool DNA test every 3 years FIT every year 	<ul style="list-style-type: none"> FIT every year Highly sensitive gFOBT every year Multitargeted stool DNA test every 3 years 	<ul style="list-style-type: none"> FIT every year gFOBT every year Multitargeted stool DNA test every 1 or 3 years (as suggested by manufacturer) 	<ul style="list-style-type: none"> FIT every 12 years gFOBT every year

EO-CRC occurs prior to recommended screening

How can we change recommendations to capture asymptomatic EO-CRC ?

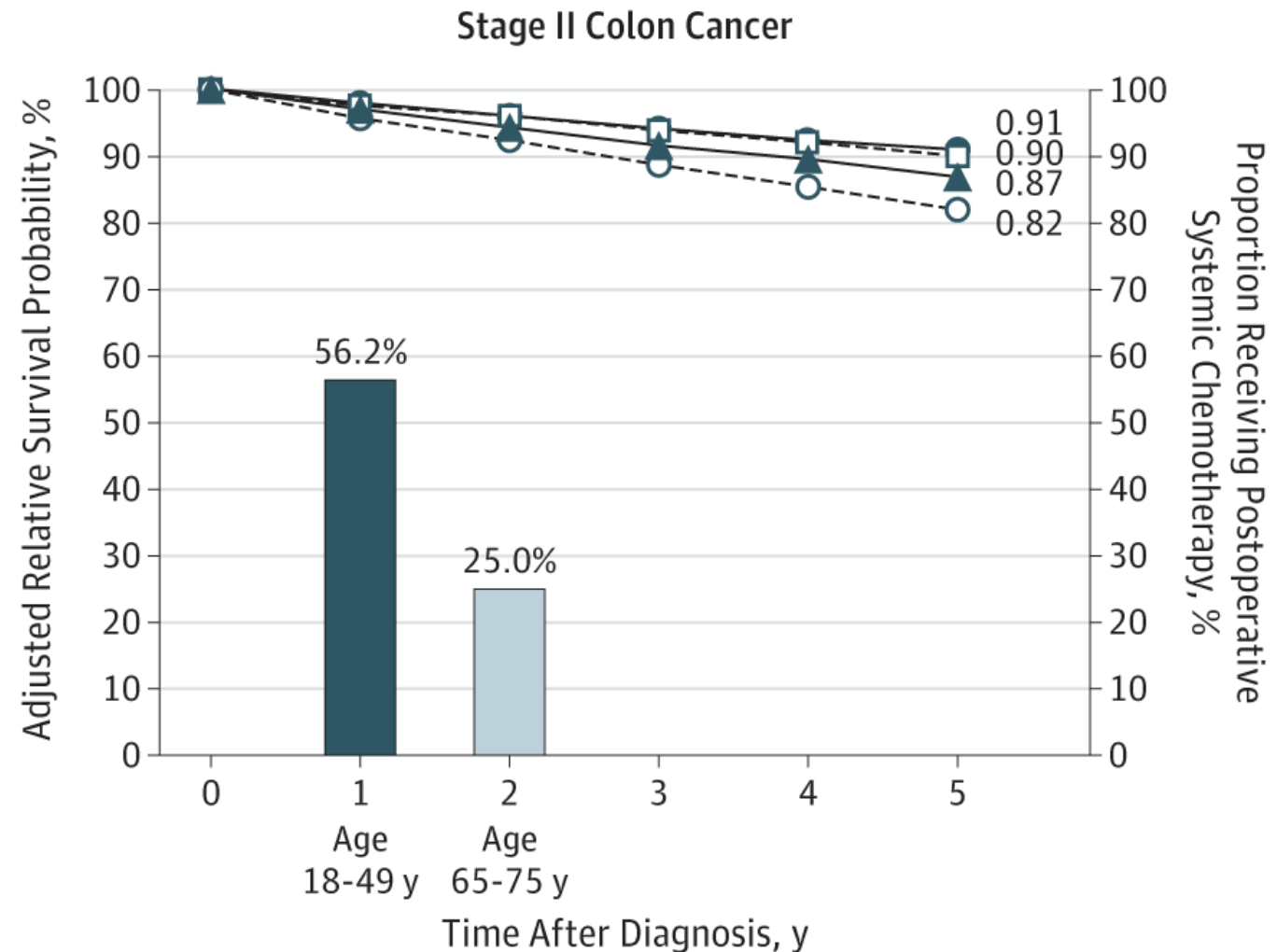
Treatment



Early age at onset is not considered in current treatment guidelines

Despite this, patients with EO-CRC are more likely to:

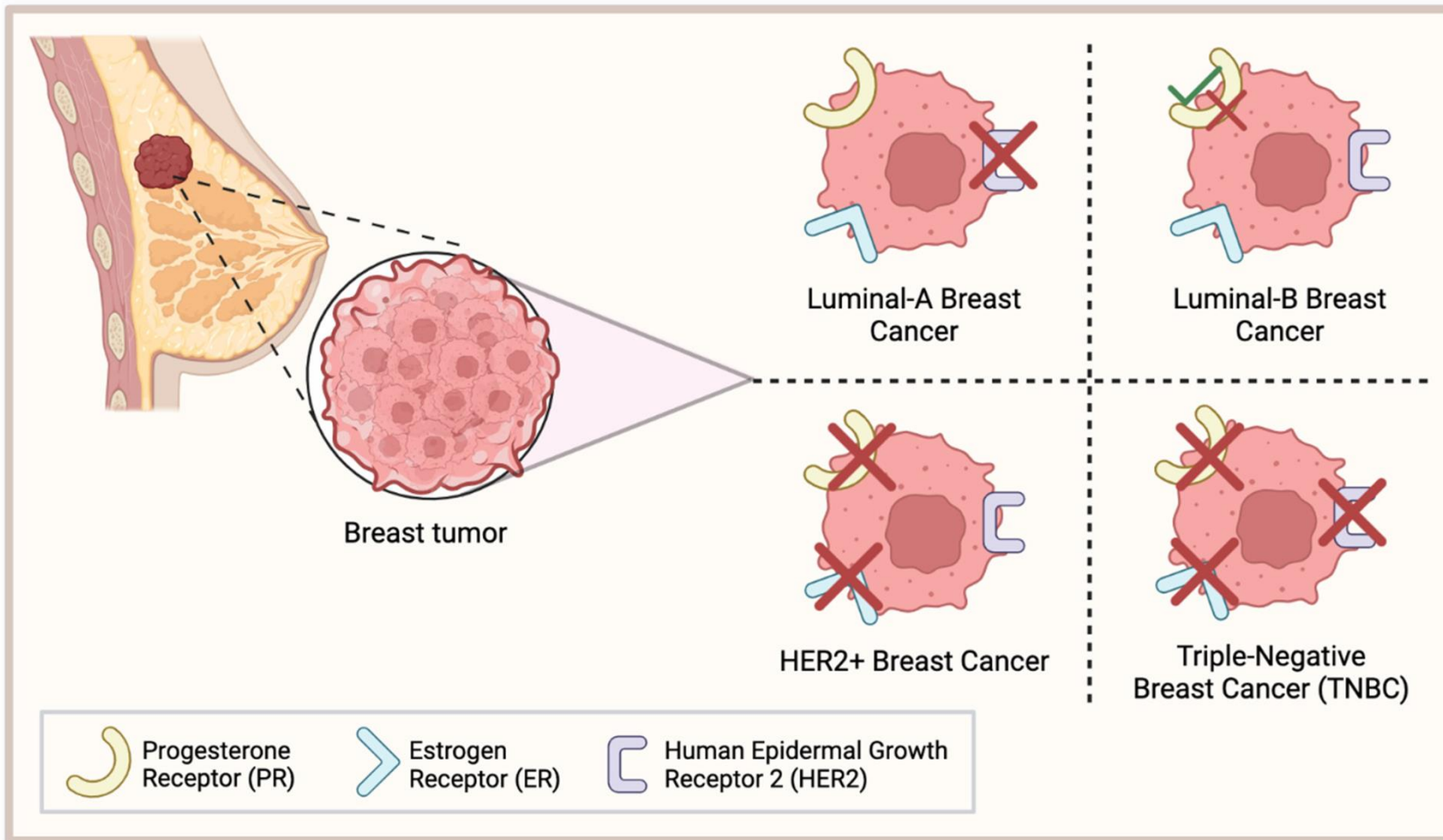
- Receive adjuvant/neoadjuvant therapy
- Receive intensified/multi-agent chemotherapy
- Receive treatment outside guidelines for early-stage disease





