Disparities in endometrial cancer outcomes - what more can we do?

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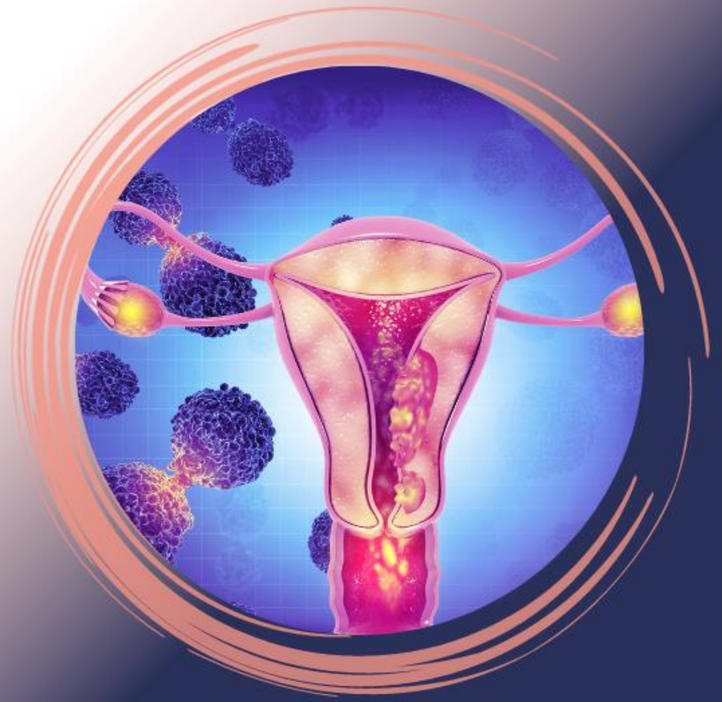
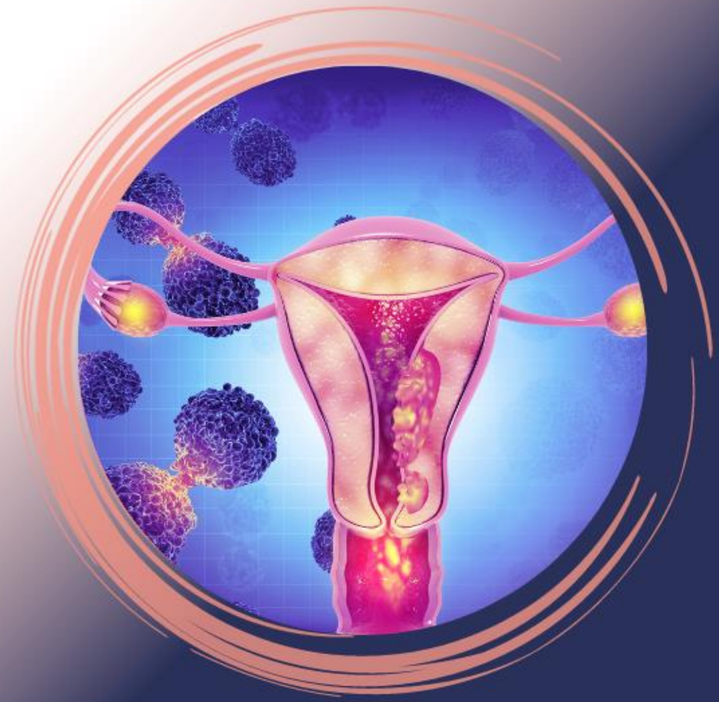


Agenda

- The present and the future of endometrial cancer worldwide
- Disparities in endometrial cancer outcomes
- Strategies to reduce mortality and improve treatment outcomes



The present and the future of endometrial cancer worldwide

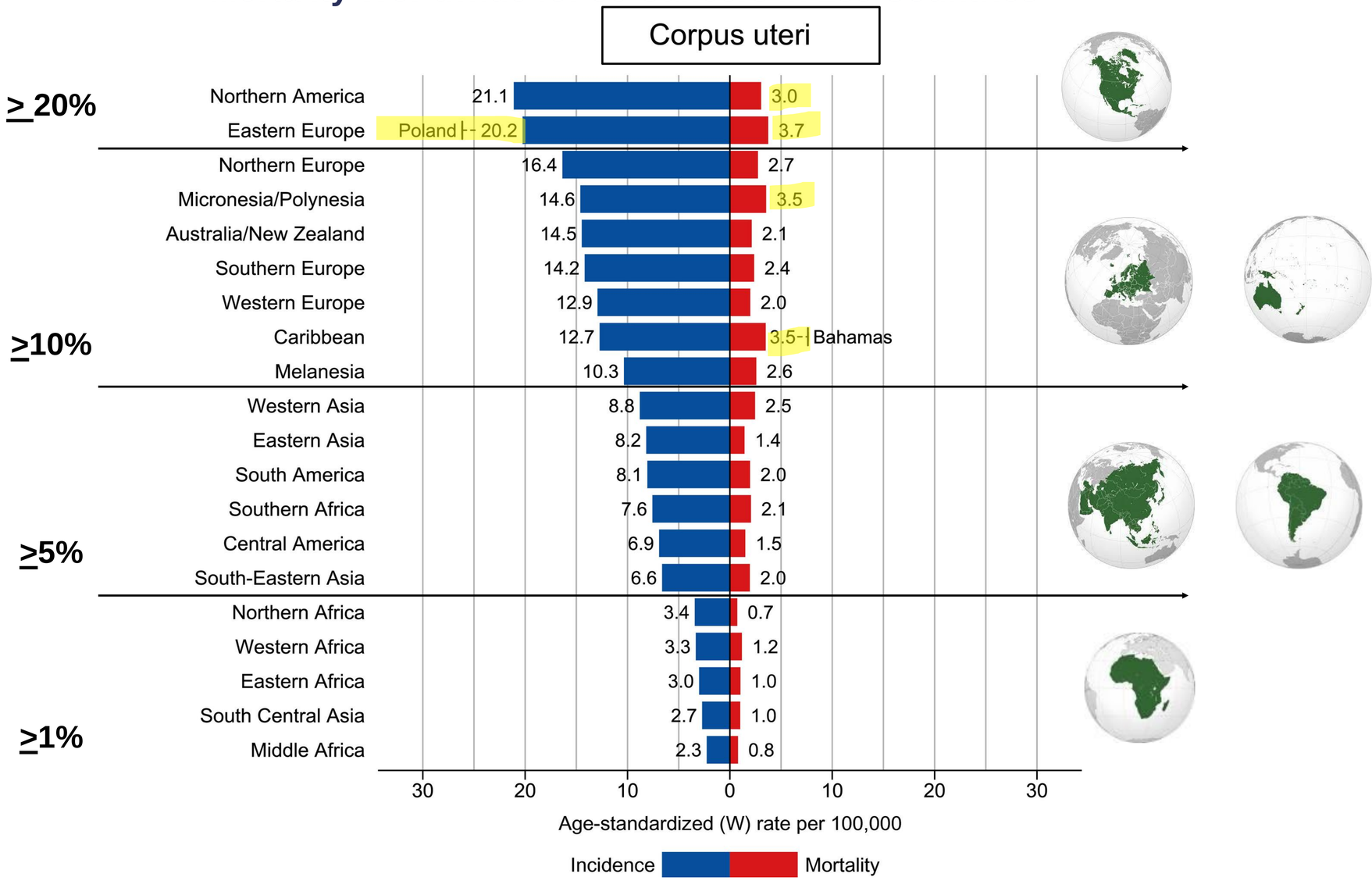
- Endometrial cancer is the **6th most commonly** occurring cancer in women, and the 15th most common cancer overall.
-
- **In 2020**, there were more than 417,000 new cases of endometrial cancer and 97,370 deaths worldwide

World Cancer Research Fund International

International Agency for Research on Cancer

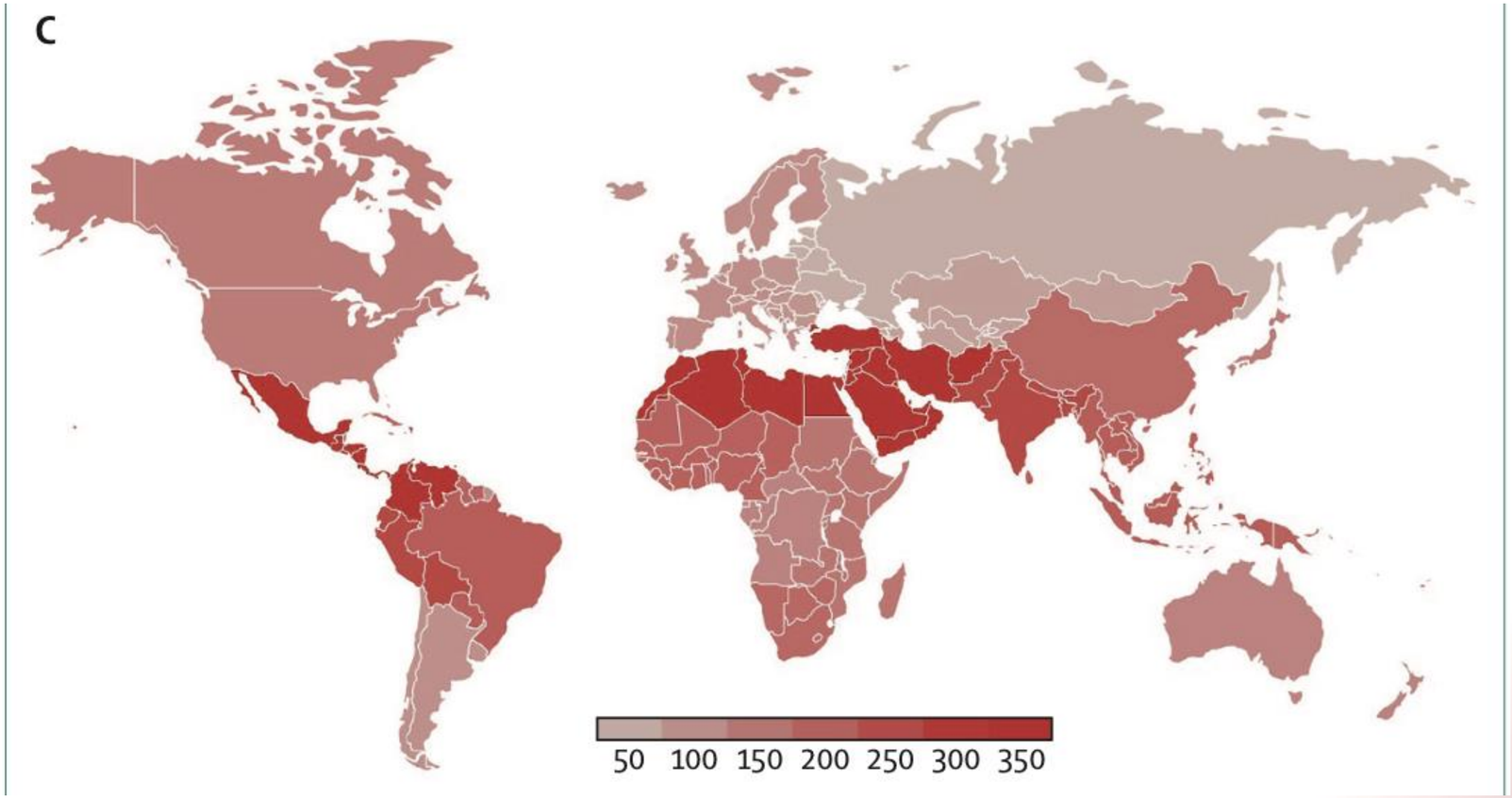
World Health Organization

Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries

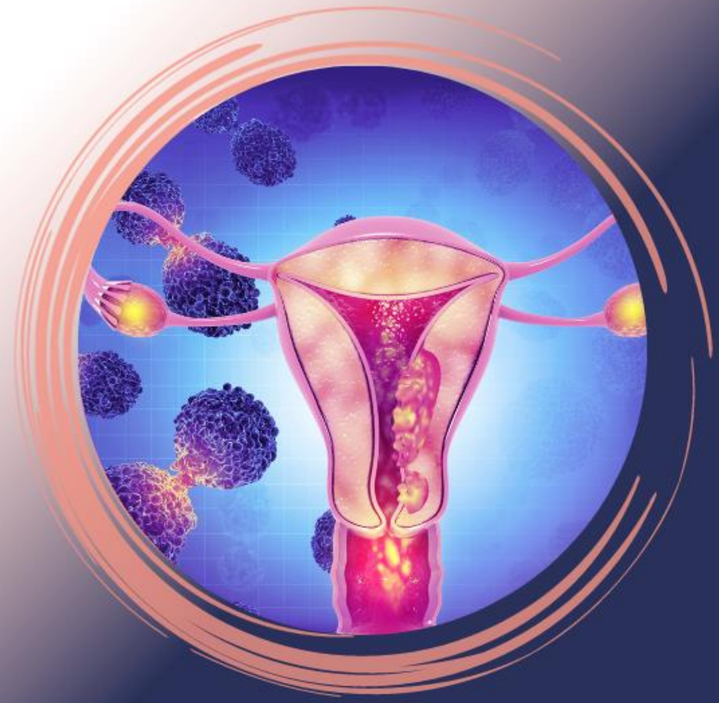


CA A Cancer J Clinicians, Volume: 71, Issue: 3, Pages: 209-249,
First published: 04 February 2021, DOI: (10.3322/caac.21660)

Global increase in endometrial cancer incidence 1990–2019



In many low-income and middle-income countries, the faster growing trend and a birth cohort effect reflect a change in lifestyle and a higher prevalence of risk factors (obesity and inactivity levels) in younger generations.

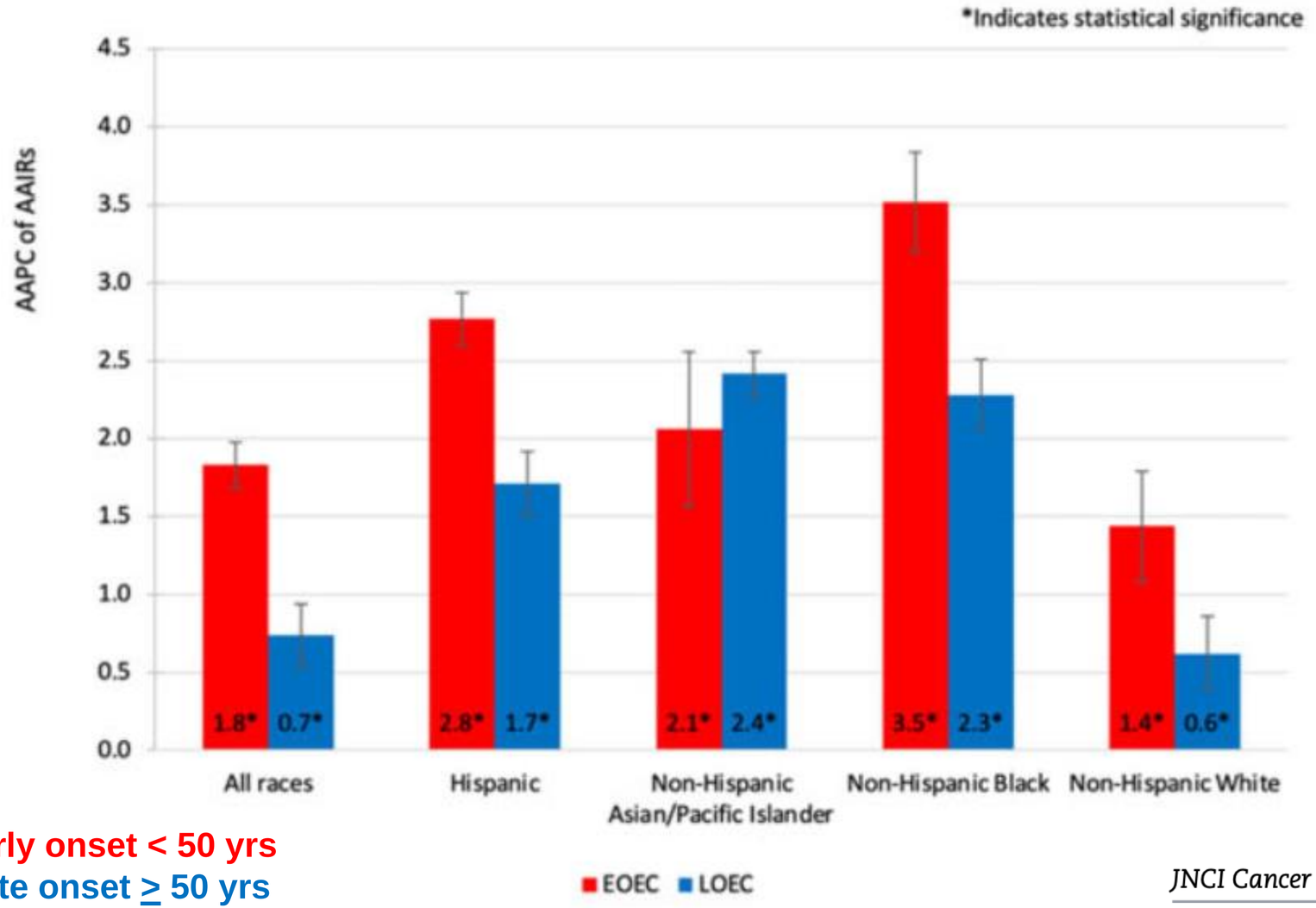


www.thelancet.com Vol 399 April 9, 2022

Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with endometrial cancer

- A rising trend in EC is being observed in several Asian countries.
- **In 2020,** the number of new cases was: 16,413 in India, 4,524 in Thailand, 4,374 in the Philippines, 3,425 in South Korea, 1,401 in Malaysia and 775 in Singapore.
- There is a higher proportion of **younger women** being diagnosed with EC **in China**, with 40% of patients diagnosed before their menopause, compared with <25% of Western women.

Average Annual Percent Change (AAPC) in annual age-adjusted incidence rates (AAIRs) [1995-2018]

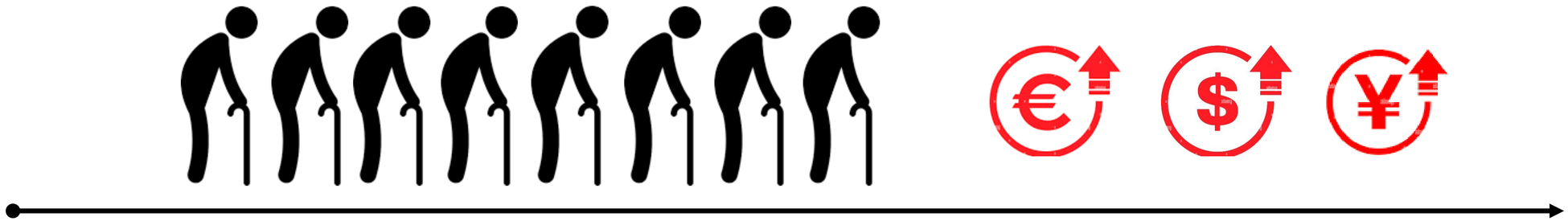


Public Use incidence dataset from the North American Association of Central Cancer Registries

Early onset < 50 yrs
Late onset ≥ 50 yrs

JNCI Cancer Spectrum, 2023, **7(1)**,
https://doi.org/10.1093/jncics/pkad001

Endometrial Cancer Projections

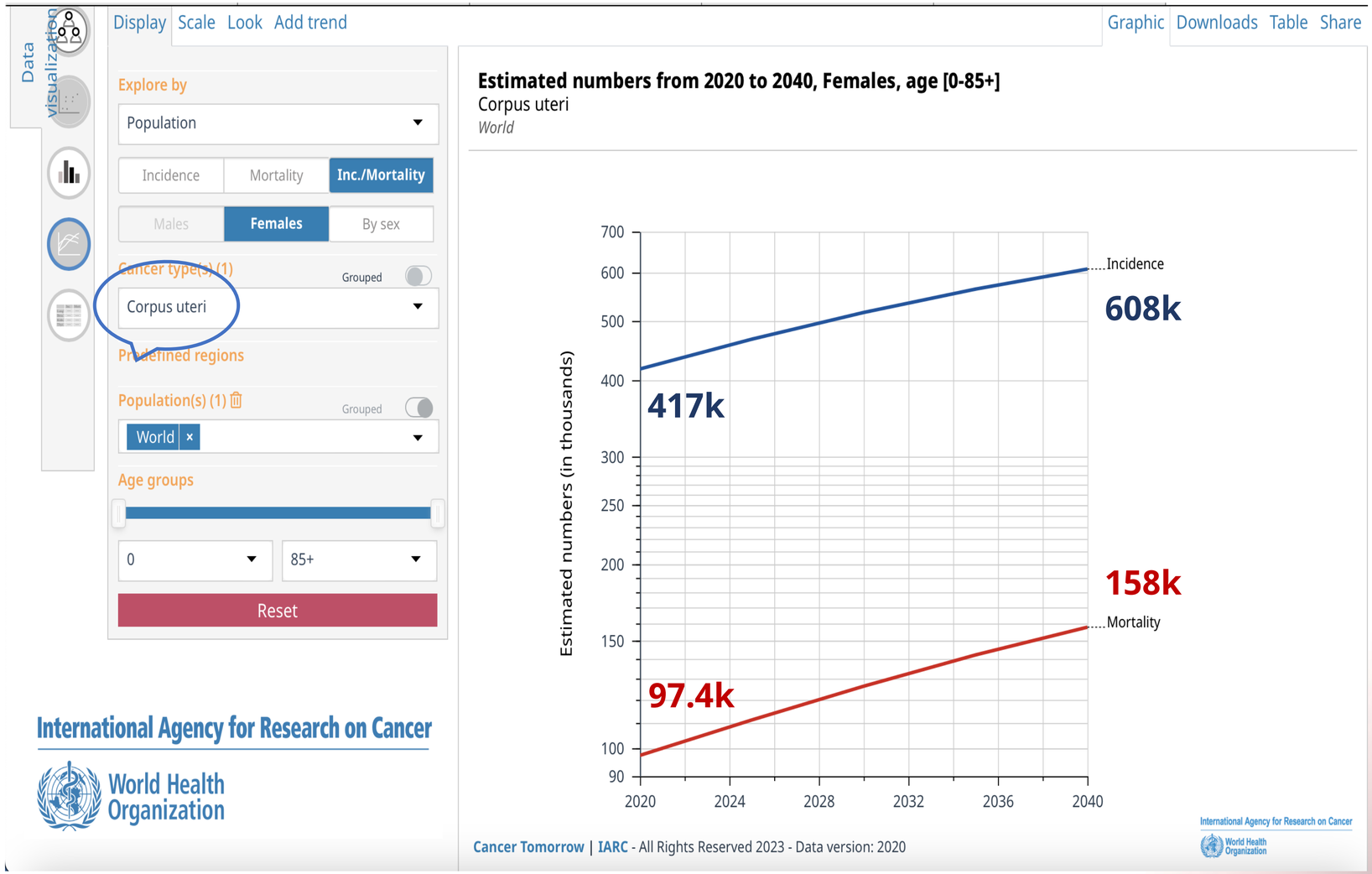


- **By 2040**, endometrial cancer is projected to be **the 3rd most prevalent** cancer and **the 4th leading cause** of cancer death in women worldwide.
- In USA, in the year 2040 alone, there may be over 100,000 new cases.
- In Australia, we obsrved a doubling of case numbers over the last 20 years, and globally, the rise in endometrial cancer diagnoses is projected to continue; estimates suggest another increase of over 50% by 2040.