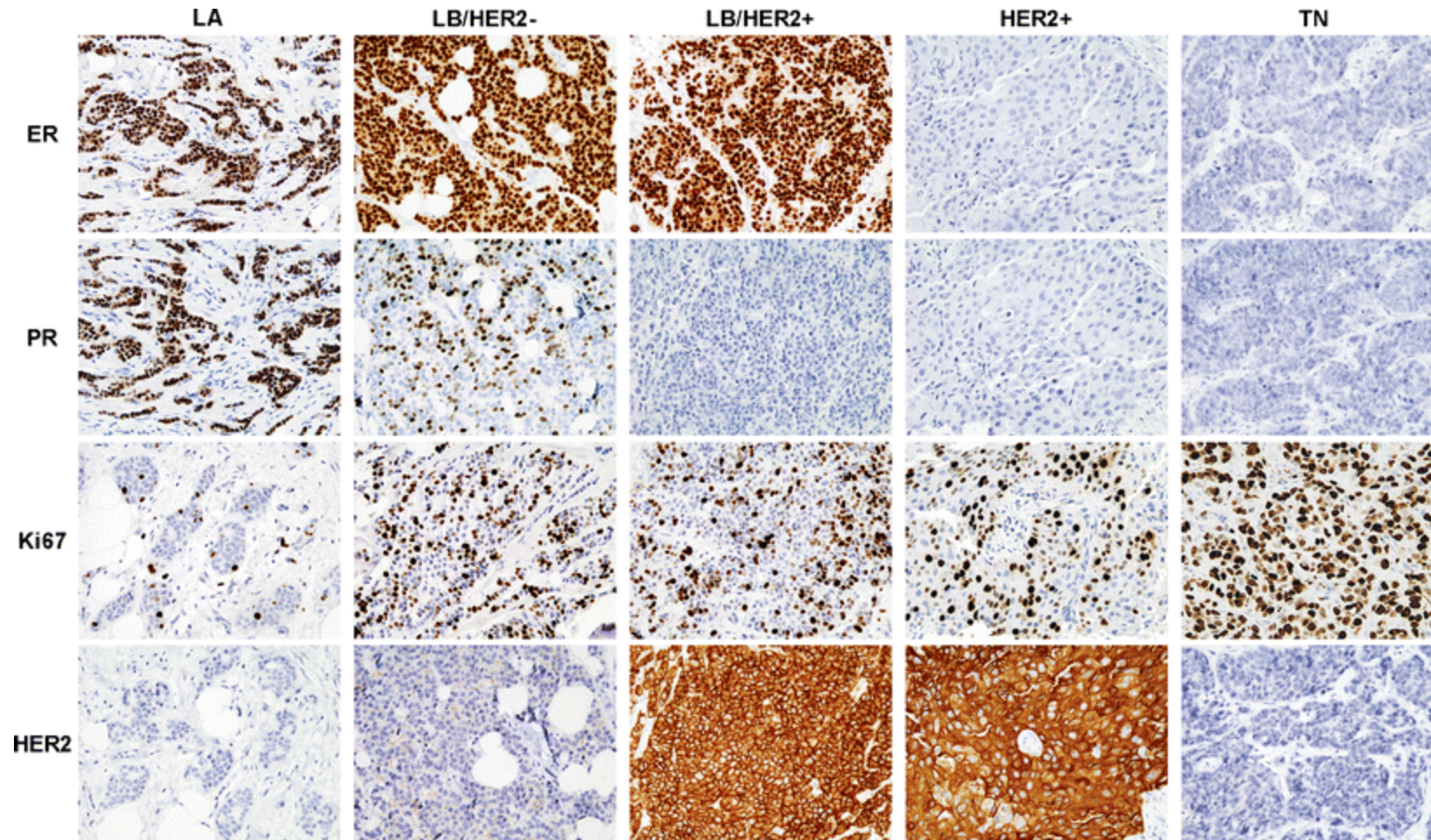
Triple-Negative Breast Cancer

TNBC



Triple-Negative Breast Cancer (TNBC) lacks expression of hormone receptors, making treatment difficult

IHC can help define these subtypes

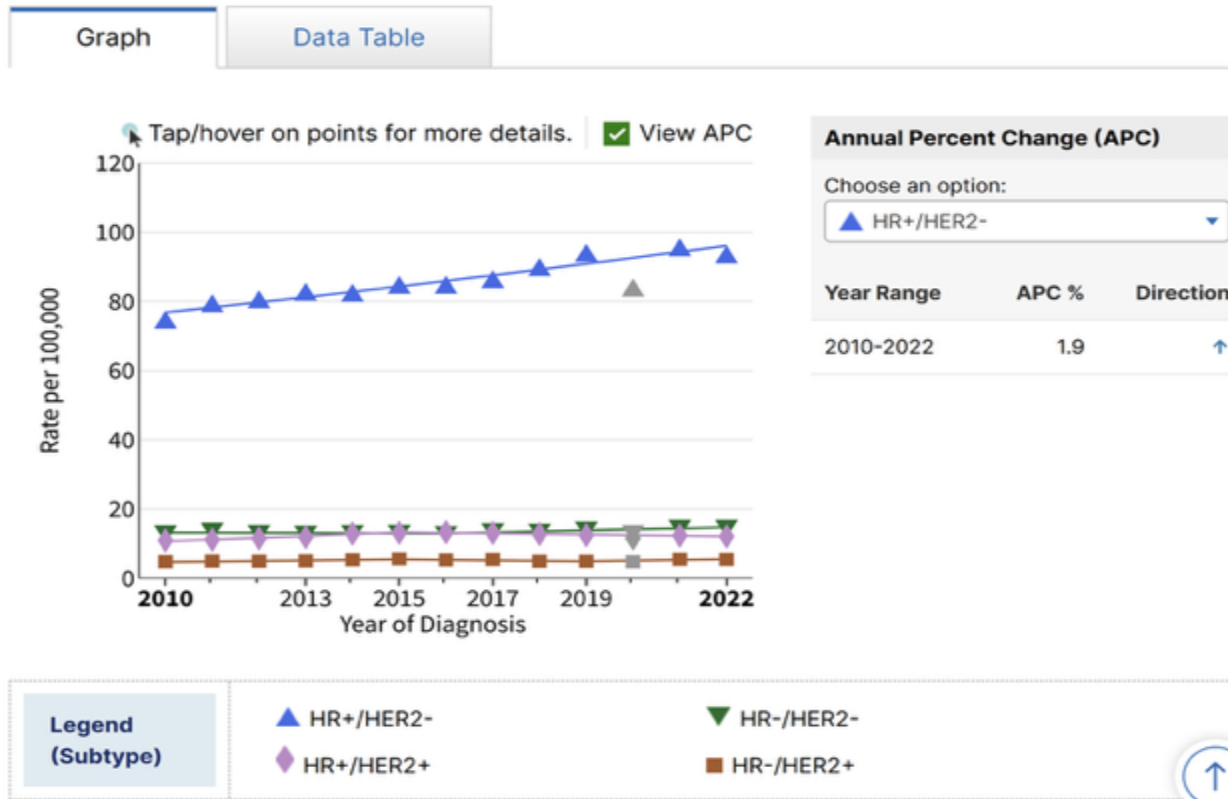


Ki67 = Proliferating cells

Breast Cancer Incidence



"Importantly, TNBC is overrepresented in patients with early-onset breast cancer, **afflicting 26% of this population** compared to 12% overall" - Zheng et al., 2022 (PMID 36387138)



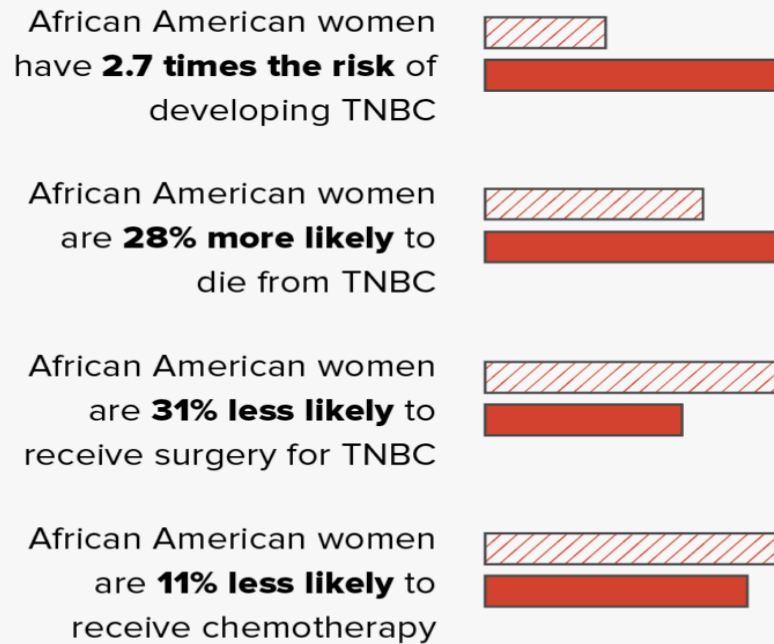
While global incidence of early-onset breast cancer is increasing, in the US TNBC rates are stable, with a slight increase in HR+/HER2- breast cancer instead

However...

Racial Disparity of TNBC

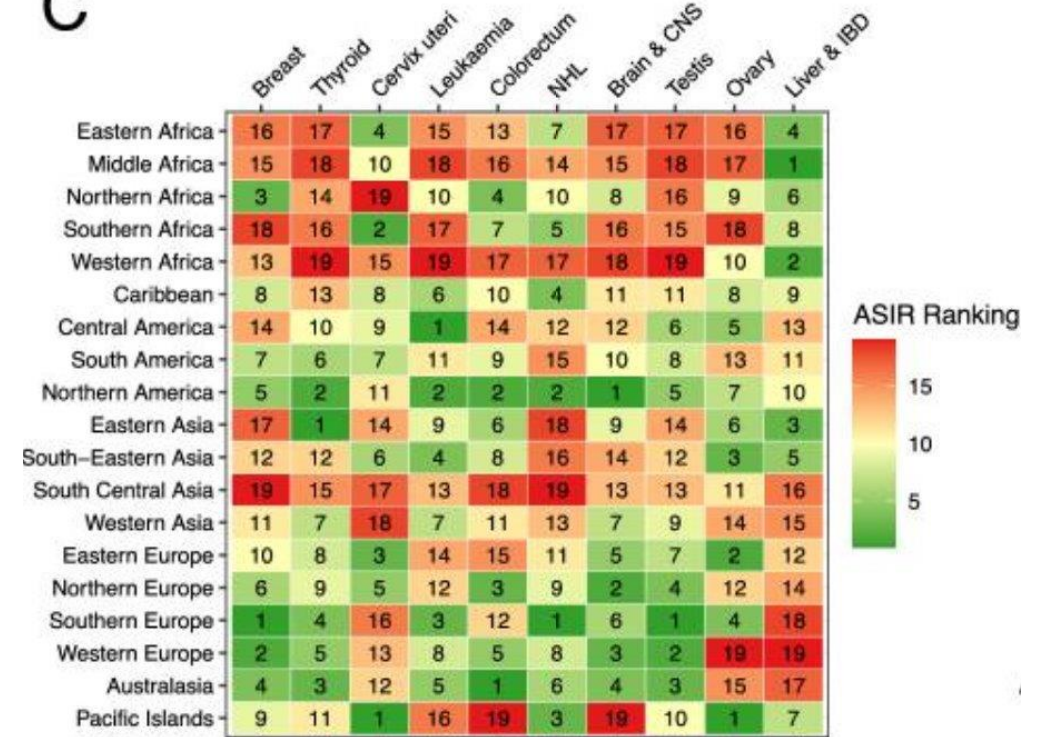


COMPARED WITH WHITE WOMEN



MEDICALNEWS TODAY

C



Ranking of AYA cancers across regions

Women of African descent remain at increased risk of TNBC, and AYA breast cancer burden is increased in African populations

Contributing Factors:



- The rise is not fully understood to date, but there are several potential contributors
 - **Obesity:** linked to increased TNBC, especially in premenopausal women
 - **Unopposed Estrogen:** earlier menarche, later childbirth, earlier or prolonged oral contraception use
 - **Alcohol Use:** linked to breast cancer development, although unclear link to TNBC
 - **Racial Disparities:** more common in Black women
- **Many other possibilities:** microbiome, hormone disruptors, diet, etc