World Cancer Research Fund International

NIH Return Home NATIONAL CANCER INSTITUTE Surveillance, Epidemiology, and End Results Program

ANZ GOG



The increase of endometrial cancer incidence and mortality will reflect in an INCREASED GAP IN OUTCOMES

Eisai

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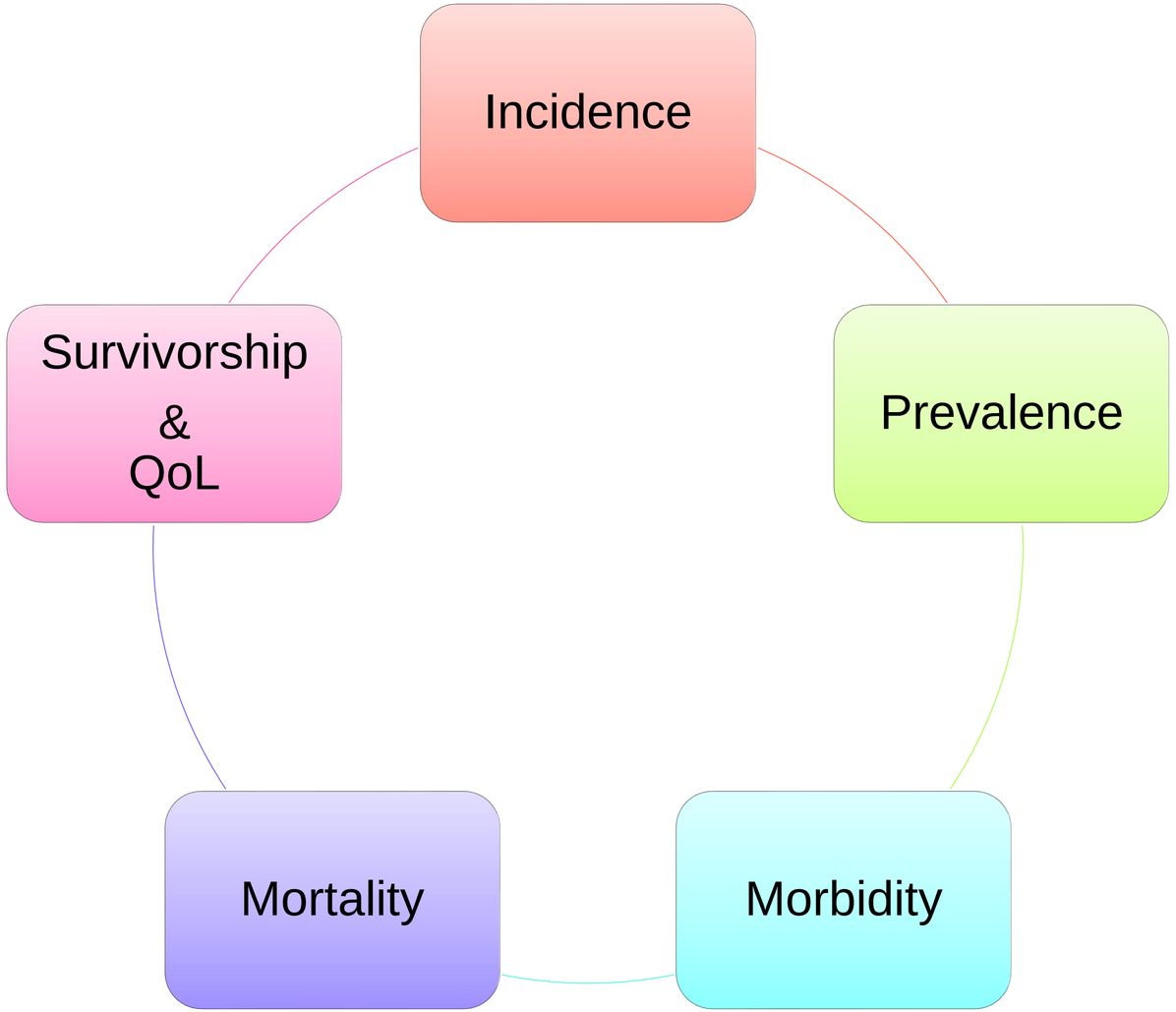
Disparities in endometrial cancer outcomes



Disparities in endometrial cancer outcomes

Estimated New Cases

Females

Breast	287,850	31%
Lung & bronchus	118,830	13%
Colon & rectum	70,340	8%
Uterine corpus	65,950	7%
Melanoma of the skin	42,600	5%
Non-Hodgkin lymphoma	36,350	4%
Thyroid	31,940	3%
Pancreas	29,240	3%
Kidney & renal pelvis	28,710	3%
Leukemia	24,840	3%
All Sites	**934,870**	**100%**

Estimated Deaths

Females

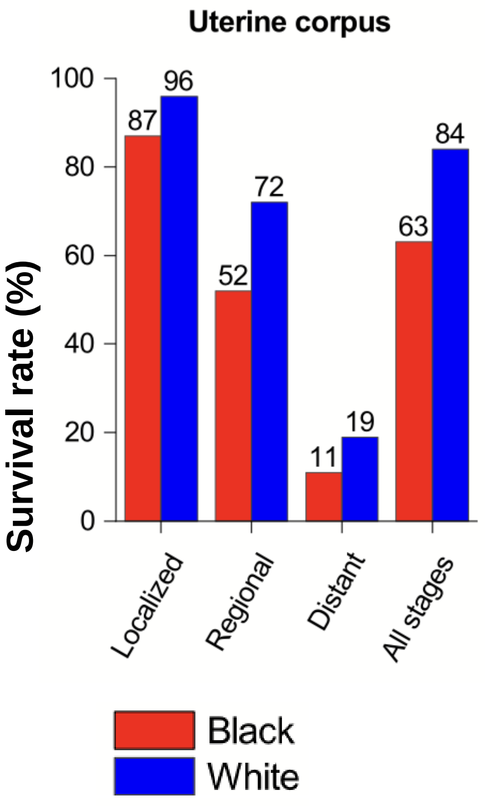
Lung & bronchus	61,360	21%
Breast	43,250	15%
Colon & rectum	24,180	8%
Pancreas	23,860	8%
Ovary	12,810	4%
Uterine corpus	12,550	4%
Liver & intrahepatic bile duct	10,100	4%
Leukemia	9,980	3%
Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	7,570	3%
All Sites	**287,270**	**100%**

Female

Breast	36,260	32%
Lung & bronchus	12,490	11%
Colon & rectum	10,110	9%
Uterine corpus	9,030	8%
Pancreas	4,410	4%
Kidney & renal pelvis	4,010	4%
Myeloma	3,970	4%
Non-Hodgkin lymphoma	3,240	3%
Thyroid	2,890	3%
Leukemia	2,650	2%
All sites	**112,090**	

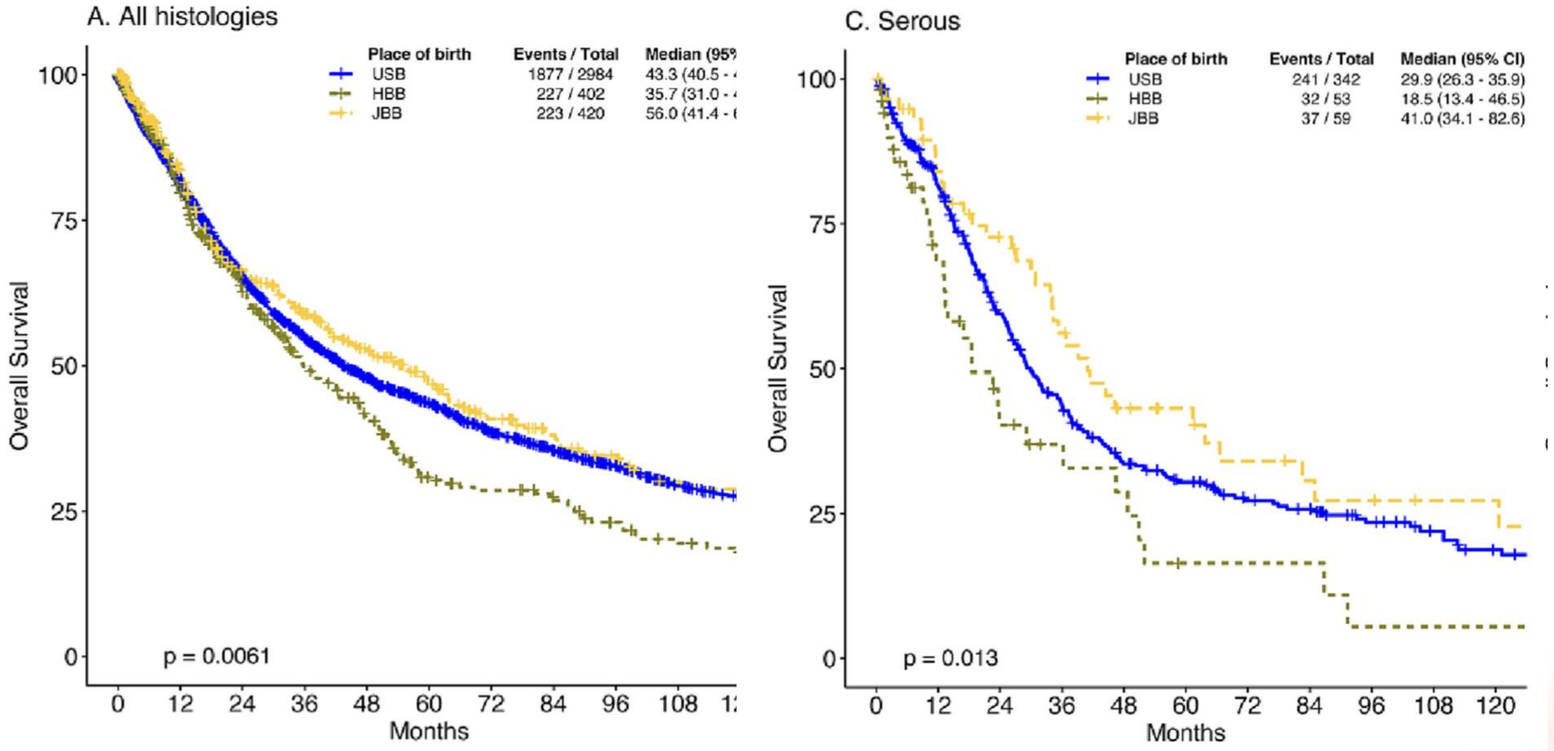
Female

Breast	6,800	18%
Lung & bronchus	6,270	17%
Colon & rectum	3,310	9%
Pancreas	3,300	9%
Uterine corpus	2,680	7%
Ovary	1,480	4%
Myeloma	1,270	3%
Liver & intrahepatic bile duct	1,150	3%
Leukemia	1,040	3%
Uterine cervix	780	2%
All sites	**37,250**	