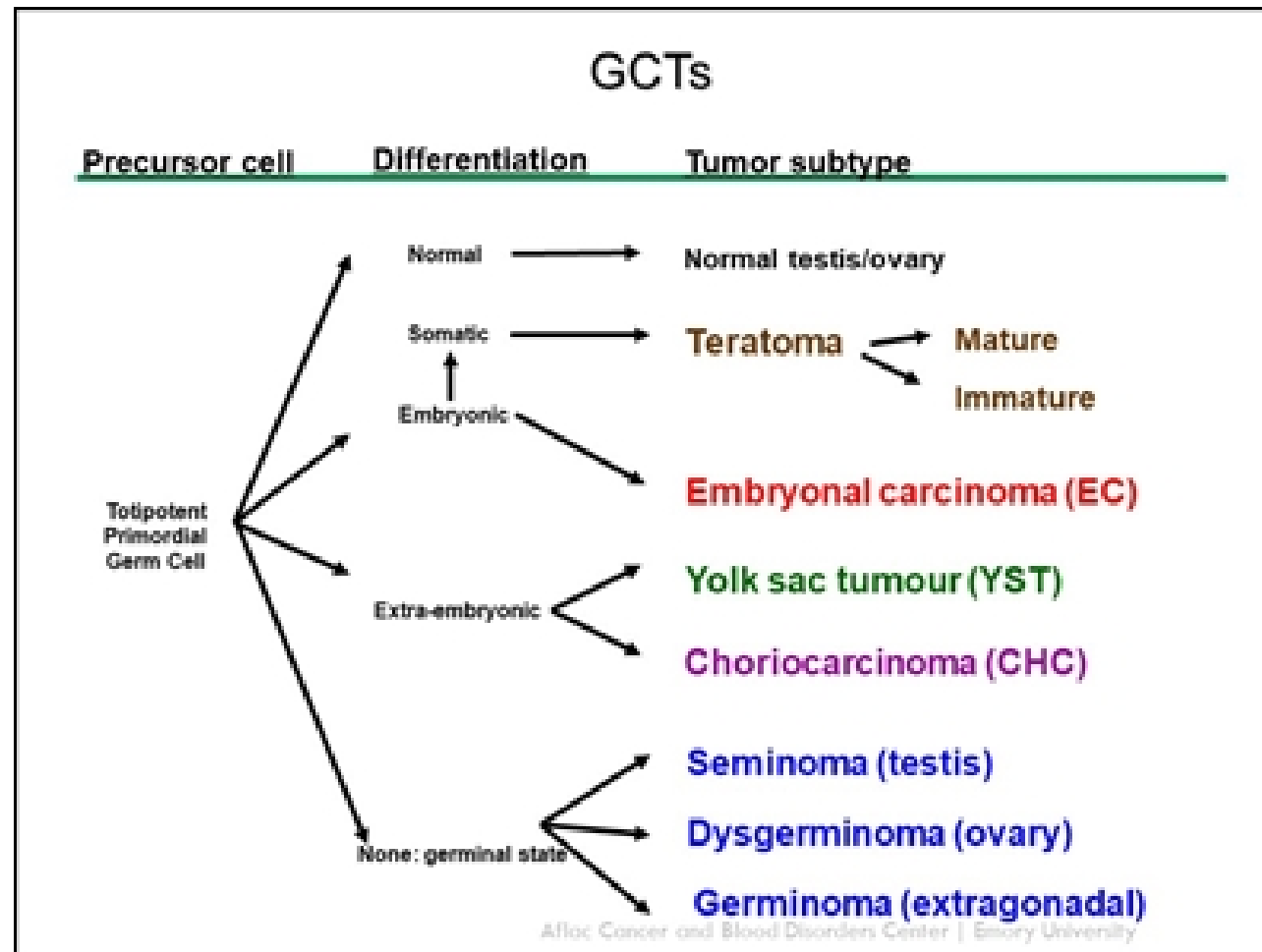


Nonseminomatous Germ Cell Tumors

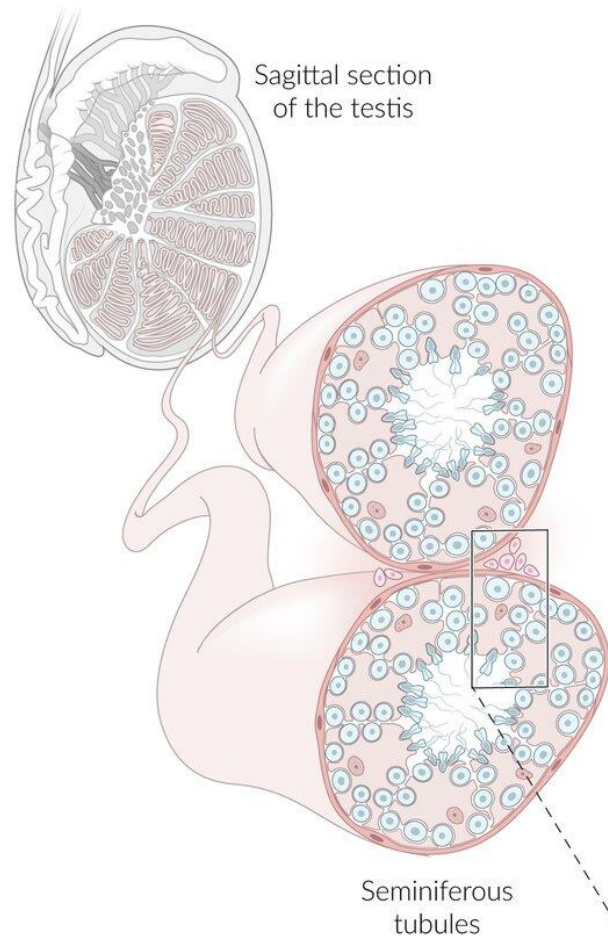
Germ Cell Tumors



Germ cell: A cell that develops into a reproductive cell (egg, sperm)



Testicular Cancer, Cells of Origin



Cell type	Distribution of primary tumors (%)	Tumor type
Leydig cells	Non-germ cell tumors (5%)	Leydig cell tumor
Sertoli cells		Sertoli cell tumor
Germ cells	Germ cell tumors (95%)	Seminoma
		Nonseminomas: Embryonal carcinoma Teratoma Testicular choriocarcinoma Yolk sac tumor

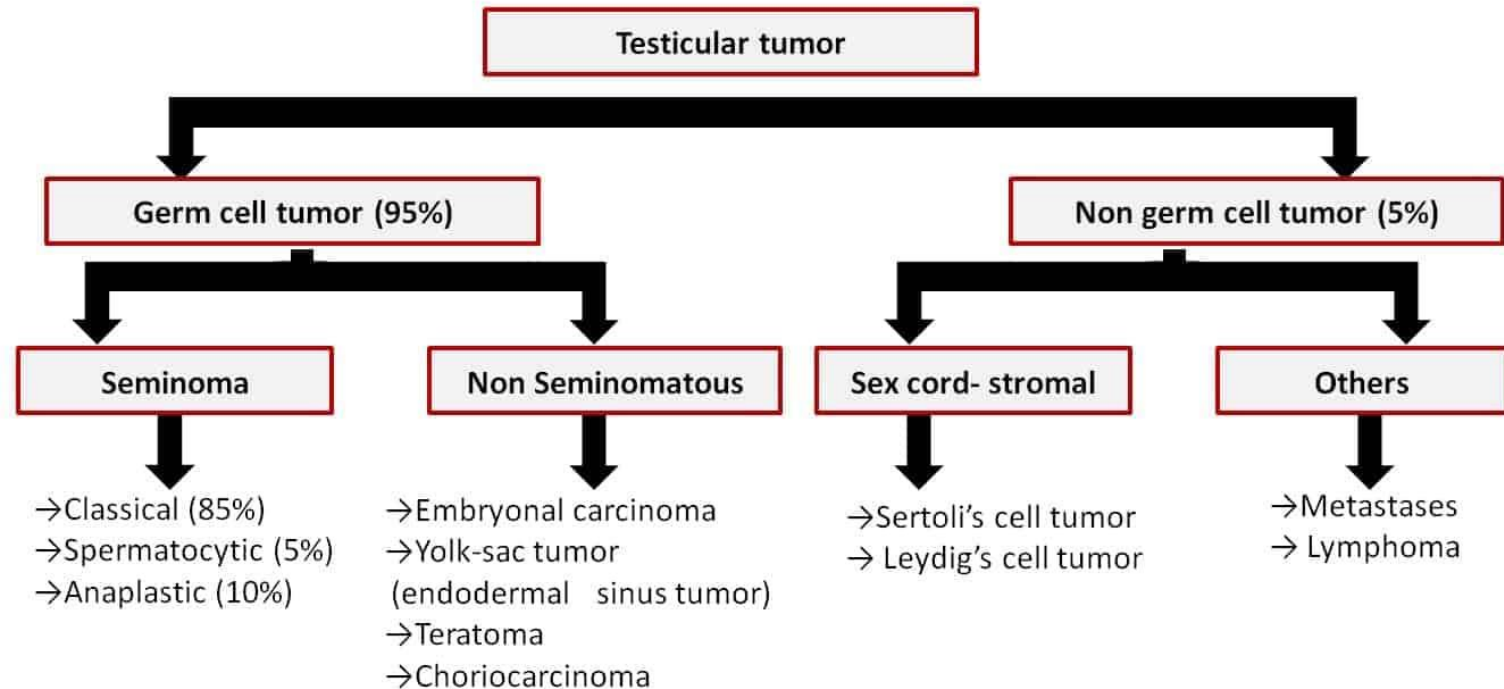
Non-seminomatous Germ Cell Tumors



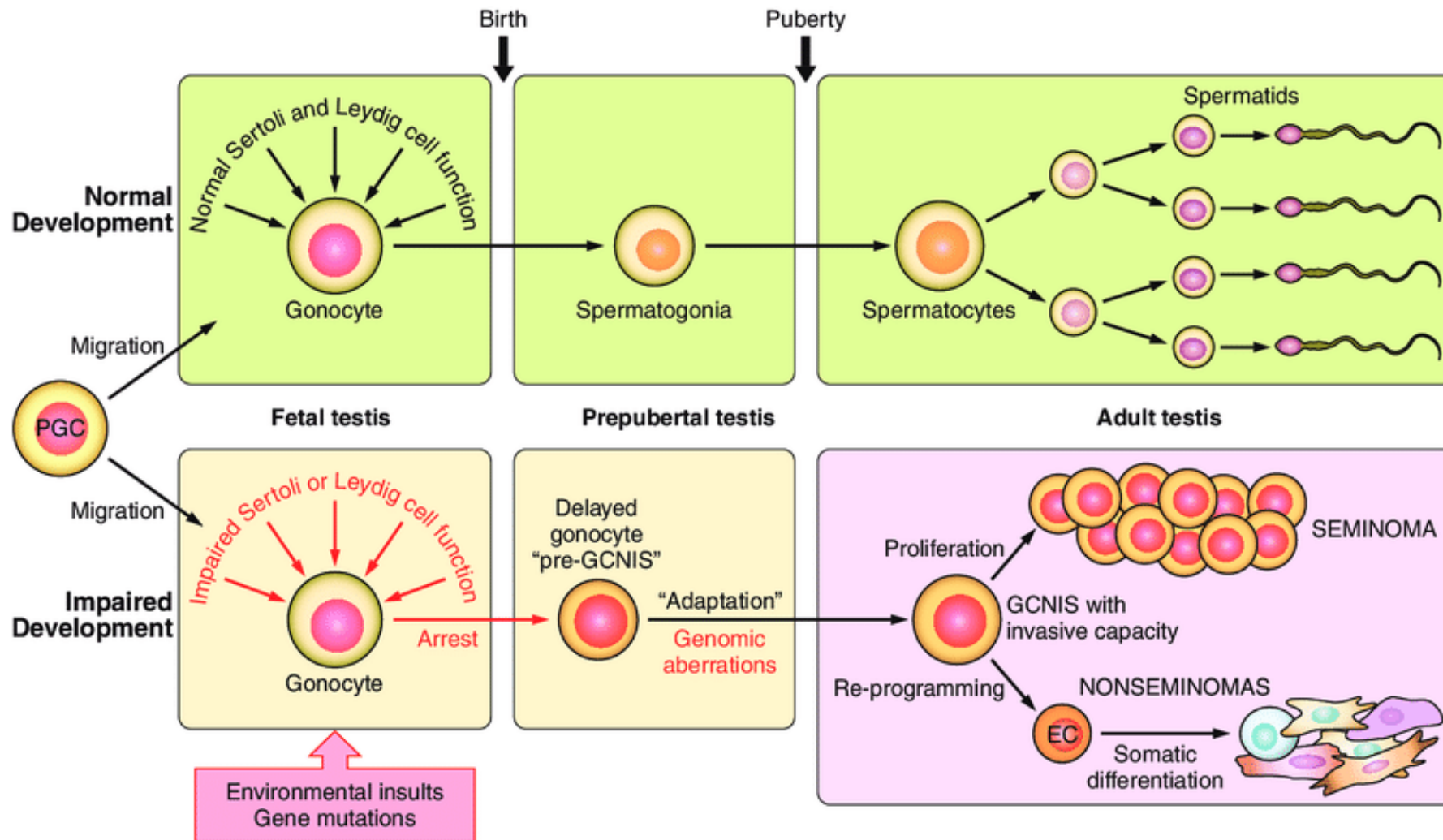
- **Seminoma:** Comes from a YOUNG germ cell that stays relatively immobile and grows slowly
- **Non-Seminoma:** Comes from more mature germ cells, is faster growing, and may spread to other parts of the body

Germ Cell Tumors

	Seminoma	Nonseminomatous
	localized to the testis	extension to the epididymis, spermatic cord, or scrotal sac
Stage	I or II	II or III
Metastasis	Lymphatic	lymphatic Hematogenous to lung or liver
Treatment	Radiotherapy	Chemotherapy
Prognosis	good	Depend on the tumor type



Pathogenesis



"[Nonseminomas] arise from a precursor lesion, germ cell neoplasia in situ (GCNIS), which develops from arrested spermatocytes that failed to differentiate."

Matsumoto et al., 2010

DOI: 10.1093/humrep/de.25.s1.001

<https://www.ncbi.nlm.nih.gov/books/NBK568754/>

Treatment



- Surgical removal of the afflicted teste (radical orchiectomy)
 - Curative of 75% of stage I disease
- Primary Retroperitoneal Lymphadenectomy
 - Surgical removal of the draining lymph nodes
- Active surveillance
 - May have missed micrometastases
- Higher-risk disease or relapse may receive neo-adjuvant or adjuvant chemotherapy*
 - NSGCTs are the most sensitive testicular cancers to cisplatin-based chemotherapy

Age is considered for administration of pediatric vs adult chemotherapy regimens*

Increasing incidence



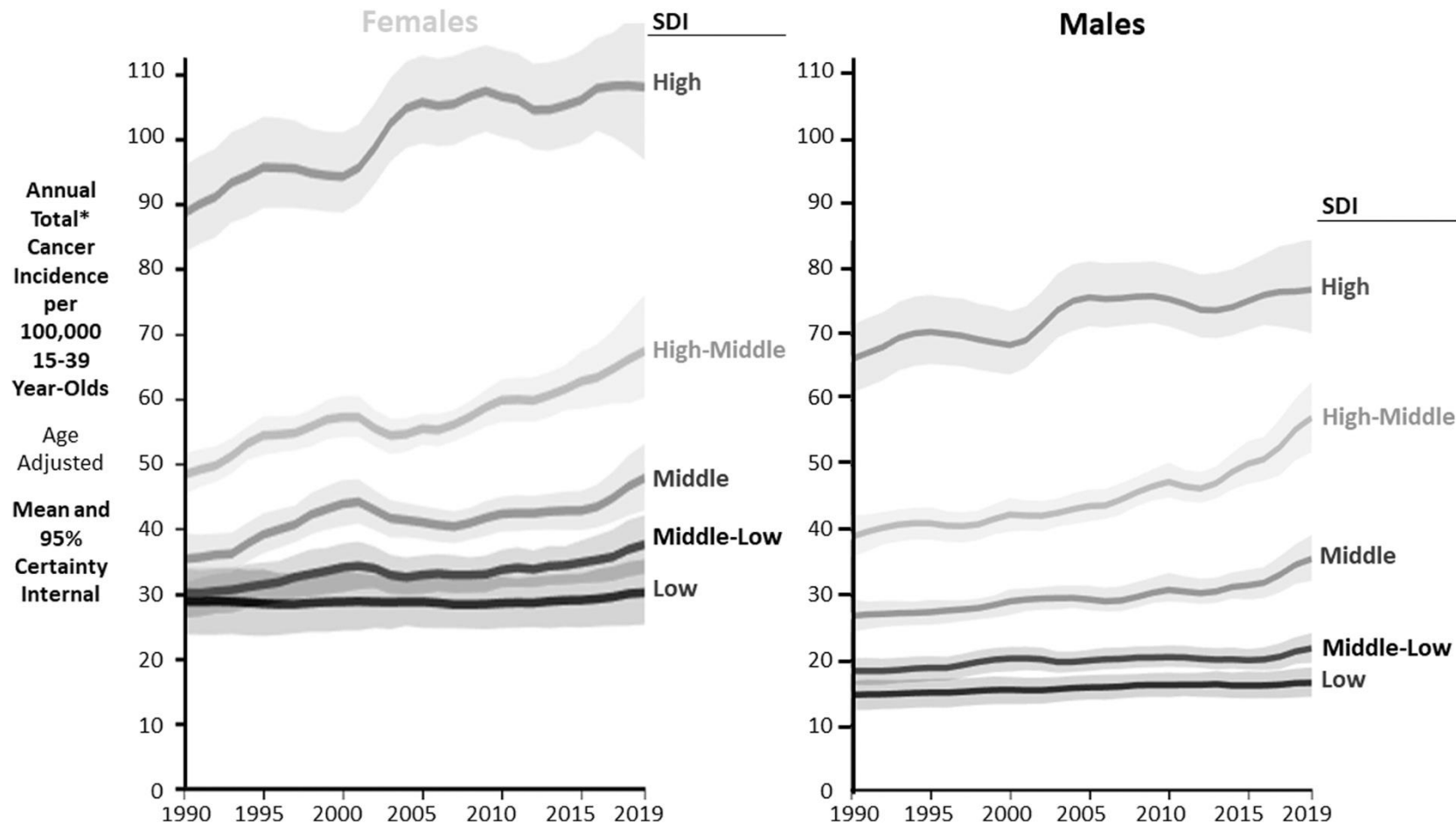
Cannabis use linked to increased risk of GCTs, but mechanisms remain unknown



Why is AYA cancer increasing in incidence?