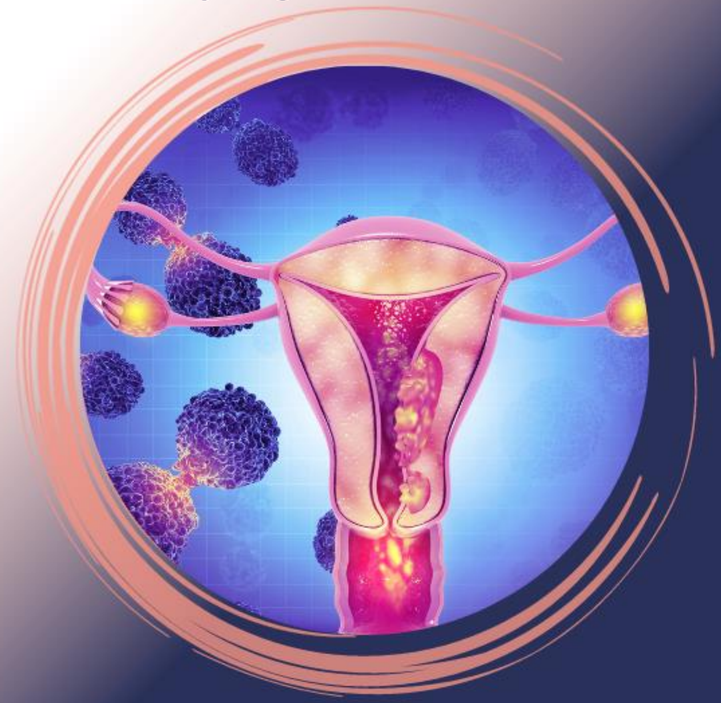


Gianquinto et al.
Cancer statistics for African American/Black People 2022

BW with EC are not all the same



Although the extent of the differences has not yet been established, there may be subgroups of women diagnosed with EC which may require modifications to treatment and surveillance based on characteristics other than race as an identifying characteristic.



USB = US born Black
HSB = Haiti born Black
JBB = Jamaica born Black

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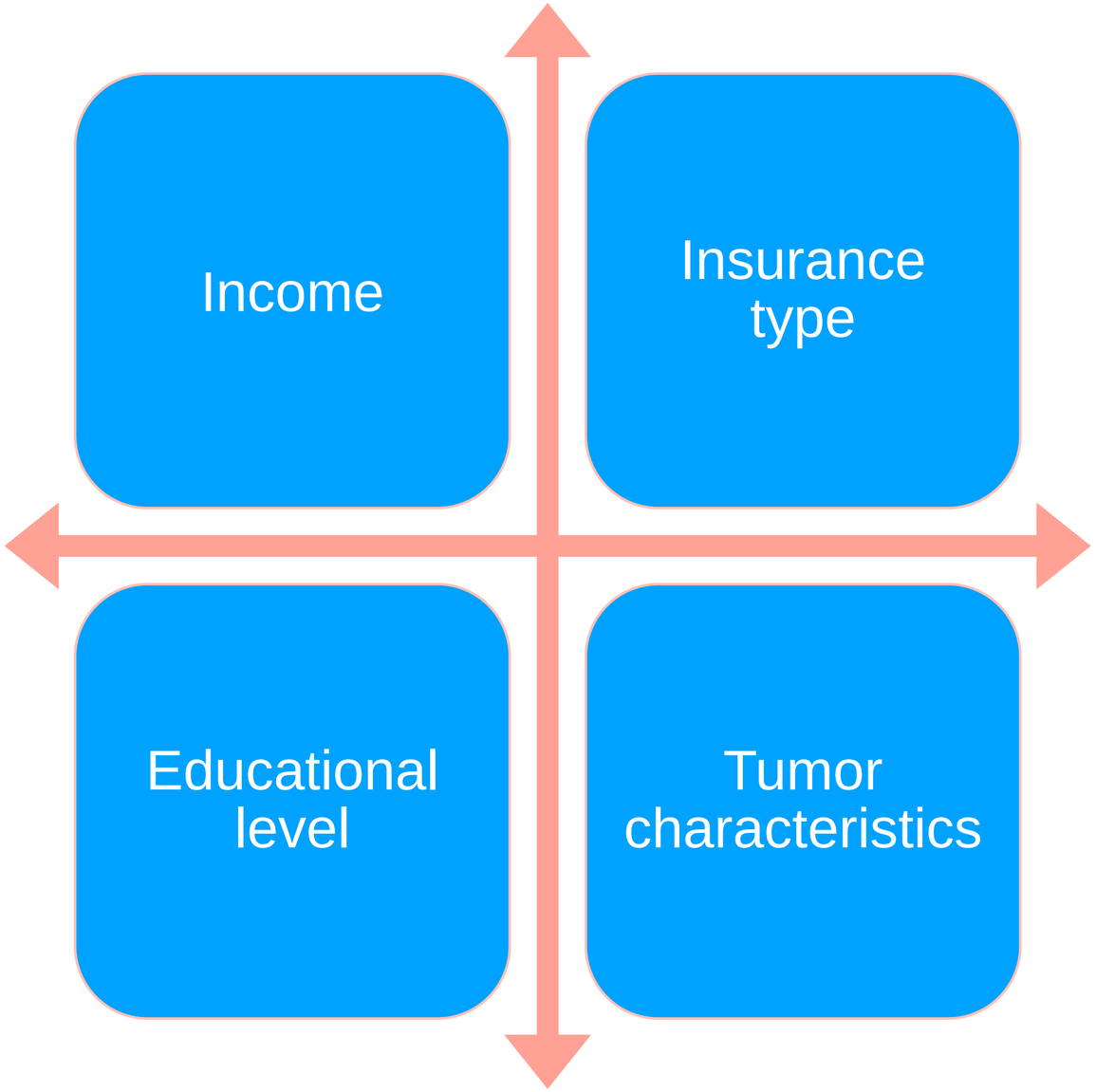
Factors contributing to disparities



- **Preventable**
- **Actionable**

Inequalities across the spectrum of care in black women with high-risk endometrial cancer

- **Early diagnosis** with TV-US impaired in BW due to higher prevalence of fibroids and non-endometrioid cancer *(Doll, Jama Oncol 2021)*
- **5 evidence-based quality** metrics for EC treatment (surgical treatment within 6 weeks of diagnosis, use of a MIS approach, nodal assessment, adjuvant radiation and systemic chemotherapy) less likely offered to BW ($p < 0.05$ for all) *(Huang, AJOG 2020; Corey, AJOG 2022)*
- **Post-op complications and SAE** more frequently observed in BW (ASO 2022)
- **Treatment refusals** more frequent in BW (Barrington, AJOG 2022)

Curr Opin Obstet Gynecol 2023, 35:15 – 20
DOI:10.1097/GCO.0000000000000832

FIGURE 3
Kaplan-Meier overall survival curves comparing Black and White women who either received or refused radiation (n=75,447)

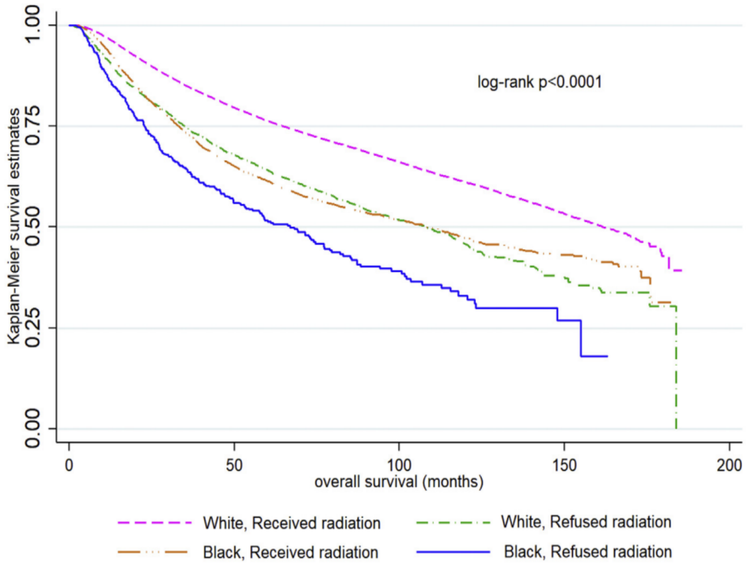
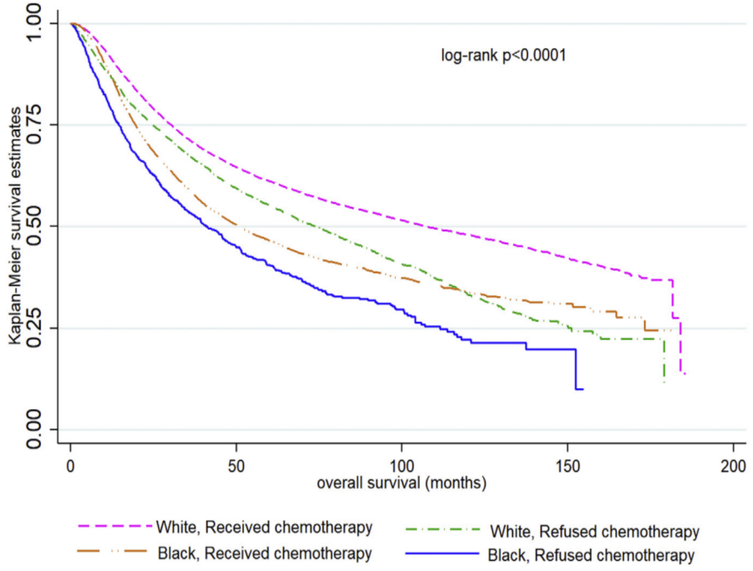


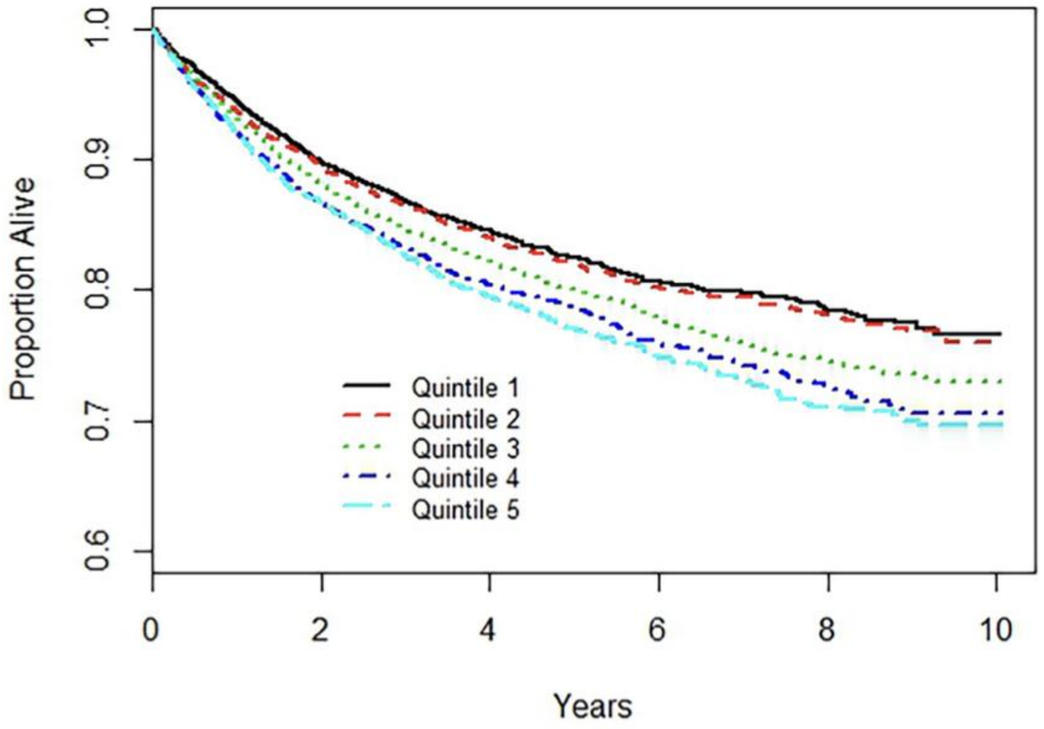
FIGURE 4
Kaplan-Meier overall survival curves comparing Black and White women who either received or refused chemotherapy (n=60,187)



Am J Obstet Gynecol 2022;227:244.e1-17.

- ✓ No difference in radiation refusal was detected.
- ✓ BW were significantly more likely than WW to refuse **Cht** in multivariable-adjusted models (data adjusted for sociodemographic variables, facilities characteristics, tumor characteristics).
- ✓ CHT refusal mediated only **4.9%** of survival disparities between Black and White women.
- ✓ Among women **with serous tumors, 6.8%** of survival disparities between BW and WW may be attributable to chemotherapy refusal.
- ✓ **Treatment refusal among BW is a small contributor to the disparity in mortality.**

OS in EC patients according to mariginalization quintile



20,228 women with EC between 2009 and 2017

Gynecologic Oncology 167 (2022) 532–539

- **Residential instability index**

housing instability, number of residents per dwelling, family unit size and composition

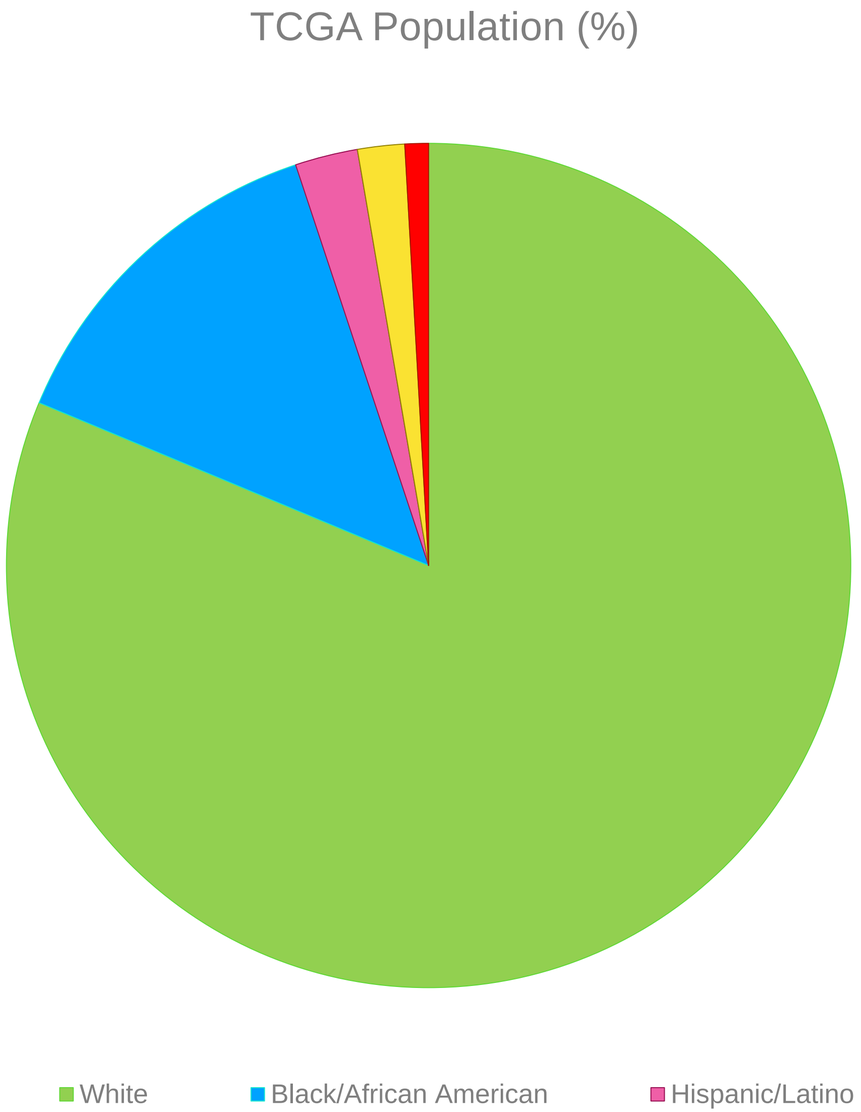
- **Material deprivation index**

information on education, income, government support and unemployment

- **Ethnic concentration index**

proportion of new immigrants (<5 years) in the community and those who self-identify as a minority

Living in highly marginalized neighborhoods is associated with more limited survival in this patient population, even after adjusting for patient age, comorbidities, obesity, and disease factors such as histology and stage.



Integrated genomic characterization of endometrial carcinoma

The Cancer Genome Atlas Research Network*

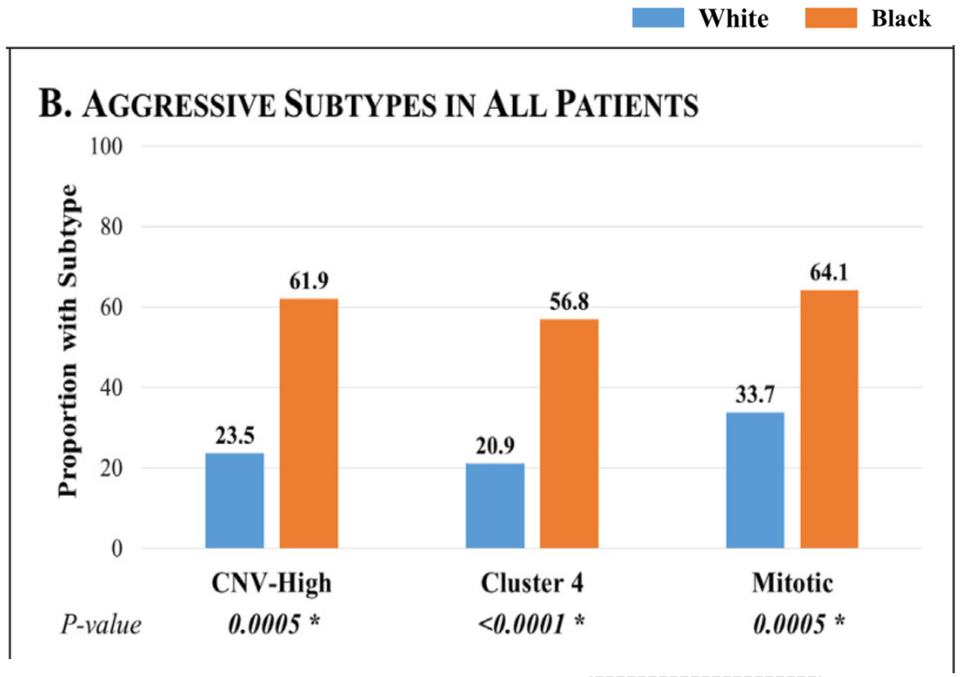
- ✓ TCGA analysis included 46 patients self-reported as Black/African American (13.6%). Other ethnicities were least represented.
- ✓ The prognostic value of molecular characterization in underrepresented minorities has been limited by a lack of data.
- ✓ Validation studies (PORTEC, ProMisE) do not report any data about patient ethnicity.

Table 2: Recurrently mutated genes differing by ethnicity

Caucasian		Asian		BoAA	
Gene	**n (%)**	**Gene**	**n (%)**	**Gene**	**n (%)**
PTEN	229 (63.26)	*PTEN*	17 (85)	*TP53*	52 (49.06)
PIK3CA	181 (50)	*PIK3CA*	13 (65)	*PTEN*	41 (38.68)
ARID1A	159 (43.92)	*ARID1A*	9 (45)	*PIK3CA*	41 (38.68)
TP53	115 (31.77)	*PIK3R1*	6 (30)	*ARID1A*	30 (28.3)
CTNNB1	98 (27.07)	*ARID5B*	6 (30)	*FBXW7*	24 (22.64)
CTCF	86 (23.76)	*CTNNB1*	6 (30)	*CTCF*	20 (18.87)
KRAS	76 (21)	*TP53*	5 (25)	*PIK3R1*	18 (16.98)
PIK3R1	71 (19.61)	*KRAS*	5 (25)	*CTNNB1*	17 (16.04)
FBXW7	64 (17.68)	*CTCF*	5 (25)	*KRAS*	15 (14.15)
PPP2R1A	62 (17.13)	*FBXW7*	3 (15)	*PPP2R1A*	13 (12.26)
ARID5B	50 (13.81)	*RPL22*	3 (15)	*ARID5B*	12 (11.32)
RPL22	41 (11.33)	*PPP2R1A*	2 (10)	*RPL22*	8 (7.55)