What trends can we identify, and what do we still not know?

Environmental Factors: Sociodemographic Index

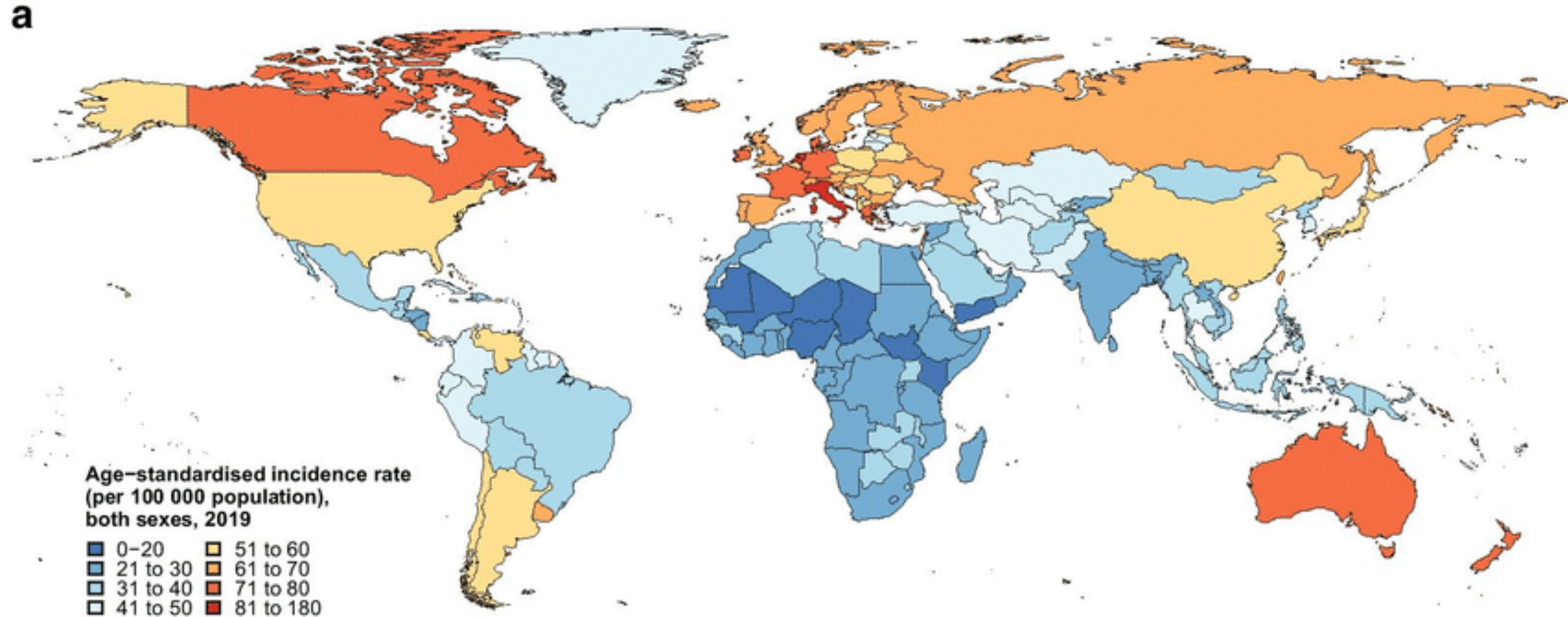


AYA Cancer rates
highest in high
income countries

FIG. 4. Annual World Total* Cancer Incidence, 1990–2019, Age 15–39 Years, by Sociodemographic Index (SDI).

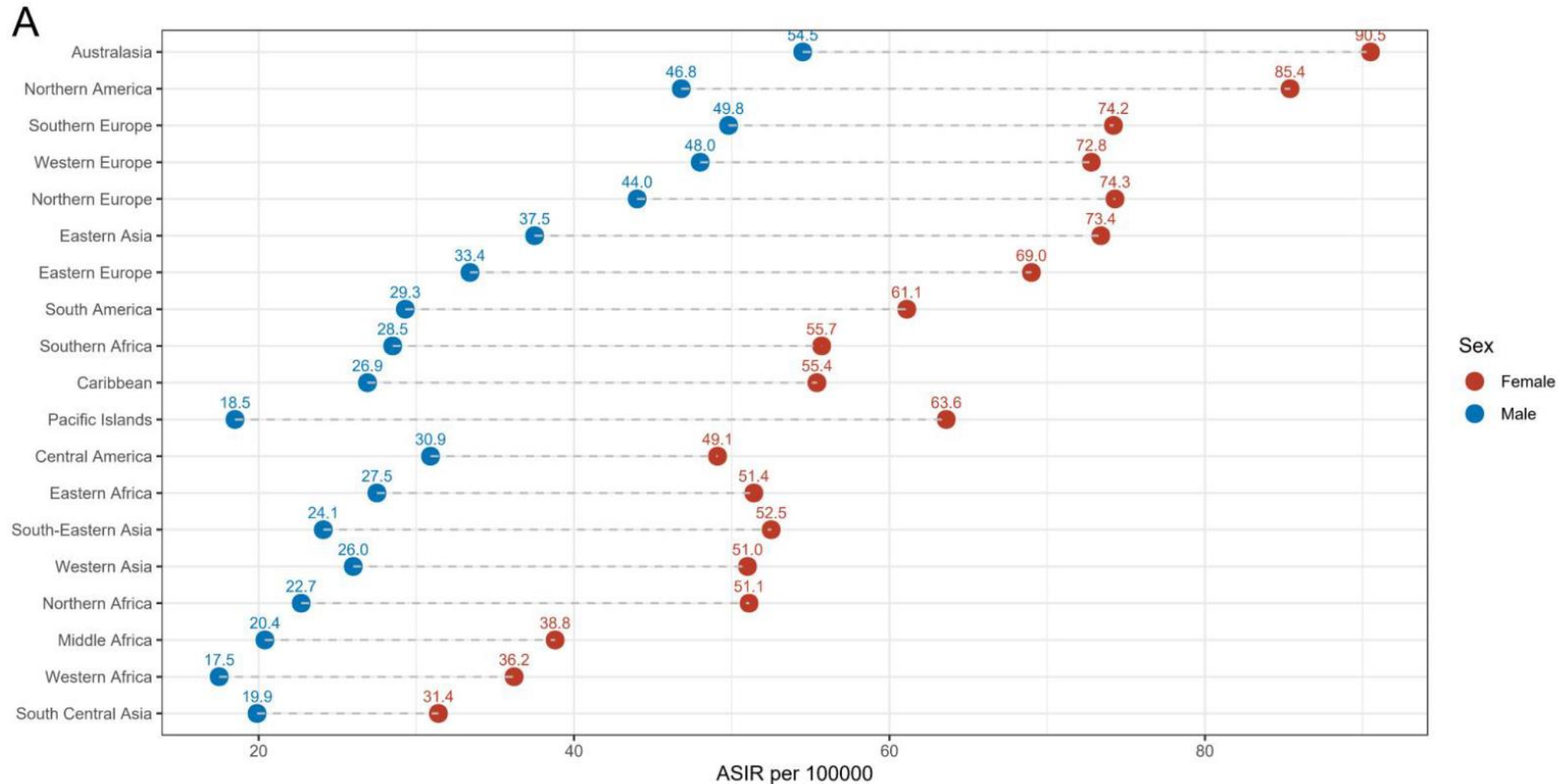
*Total according to IHME includes several neoplasms that are not invasive.