Oncotarget, 2018, Vol. 9, (No. 24), pp: 17093-17103

Molecular differences between Black and White women with endometrial cancer



E.A. Dubil et al. / Gynecologic Oncology 149 (2018) 106–116

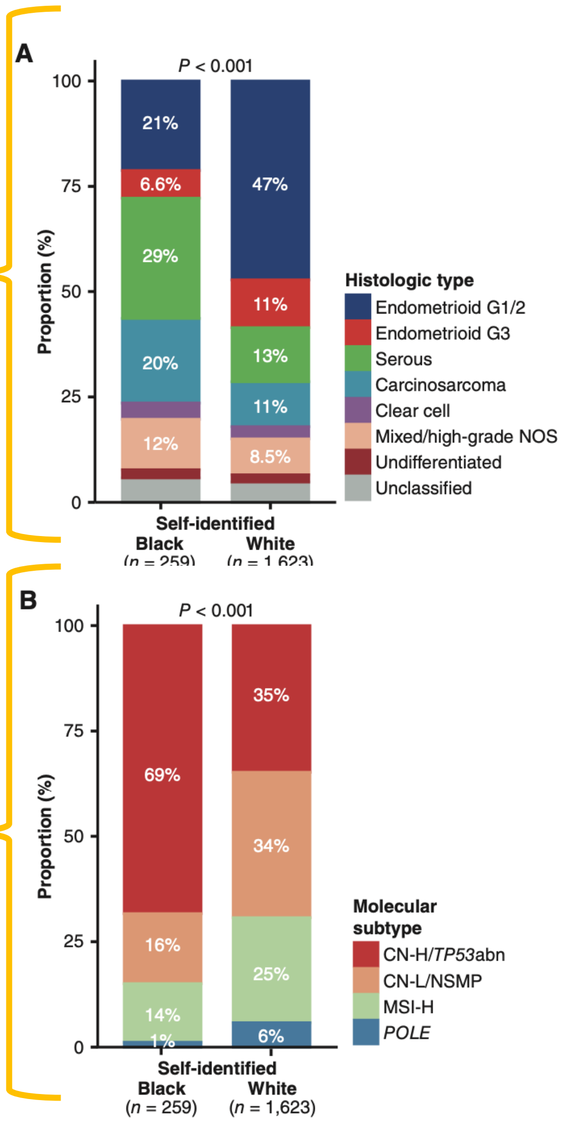
The aggressive molecular subtypes from TCGA were more common in Black endometrial cancer patients and indicated worse PFS in both Black and White patients. The mitotic subtypes also indicated worse PFS in Black patients with endometrioid histology.

Black patients are more likely to have TP53-mutated and p53-abnormal EC, which are associated with worse survival outcomes than TP53- and p53-wildtype EC. The higher frequency of these subtypes among Black patients may contribute to survival disparities.

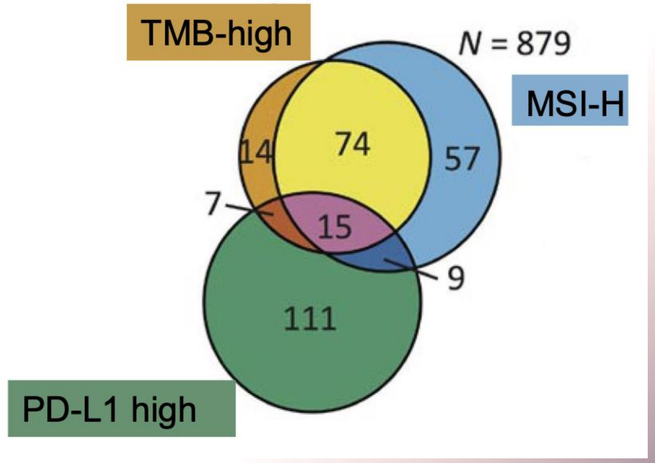
	Black ($N = 184$)	White ($N = 543$)	p-value
p53 Expression (IHC)	$N = 97$	$N = 265$	0.003
Normal	28	124	
Abnormal	69 (71.1%)	141 (53.2%)	
TP53 Sequence (NGS)			<0.001
Mutation	132 (71.7%)	270 (49.7%)	
No Mutation	52 (28.3%)	273 (50.3%)	
TP53 Variant			0.83
R273	18 (13.6%)	36 (13.3%)	
R248	13 (9.8%)	25 (9.3%)	
R175	6 (4.5%)	17 (6.3%)	
G245	2 (1.5%)	9 (3.3%)	
S241	2 (1.5%)	8 (3.0%)	
Other	91 (68.9%)	175 (64.8%)	

K. Whelan, M. Dillon, K.C. Strickland et al. Gynecologic Oncology 178 (2023) 44–53

Characteristic	All cases $n = 1{,}882$[a]	Black $n = 259$[a]	White $n = 1{,}623$[a]	P value[b]
Ethnicity				0.6
Hispanic	105 (5.8%)	13 (5.2%)	92 (5.9%)	
Non-Hispanic	1,695 (94%)	237 (95%)	1,458 (94%)	
Not available	82	9	73	
Histology				**<0.001**
Endometrioid G1/2	821 (44%)	55 (21%)	766 (47%)	
Endometrioid G3	201 (11%)	17 (6.6%)	184 (11%)	
Serous	283 (15%)	74 (29%)	209 (13%)	
Clear cell	57 (3.0%)	10 (3.9%)	47 (2.9%)	
Carcinosarcoma	225 (12%)	52 (20%)	173 (11%)	
Mixed/high-grade NOS	169 (9.0%)	31 (12%)	138 (8.5%)	
Un/dedifferentiated	33 (1.8%)	5 (1.9%)	28 (1.7%)	
Unclassified	93 (4.9%)	15 (5.8%)	78 (4.8%)	
MSK-IMPACT sequencing				0.3
Primary	1,579 (84%)	222 (86%)	1,357 (84%)	
Recurrence	301 (16%)	35 (14%)	266 (16%)	
Not available	2	2	0	
Molecular subtype				**<0.001**
CN-H/*TP53*abn	746 (40%)	178 (69%)	568 (35%)	
CN-L/NSMP	599 (32%)	42 (16%)	557 (34%)	
MSI-H	440 (23%)	36 (14%)	404 (25%)	
POLE	97 (5.2%)	3 (1.2%)	94 (5.8%)	
TMB (Mut/Mb)				**<0.001**
Mean	22	14	24	
Median (IQR)	6 (4, 16)	4 (3, 7)	7 (4, 19)	
Range	0, 668	1, 611	0, 668	
TMB category (Mut/Mb)				**<0.001**
<10	1,311 (70%)	220 (85%)	1,091 (67%)	
≥10	571 (30%)	39 (15%)	532 (33%)	
TMB category 2				**<0.001**
MSI-H	440 (23%)	36 (14%)	404 (25%)	
Non-MSI-H/TMB ≥10	173 (9.1%)	7 (2.7%)	166 (10%)	
TMB <10	1,269 (67%)	216 (83%)	1,053 (65%)	

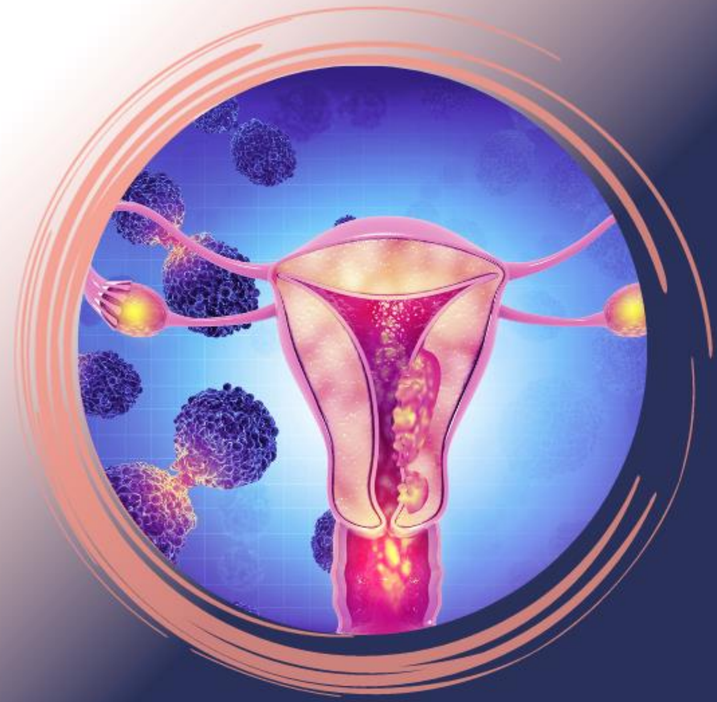


Immune checkpoint response markers by histologic subtype in black and white women



	All histologies		Endometrioid		Serous		Carcinosarcoma	
	B	W	B	W	B	W	B	W
TMB	5.9%	10.4%	20.0%	19.0%	1.7%	2.0%	7.7%	4.5%
MMRd/MSI-H	9.6%	14.0%	38.9%	27.5%	1.7%	0	7.7%	4.5%
PDL-1	3.9%	6.4%	0.0	4.5%	5.0%	7.8%	3.8%	9.1%

Gynecologic Oncology 166 (2022) 108–116



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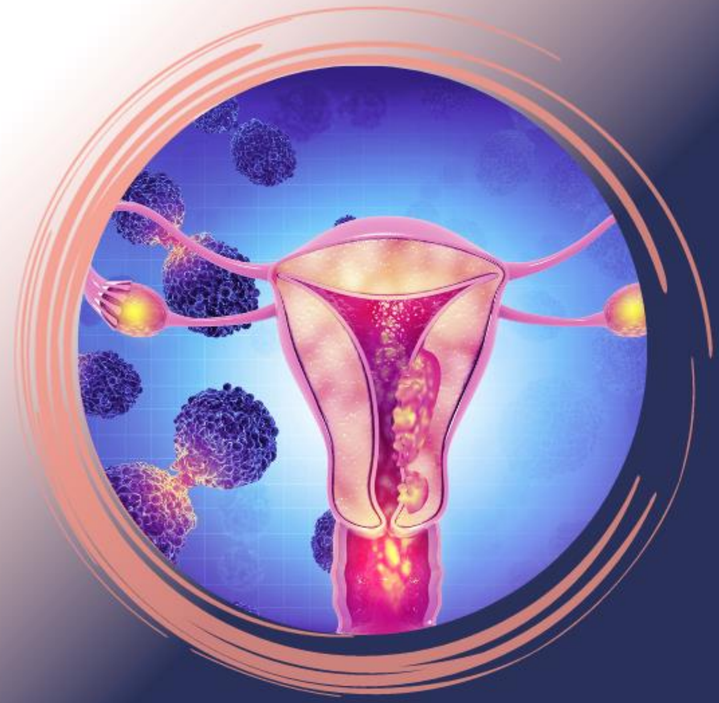
Key gaps in the literature !

- Significantly fewer studies involved **other races or ethnicities**, rather than White and Black Women
- Most studies were done with **national databases**, which do not provide enough details
- Most studies are limited by the **conceptualization and interpretation of race**
- Race was rarely defined beyond the **self-reported racial categories** used in data collection
- We must ensure "**race is not treated as a biologic factor**" only, to focus health disparities research in uterine cancer to modifiable, nonbiological factors that affect and perpetuate disparities.
- No/few published studies of **interventions** to reduce racial disparities in uterine cancer care are available.

(Obstet Gynecol 2022;139:645–59)

Strategies to reduce mortality and improve treatment outcomes



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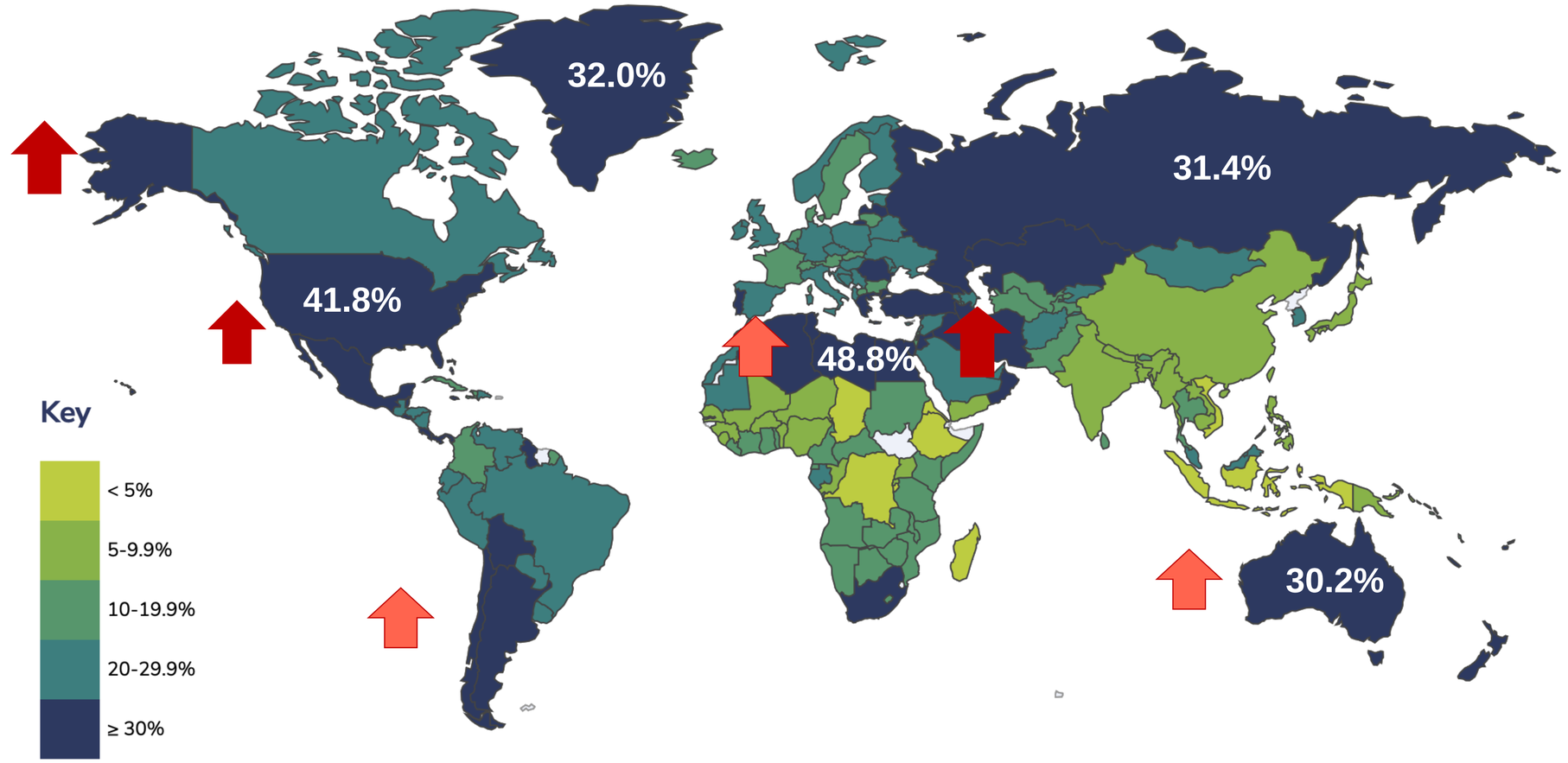
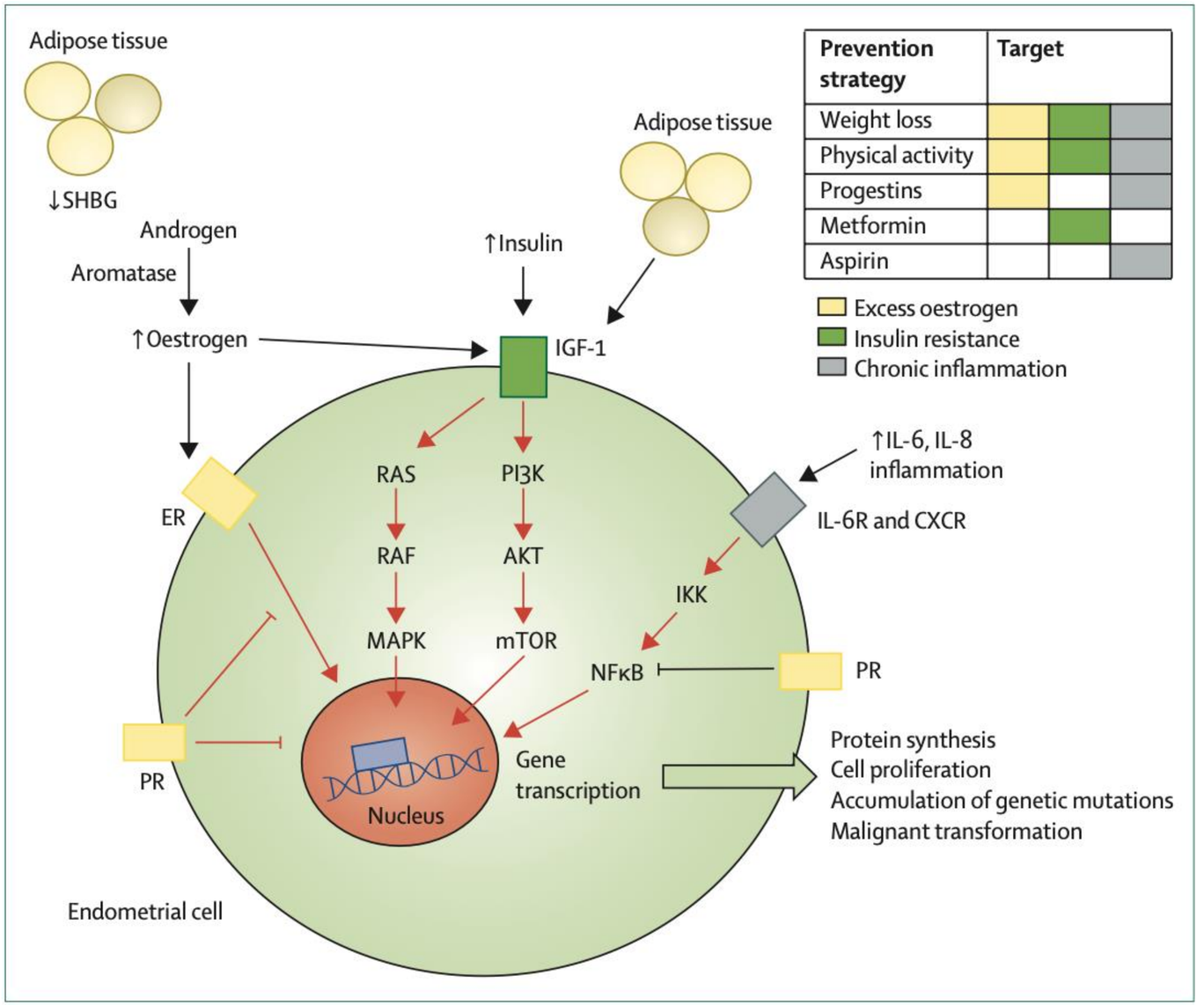
Projections of obesity in 2035 worldwide

World Obesity | Global Obesity Observatory

Women living with obesity. Newest available data



Obesity-associated endometrial cancer



Pathways to carcinogenesis and targets for prevention

Life style changes

Changes of lifestyle, exercise of precaution and preferences: Interim results of an international survey for endometrial cancer patients

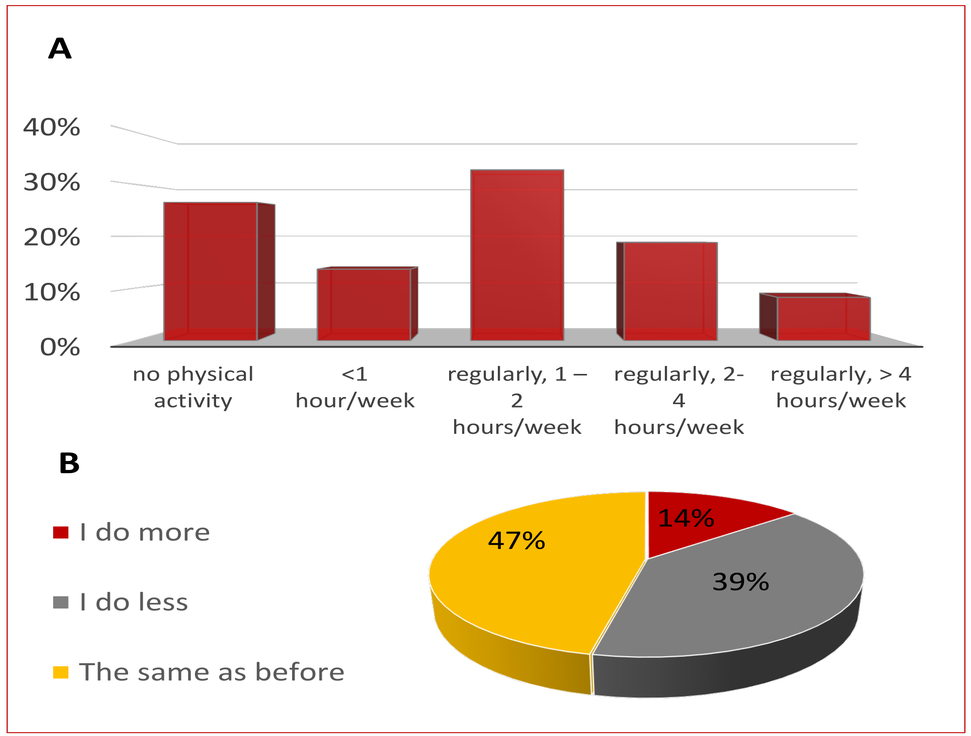
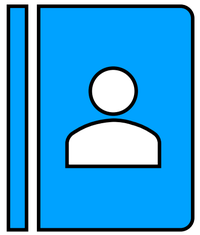


Figure 2. Physical activity before (A) and after (B) diagnosis

- From 12/2021 to 04/2023
- Survey with 80 items
- To 669 pts with EC
- Median age 65 (20-92) y.o.
- 77.4% in follow up; the rest under treatment
- A majority of patients believe in a potential positive impact of lifestyle changes, such as exercising and diets.
- Nevertheless, physical activity appeared to be relatively low and most patients did not change their diet after diagnosis.