Environmental Factors: Sociodemographic Index

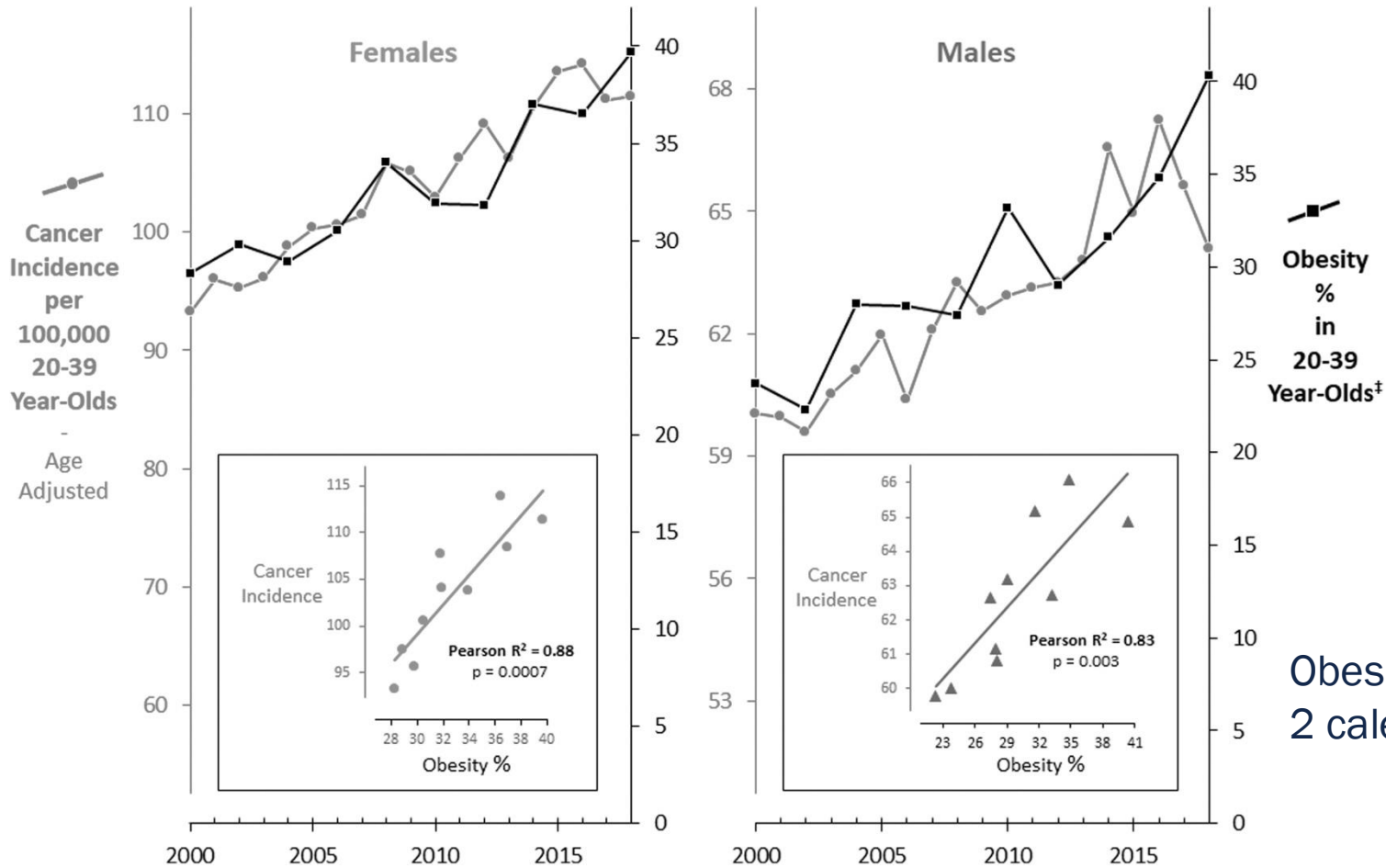


Burden of AYA cancers across 204 countries and territories in both sexes, 2019. Age-standardized rates of incidence

Environmental Factors: Sociodemographic Index & Gender



Environmental Factors: Obesity



AYA Cancer rates highly correlated with increasing obesity prevalence

Obesity = BMI >30 kg/me for 2 calendar year intervals

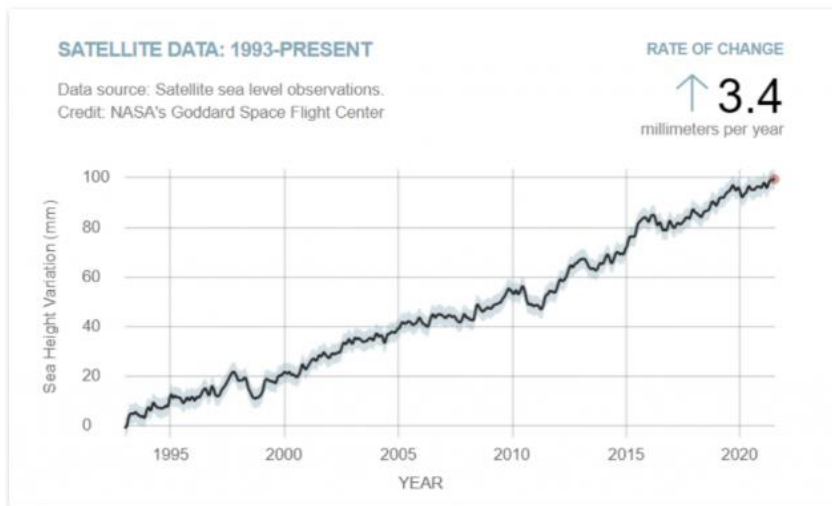
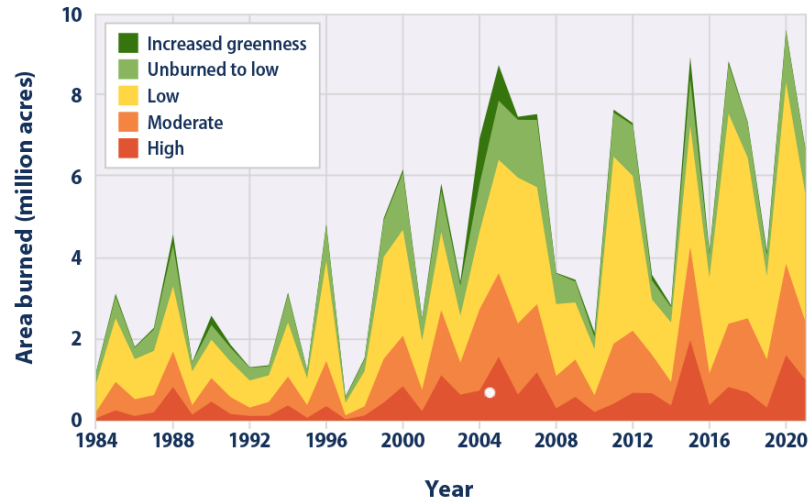
FIG. 7. Correlations of Annual Cancer Incidence in 20–39-Year-Olds, U.S. SEER17, and Obesity Rate in 20–39-Year-Olds, United States, by Sex.

Insets: Annual cancer incidence versus national obesity proportion.

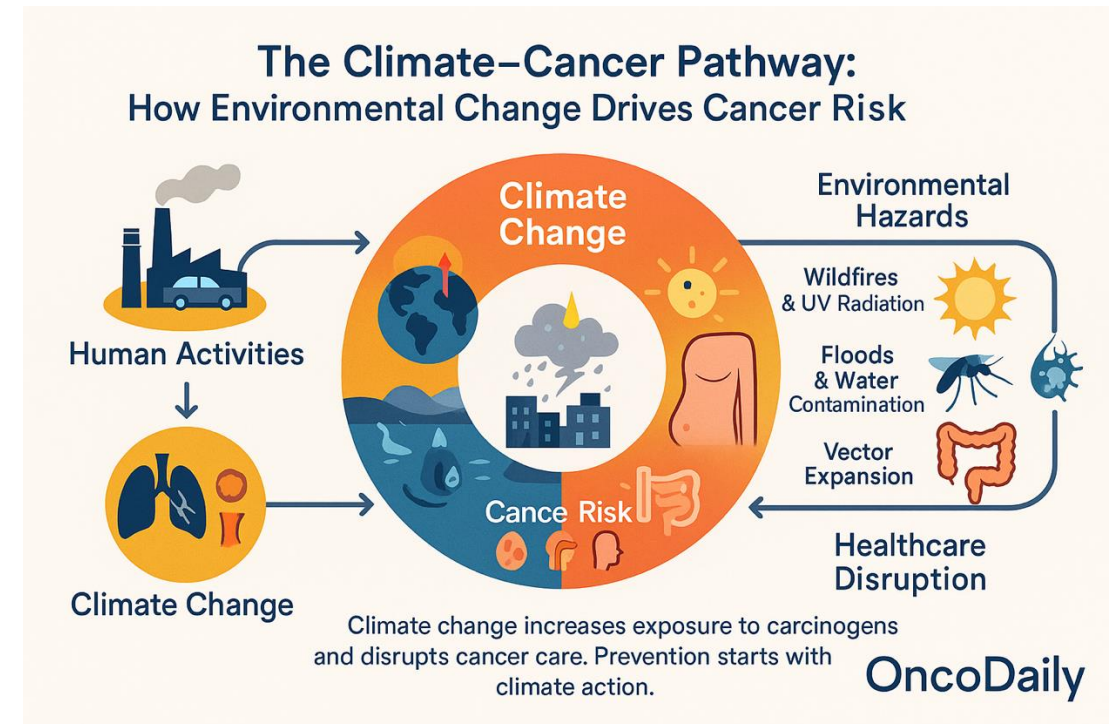
Environmental Factors: Climate Change



Figure 3. Damage Caused by Wildfires in the United States, 1984–2021



Graph showing time on the horizontal axis and sea level on the vertical axis (from NOAA, 2021).



Why is cancer increasing in incidence in younger populations?



- “Chronic inflammation: The body’s response to injuries and “invaders” can be caused by low physical activity, obesity, chronic stress, prolonged infections or chronic exposure to toxins.
- Later-in-life birth and/or having fewer children: Reproductive factors can lead to a slightly higher breast, ovarian or endometrial cancer risk.
- Gut microbiome changes: When this delicate network of bacteria is thrown off balance — possibly by processed foods, microplastics or other substances — it could be easier for tumors to grow.
- Healthcare disparities: Inequities in care can limit access to healthy food and timely treatment.”

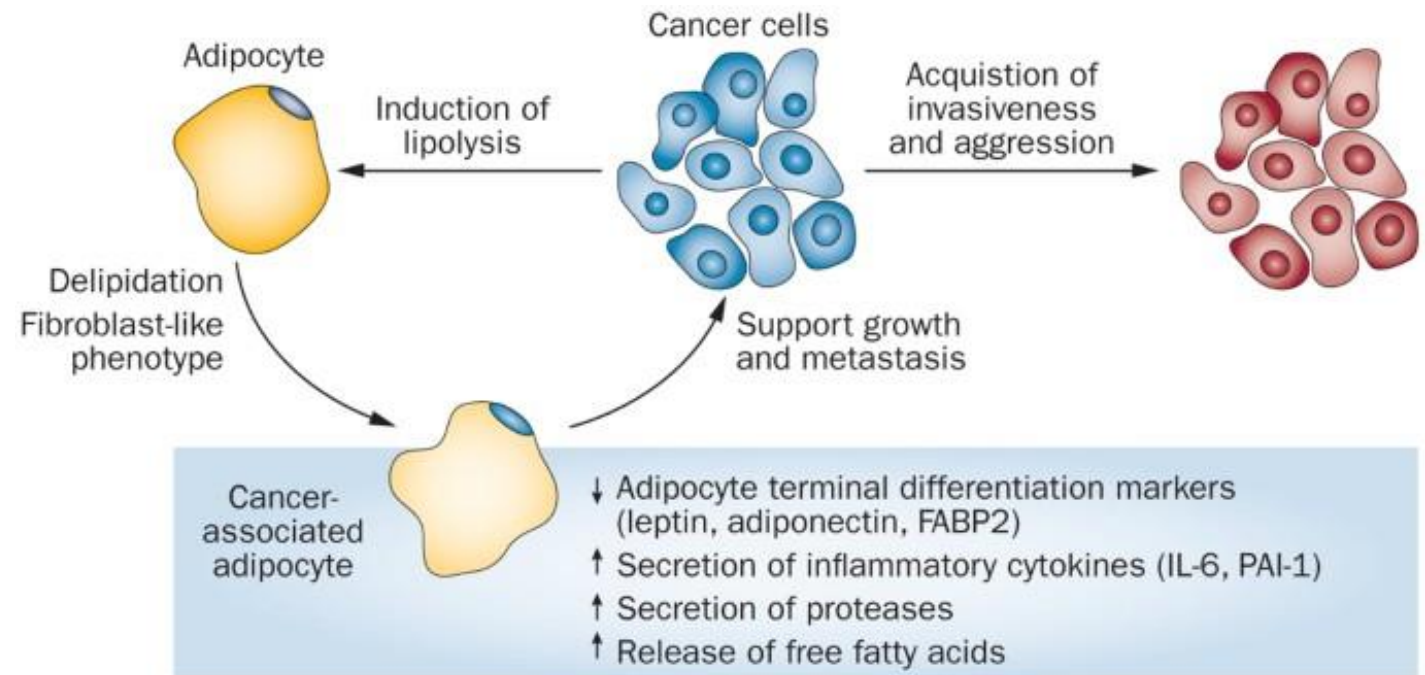
-UChicagoMedicine, 2024

Links between diet and cancer risk



What biological mechanisms contribute to this link?

- Microbiome alterations
- Adipocyte participation in cancer & TME
- Chronic inflammation
- Hormone signaling



Health Disparities



- Ample evidence of racial and sociodemographic gaps for young adults (YAs) with cancer
- **Access:** gaps in insurance coverage, lack of primary care
- **Health system not designed for YAs:** concerns dismissed, diagnoses delayed, inflexible with childcare, education, career
- **Finances:** lack of accrued wealth, YAs face greater financial “toxicity” from cancer treatment, persists life long
- **Structural Inequities:** these barriers are compounded for Black, rural, LGBTQ individuals

Takeaways



- Some adolescent and young adult (AYA) cancers are increasing in incidence
 - Testicular, colorectal, breast (know the features of these cancers we discussed!)
- While many of these increases can be linked to environmental and socioeconomic features, there are still many things we don't understand
 - Key contributors are lifestyle factors (diet, exercise, obesity), genetics, climate, and health disparities



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