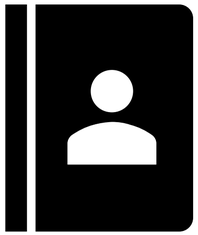
Lukas Chinczewski Poster Abstract ID ESGO-2023-435

Endometrial Cancer
A variety of tumors with potential therapeutic implications



MMR-d

p53



L1CAM

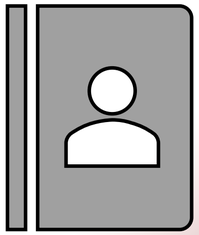
ER/PgR

TROP-2

POLE

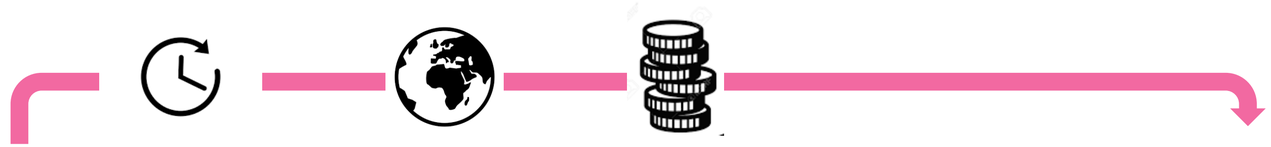
HER2

PD-L1/TMB



HRR

Molecular information



	NGS	IHC
POLE	PTEN 94% KRAS 53% PIK3CA 71% PIK3R1 65% ARID1A 76% FBXW7 82% ARID5B 47%	
MSS	PTEN 77% CTNNB1 52% PI3KCA 53% PI3KR1 33% ARID1A 42%	
MSI	PTEN 88% KRAS 35% PIK3CA 71% RPL22 33% PI3KCA 54% PIK3R1 40 % ARID1A 37%	MLH1, MSH2, PMS2, MSH6
HCN	Tp53 92% PPP2R1A 22% PI3KCA 47% Chromosomal Instability (MYC, erb-B2, CCNE1, FGFR3, SOX17)	p53

Interpretable deep learning model to predict the molecular classification of endometrial cancer from haematoxylin and eosin-stained whole-slide images: a combined analysis of the PORTEC randomised trials and clinical cohorts

***Lancet Digit Health* 2023; 5: e71–82**

***QPOLE*: A Quick, Simple, and Cheap Alternative for *POLE* Sequencing in Endometrial Cancer by Multiplex Genotyping Quantitative Polymerase Chain Reaction**

JCO Global Oncol 9:e2200384. © 2023

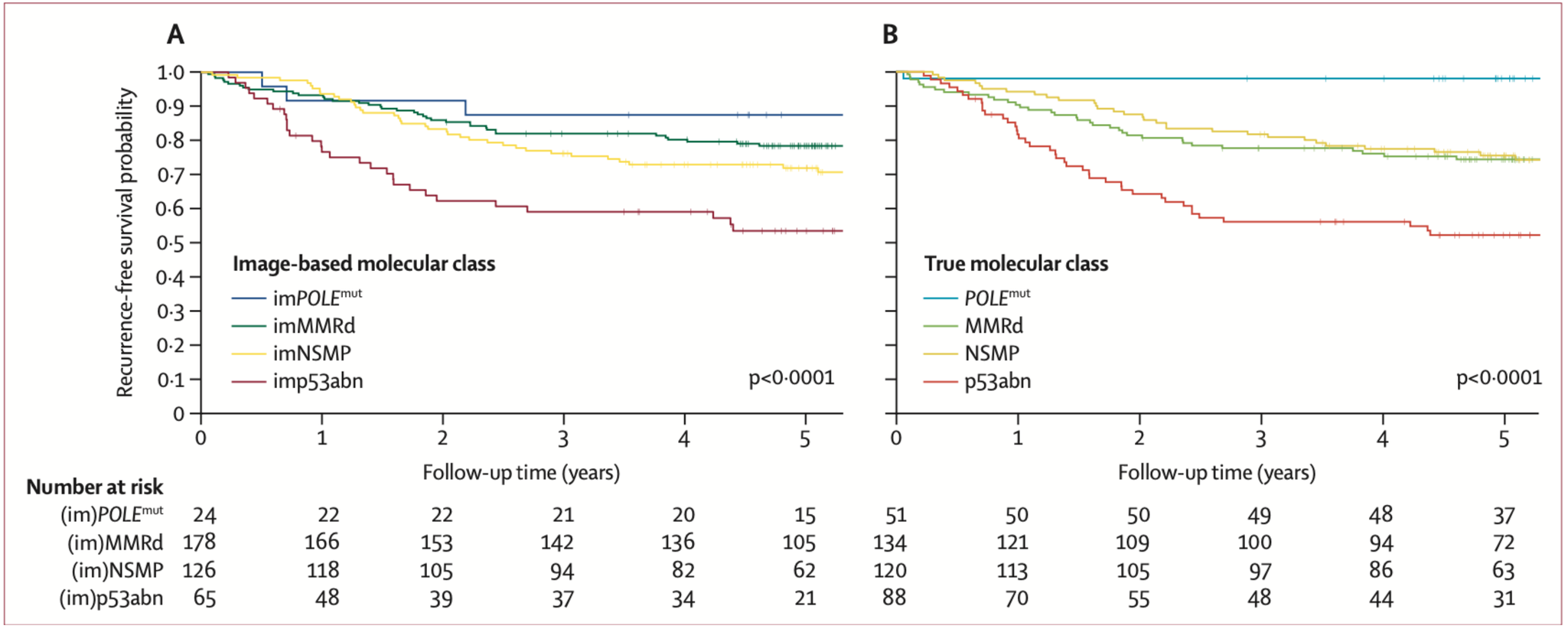
Kommoss, Ann Oncol 2018

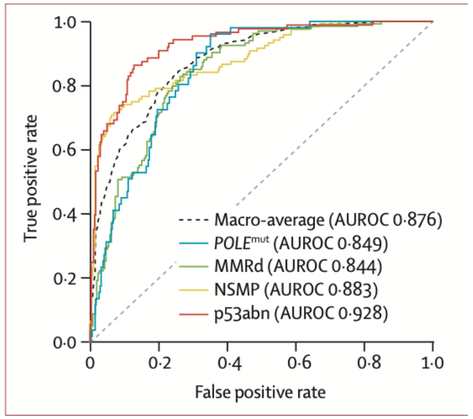
Talhouk, Cancer 2017

TGCA, Nature 2013

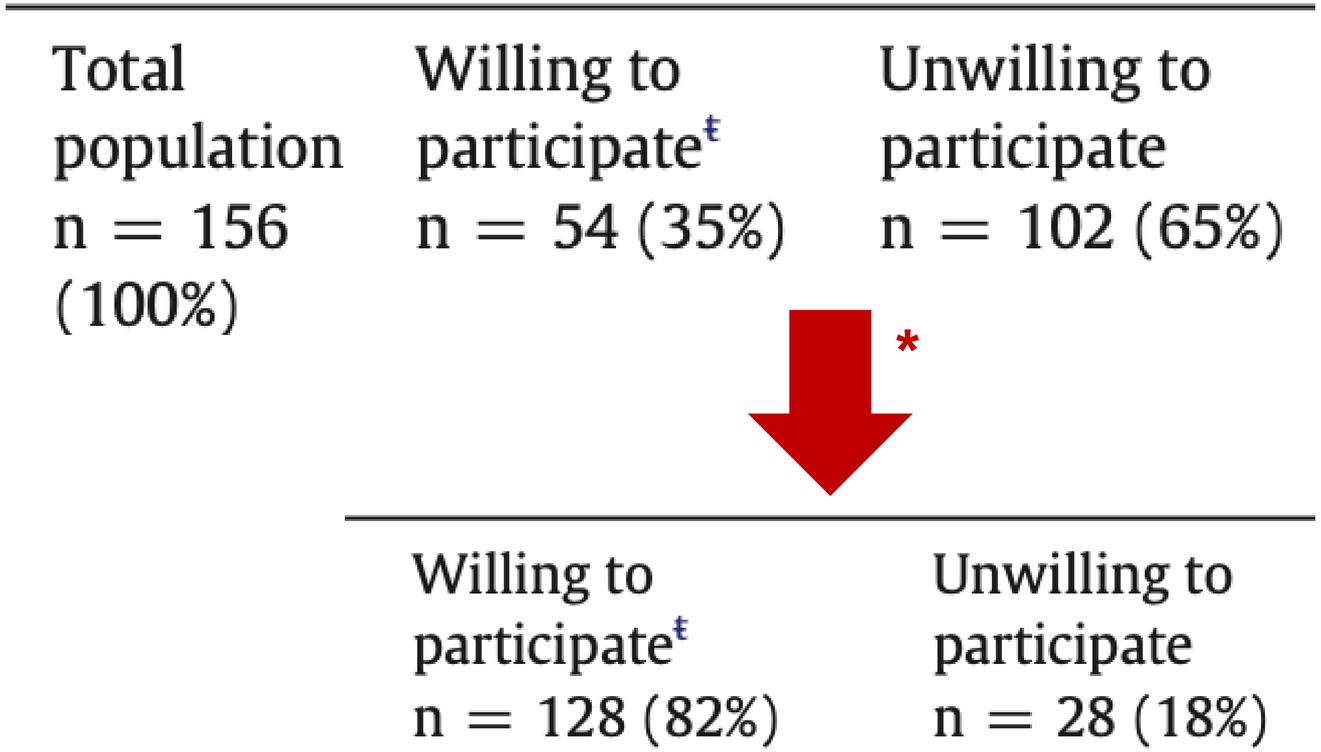
- PORTEC-1 (n=466), PORTEC-2 (n=375), and PORTEC-3 (n=393)
- TransPORTEC pilot study (n=110), the Medisch Spectrum Twente cohort (n=242)
- The Leiden Endometrial Cancer Repository case series of patients with *POLE*mut endometrial cancer (n=47)
- The Cancer Genome Atlas-Uterine Corpus Endometrial Carcinoma cohort (n=395)

Deep learning pipeline that can predict the four class molecular EC classification from **digitised haema-toxylin and eosin stained whole slide images in 2028 EC patients.**





Lancet Digit Health 2023; 5: e71–82



Following the educational intervention, there was willing to participate (88% vs **a higher proportion of Whites** 75%, p = 0.04) and **a lower proportion of those with less education** willing to participate (75% with high school degree or less vs 94% with graduate degree, p = 0.05).

*** ARTQ *(Attitudes to Randomized Trials Questionnaire)***

Gynecol Oncol. 2020 May;157(2):323-328. doi: 10.1016/j.ygyno.2020.01.040.

Zinzi D. Bailey et al N Engl J Med 2021; 384:768-773

EMPaCT
(Enhancing Minority Participation in Clinical Trials) consortium

- Established in 2009, involves 5 NCI-designated comprehensive cancer centers
- **Participation in clinical trials** often requires **time, travel, and resources** with limited reimbursement that may influence a patient's decision to enroll, whereas that burden is often less for those receiving standard of care
- Despite a carefully crafted integrated clinical workflow, racial disparities were found in the number of black versus non-black patients initiated on targeted therapies (28.2 vs. 38.2%, respectively) and enrolled in clinical trial (15 vs. 22.6%, respectively)

ecana
Endometrial Cancer Action Network for African-Americans

SISTER Study

The SISTER Study is the first national randomized trial to focus on improving outcomes for Black/African American women with endometrial cancer.

To compare two evidence-based interventions (group-based peer support and one-on-one peer support) against each other and against usual care delivery, to understand which is more effective at improving treatment.

Conclusions

- EC incidence is going to **dramatically increase** in the next future
- Several factors may contribute to disparities in outcome of EC patients
- **Lifestyle changes, inclusive policies and precision medicine** are **urgently needed** to reduce gaps in mortality and improve treatment outcomes of EC patients